Oregon Chiropractic Association

April 2026

Fours Hours Low-Level Laser For Healing and Pain

Dan Murphy, DC

PubMed zhang y and song s and fong

Format: Abstract

Full text links

ELSEVIER OPEN ACCESS

J Invest Dermatol. 2003 May;120(5):849-57.

cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light.

Zhang Y[1], **Song S**, **Fong** CC, Tsang CH, Yang Z, Yang M.

Author information

1 Applied Research Center for Genomic Technology, City University of Hong Kong, Kowloon, Hong Kong, China.

Abstract

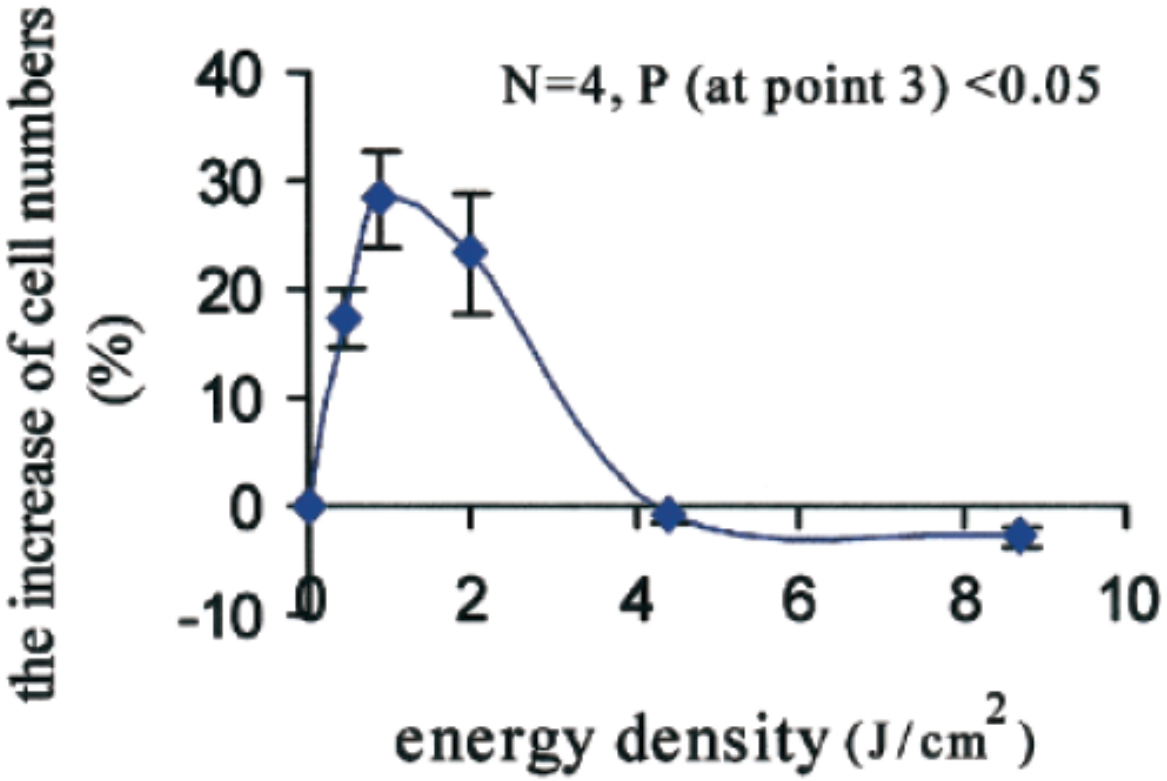
In this paper, the cDNA microarray technique was used to investigate the gene expression profiles of human fibroblasts irradiated by low-intensity red light. Proliferation assays showed that the fibroblast HS27 cells responded with a curve effect to different doses of low-intensity red light irradiation at a wavelength of 628 nm. An optimal dose of 0.88 J per cm2 was chosen for subsequent cDNA microarray experiments. The gene expression profiles revealed that 111 genes were regulated by the red light irradiation and can be grouped into 10 functional categories. Most of these genes directly or indirectly play roles in the enhancement of cell proliferation and the suppression of apoptosis. Two signaling pathways, the p38 mitogen-activated protein kinase signaling pathway and the platelet-derived growth factor signaling pathway, were found to be involved in cell growth induced by irradiation of low-intensity red light. Several genes related to antioxidation and mitochondria energy metabolism were also found to express differentially upon irradiation. This study provides insight into the molecular mechanisms associated with the beneficial effects of red light irradiation in accelerating wound healing.

PMID: 12713592 DOI: 10.1046/j.1523-1747.2003.12133.x

[Indexed for MEDLINE] **Free full text**

MeSH terms, Substances

merous applications and controlled studies on the method have been reported. Low-intensity red laser light therapy has been applied to various medical conditions such as wound repair and dermatologic diseases, neurologic damage, blood disorders, musculoskeletal complications, and pain and inflammation (Ab[illegible] *et al*, 1984; Mester *et al*, 1985; [illegible] *et al*, 1987; [illegible] *et al*, 2001). Previous studies showed that low-intensity red laser light was capable of affecting cellular processes in the absence of significant thermal effects (Karu, 1989). Fibroblasts are an important cellular component of wound healing, and it has been reported [illegible] (Lubart *et al*, 1992; [illegible] *et al*, 2000). Red light irradiation has also been reported to enhance the activity of succinic dehydrogenase and promote the synthesis of procollagen and the release of basic fibroblast growth factor (Conlan *et al*, 1996; Yu *et al*, 1994a; Bolton *et al*, 1995; Yamamoto *et al*, 1996). Although the evidence of the beneficial [illegible] of the tissue culture plates at the irradiation distance of 0.75 cm. Samples were irradiated for various time periods to yield final energy doses of 0, 0.44, 0.88, 2.00, 4.40, and 8.68 J per cm^2. The temperature was monitored [illegible] and the changes in cell number were recorded. The HS27 fibroblasts responded to the irradiation dose as a nonlinear curve and the cells grew faster than the control at energy doses of 0.44, 0.88, and 2 J per cm^2, with an optimal proliferation effect at 0.88 J per cm^2 (**Fig 1**). When the energy dose was increased to over 4 J per cm^2, the cells grew at the same rate as or slightly slower rates than control cells. Previous studies have reported that irradiation using an He–Ne laser at 632.8 nm, 660 [illegible] proliferation of HS27 fibroblasts. In addition to its effects on cell proliferation, red light irradiation may also regulate the expression of genes in relevant cells that are related to microcirculation, antiapoptosis, antioxidation, and DNA repair.


N=4, P (at point 3) <0.05
the increase of cell numbers (%)
40
30
20
10
0
-10
0
2
4
6
8
10
energy density (J/cm2)

ERCHONIA
World Leaders in Low Level Laser Technology

Erchonia Corporation

Changing Medicine Through Technology

- First company in the World to Garner FDA clearance for LLLT in 2002
- Erchonia holds 21 FDA 510K Clearances in LLLT with specific "IFU" (Indication for Use)
- In the field of LLLT there are a total of 24 FDA clearances Erchonia holding 21 of those

Erchonia 510K's

- 2002. Chronic neck and shoulder pain (PL5)
- 2004. Post surgical pain following breast augmentation
- 2005. Acne Vulgaris
- 2008. Post surgical pain following liposuction
- 2010. Circumference reduction of the waist, hips and thighs
- 2012. Circumference reduction of the arms
- 2013. Circumference reduction waist, hips, thigh 532nm
- 2013. Cellulite
- 2014. Chronic heel pain and plantar fasciitis
- 2014. Obesity circumferential reduction
- 2015. Zerona OTC (Over the Counter)
- 2015. Zerona EZ6 protocol
- 2016. Onychomycosis
- 2016. Over all body indication for body contouring
- 2018. Chronic lower back pain
- 2019. Overall musculoskeletal pain
- 2019. Chronic neck and shoulder pain using EVRL
- 2021. Overall post-operative pain
- 2021. Overall musculoskeletal pain using red and violet
- 2022. Neck and shoulder pain using green and violet

www.yourdomain.com

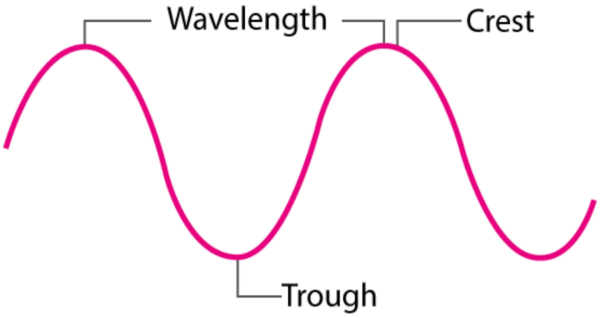
Waves & Wavelengths

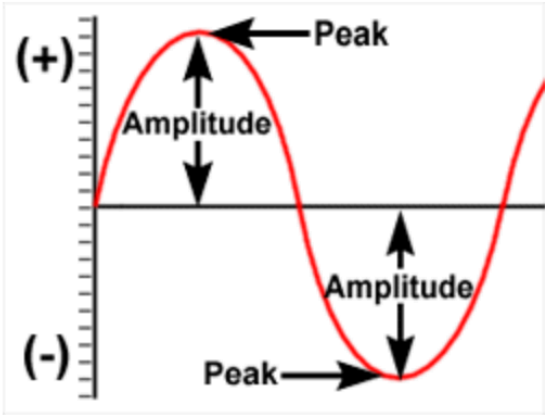
Visual and auditory stimuli both occur in the form of waves. Although the two stimuli are very different in terms of composition, wave forms share similar characteristics.

AMPLITUDE AND WAVELENGTH

Two physical characteristics of a wave are *amplitude* and *wavelength*.

Wavelength refers to the length of a wave from one peak to the next.





The *amplitude* or height of a wave is the height of a wave as measured from the highest point on the wave (peak or crest) to the lowest point on the wave (trough).

Frequency is the number of waves that pass a given point in a given time period and is often expressed in terms of hertz (Hz), or cycles per second.

Wavelength is directly related to the *frequency* of a given wave form.

Longer wavelengths will have *lower frequencies*, and *shorter wavelengths* will have *higher frequencies*.

As *wavelengths* become shorter the *frequency* increases.

LIGHT WAVES

The visible spectrum is the portion of the larger electromagnetic spectrum that we can see.

The electromagnetic spectrum encompasses all of the electromagnetic radiation that occurs in our environment and includes gamma rays, x-rays, ultraviolet light, visible light, infrared light, microwaves, and radio waves.

The visible spectrum in humans is associated with wavelengths that range from **380 to 740 nm**—a very small distance, since a nanometer (nm) is one billionth of a meter.

Other species can detect other portions of the electromagnetic spectrum:

- Honeybees can see light in the ultraviolet range.
- Some snakes can detect infrared radiation.

For humans, red is associated with longer wavelengths, greens are intermediate, and blues and violets are shorter in wavelength.

The amplitude of light waves is associated with our experience of brightness or intensity of color, with larger amplitudes appearing brighter.

Different wavelengths of light are associated with our perception of different colors.

Violet has the shortest visible wavelength in the visible spectrum (~ 400 nm), and red has the longest (700 nm).

Brightness refers to the intensity of the color and depends on the amplitude or the distance between the midpoint and the peak of the wave. The higher the amplitude of the waveform, the more intense and bright the color.

SOUND WAVES

Like light waves, the physical properties of *sound waves* are associated with various aspects of our perception of sound. Sounds waves are created by *vibrations* and can be thought of as ripples in the gasses that are constantly surrounding us. This is why sounds does not exist in space or complete vacuums. Without air or the presence of a gas to transmit the signal, sounds cannot exist.

The *frequency* of a sound wave is associated with our perception of that sound's pitch. High-frequency sound waves are perceived as high-pitched sounds, while low-frequency sound waves are perceived as low-pitched sounds. The audible range of sound frequencies is between 20 and 20,000 Hz, with greatest sensitivity to those frequencies that fall in the middle of this range.

The loudness of a given sound is closely associated with the amplitude of the sound wave. Higher amplitudes are associated with louder sounds.

Loudness is measured in terms of decibels (dB), a logarithmic unit of sound intensity. A typical conversation would correlate with 60 dB; a rock concert might check in at 120 dB.

There is the potential for hearing damage from about 80 dB to 130 dB.

Electrical Terms for Non-Engineers

Voltage: The *amount of electromotive pressure (force)* that is driving the signal. Measured in *volts* or *voltage*. The higher the voltage, the greater the *amplitude*, or height (and depth), of a wave. More voltage generally means a stronger, more intensely felt—or "louder"—signal. Applied to a frequency device, this translates to the "volume control" of the unit.

Current: The *number of electrons that flow across a given surface*, such as a wire; rate of flow. Measured in either *amps* (short for *amperes*) or *milliamps* (thousandths of an ampere). Since the exact number of electrons cannot be counted, one amp is a specific, hypothetical number of electrons flowing past a point per second. The larger and/or thicker the wire, the

An electrical supply of 1,000 volts is no deadlier than 100 volts because **the current determines the danger**. Tiny changes in a current's amperage can mean the difference between life and death when a person receives an electrical shock

Voltage is a measure of the *pressure* that allows electrons to flow. *Amperage* is a measure of the *volume* of electrons.

The following list from the U.S. Occupational Safety and Health Administration (OSHA) explains some of the most common effects of electrical shock at various amperage levels:

A *milliampere (mA)* is one-thousandth of an ampere (or amp).

A standard household circuit that supplies your outlets and switches carries 15 or 20 amps (15,000 or 20,000 mA).

1 to 5 mA: Little electrical shock is felt; upsetting but not painful

1 mA Threshold for the feeling of tingling sensation

5 mA Accepted as maximum harmless current

6 to 30 mA: Painful shock; loss of muscle control

10-20 mA Beginning of sustained muscular contraction (can't let go current)

50 to 150 mA: Extreme pain; possible severe muscle reactions; possible respiratory arrest

1,000 mA to 4,300 mA (1 amp to 4.3 amps):
Heart ceases pumping; nerve damage; death likely

10,000 mA (10 amps) (10 amps): Cardiac arrest; severe burns; death

This gives you an idea of the danger in the home wiring system we take for granted, where wires carry 15,000 or 20,000 mA (15 or 20 amps).

•••

Despite high voltages of over *5000 volts*, *electric fences* are much safer than one might assume. Hundreds of thousands of people worldwide encounter electric fences every day, and electric fences account for less than one serious injury per year worldwide.

The safety of electric fences in urban areas is achieved through two main factors: the voltage and the current (milliamps): The voltage is high, but the current is very

low, from 15 to 500 milliamps. This is a small fraction of the amperage used to power machinery which may draw up to 30 amps.

•••

Electric fences put out high voltage, around *7,000-8,000 volts*, which gets the animal's attention. However, they reduce the deadly amps to a very low amperage, usually around 120 milliamps. It is the low amps (milliamps) that that make the fence safe for the animals and humans.

Volts measure the *strength* of the electric shock when touching an electric fence. The higher the voltage, the stronger the shock.

Joules measure the *energy* delivered, which takes into account *both* the *voltage* and the *amperage*.

Joule is a measure of *energy*

Watt is a measure of *power*, a measure of how *fast* energy is used; it is energy over time (seconds)

W = J/Time (in seconds)

J = (W) X (T in seconds)

(W)	X	(T seconds)	= J
(60 W lightbulb)	X	(120 seconds)	= 7200 J

Watts is the *rate* of power flow.
A 60-watt light bulb tells you how much power flow it takes to run that bulb.
A higher watt light bulb is brighter.

Amps (A) are the unit used to measure electric current (flow of electrons).

The flow of electrons (amps) creates a current. The flow of electrons needs *energy*, which is called **voltage**.

Volts (V) is the unit for voltage.

Amps = Watts / Volts or Amps X Volts = Watts

You can use the watt value along with the voltage value to solve for the amp requirements.

A 5,000-watt electric dryer plugged into a 240-volt outlet would require just over 20 amps of current: 5,000 Watts / 240 Volts = 20.83 Amps.

•••

Voltage = *potential*, like a rock hanging overhead.

Current (amps) = the movement of the rock that kills you.

•••

Imagine that an electric current is a water pipe.
The *amps* would be the *volume* of water.
The *volts* would be the water *pressure*.

The *amps* measure the *amount* of electricity in a current.
The *volts* measure that electricity's *strength*.

•••

Your muscles, nerves, lungs, and heart all need electricity to work properly.

Electric currents (electrons) travel well through your blood and tissues, but they have a hard time passing through your skin.

Skin *resists* the flow of electrons; skin is a *resistor*. It helps keep your body safe from harmful currents, but it also *interferes* with therapeutic currents.

When the *voltage* of a current *goes up*, your skin's *resistance goes down*. This lets more current flow through your skin and into your body.

A live wire of a downed power line will have very high voltage. Its voltage will be high enough to overcome your skin's resistance. It can pass through your skin into your blood vessels and tissues. If the level of amps is high enough, it can do some serious damage to your body tissues and even kill you.

If your skin is wet, its resistance will be even lower, which is why we do not to touch electrical devices with wet hands.

Consequently, depending on the variables, both *volts* or *amps* can be dangerous.

Key Point

In part, what makes therapeutic lasers so awesome, especially as compared to LED, is that they are much better at getting the electrons through the skin to help the body, as long as the milliamps are not too high. Remember:

milliamps X volts = milliwatts and watts X seconds = joules
1 watt X 1 second = 1 joule

All light, visible and invisible, has a *Wavelength* and a *Frequency*

Wavelength X Frequency = 186,282 miles/second ALWAYS

The Electromagnetic Spectrum

Gamma	X-rays	Ultraviolet	Visible	Infrared	Microwave	Radio Waves
0.001- 0.1 nm	1-10 nm	10-400 nm	400-700 nm	700-1000 nm 1000 nm = 1 mm	1-100 mm 100 mm = 10 cm	10 cm - 100,000 cm 100,000 cm = 100 km = 62 miles

[5G has only 2% of the range of 4G]

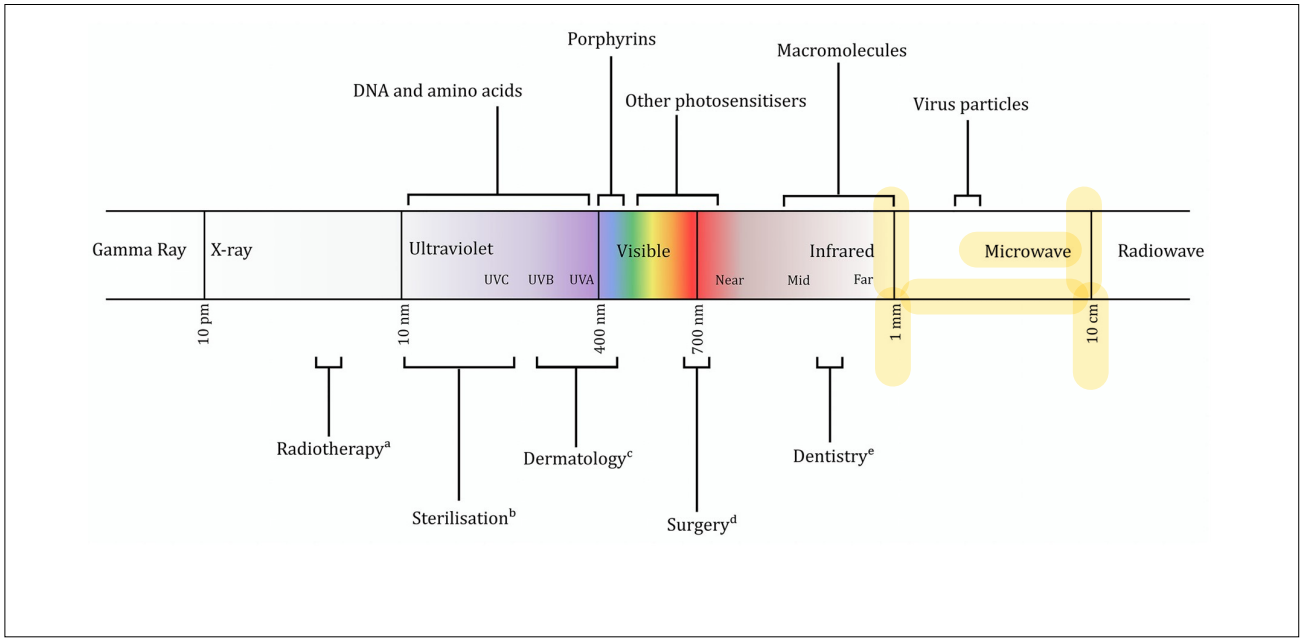


TABLE 1 | Optical properties of selected wavelengths in skin.

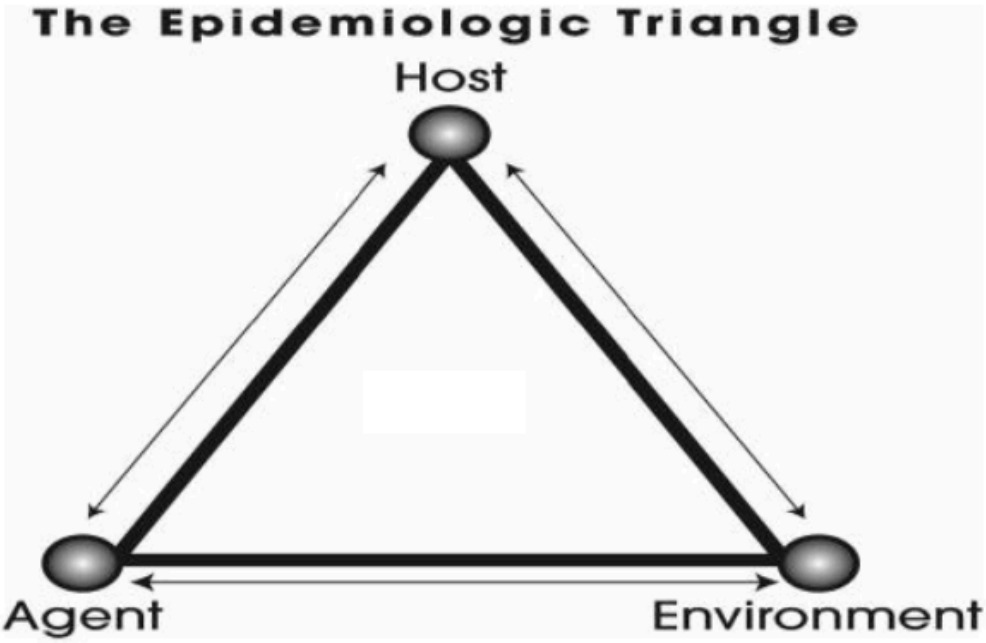
Wavelength (nm)	Absorption coefficient in skin (cm^{-1})	Scattering coefficient in skin (cm^{-1})	Approx penetration depth (μm)	Major interactions in tissue
300	45.0	260.0	6.0	Mutagenic
350	25.0	220.0	60.0	Mutagenic
400	13.5	34.3	90.0	Mutagenic, photochemical
500	6.2	25.1	230.0	Photochemical
600	3.8	18.6	550.0	Photochemical
700	2.4	14.8	750.0	Photochemical, thermal
800	1.9	12.4	1200.0	Photochemical, thermal
1000	1.6	9.2	1600.0	Thermal
1200	1.8	7.1	2200.0	Thermal

In general, shorter wavelengths scatter and are absorbed more in tissues, limiting penetration depth. Data from Anderson and Parrish (1981) and Bashkatov et al. (2011).

The Epidemiological Triad

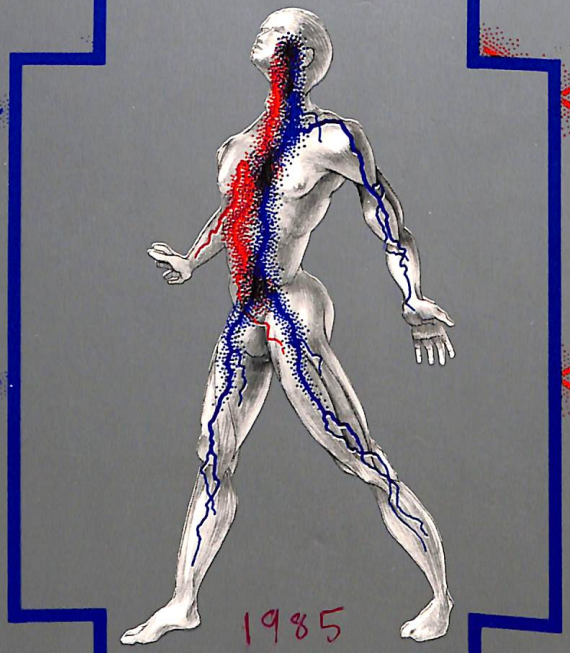
Centers for Disease Control and Prevention

Atlanta, Georgia
2020



THE BODY ELECTRIC

ELECTROMAGNETISM AND THE FOUNDATION OF LIFE



1985

ROBERT O. BECKER, M.D.,
AND GARY SELDEN

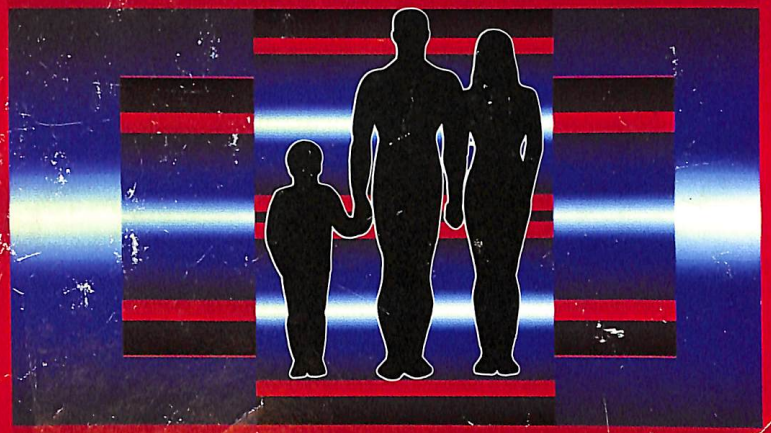
ILLUSTRATED BY DAVID BICHELL

A Startling Look at the Effects of Electromagnetic Radiation on Your Health

CROSS CURRENTS

1990

The Perils of Electropollution



The Promise of Electromedicine

ROBERT O. BECKER, M.D.

author of The Body Electric

Copyrighted Material

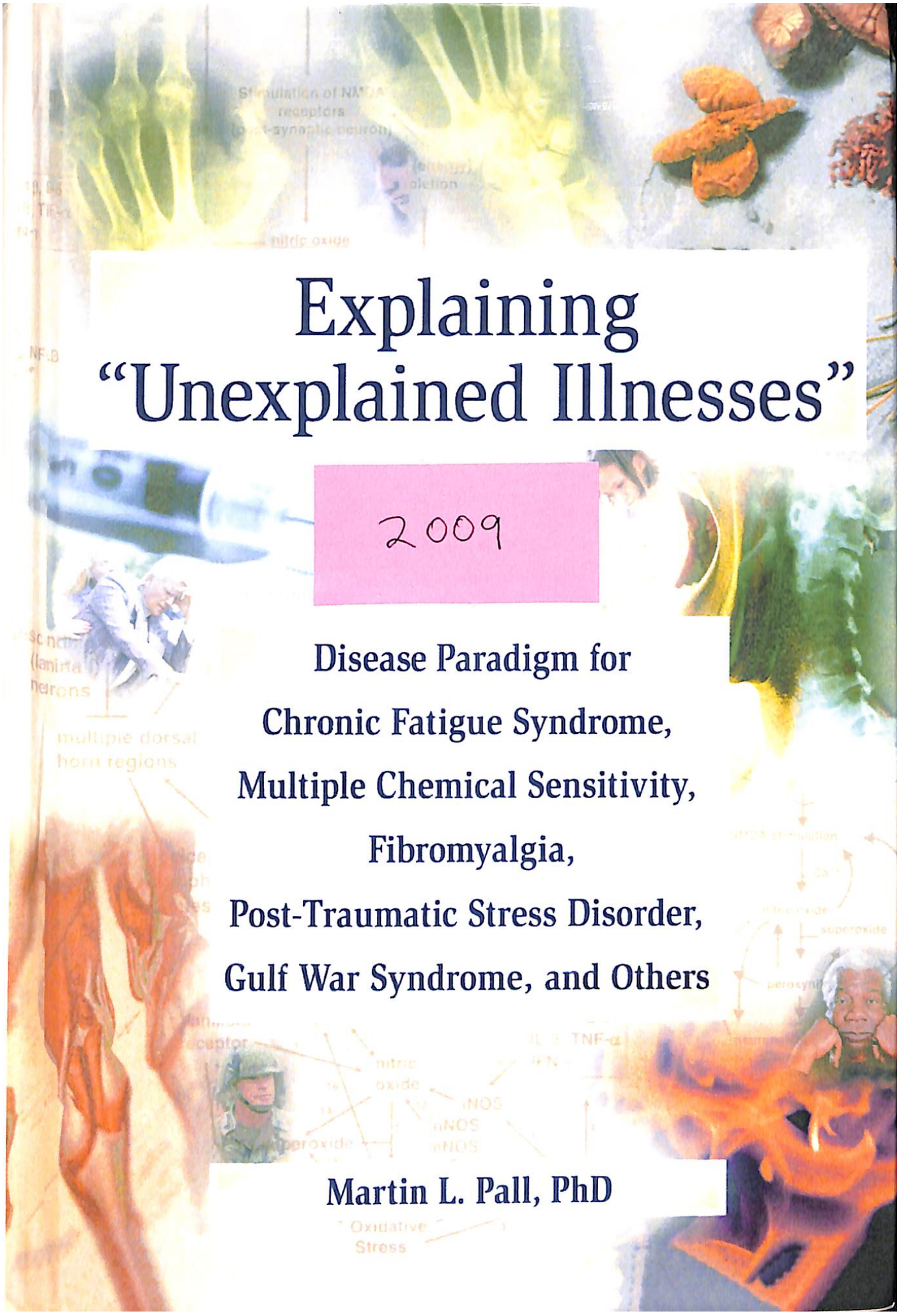
"The authors raise serious questions about the integrity of the cell phone industry and the FDA." —*San Francisco Chronicle*

Cell Phones

Invisible Hazards in the Wireless Age

DR. GEORGE CARLO
Chief Scientist of the World's Largest Research Effort into Wireless Safety
and MARTIN SCHRAM

Copyrighted Material



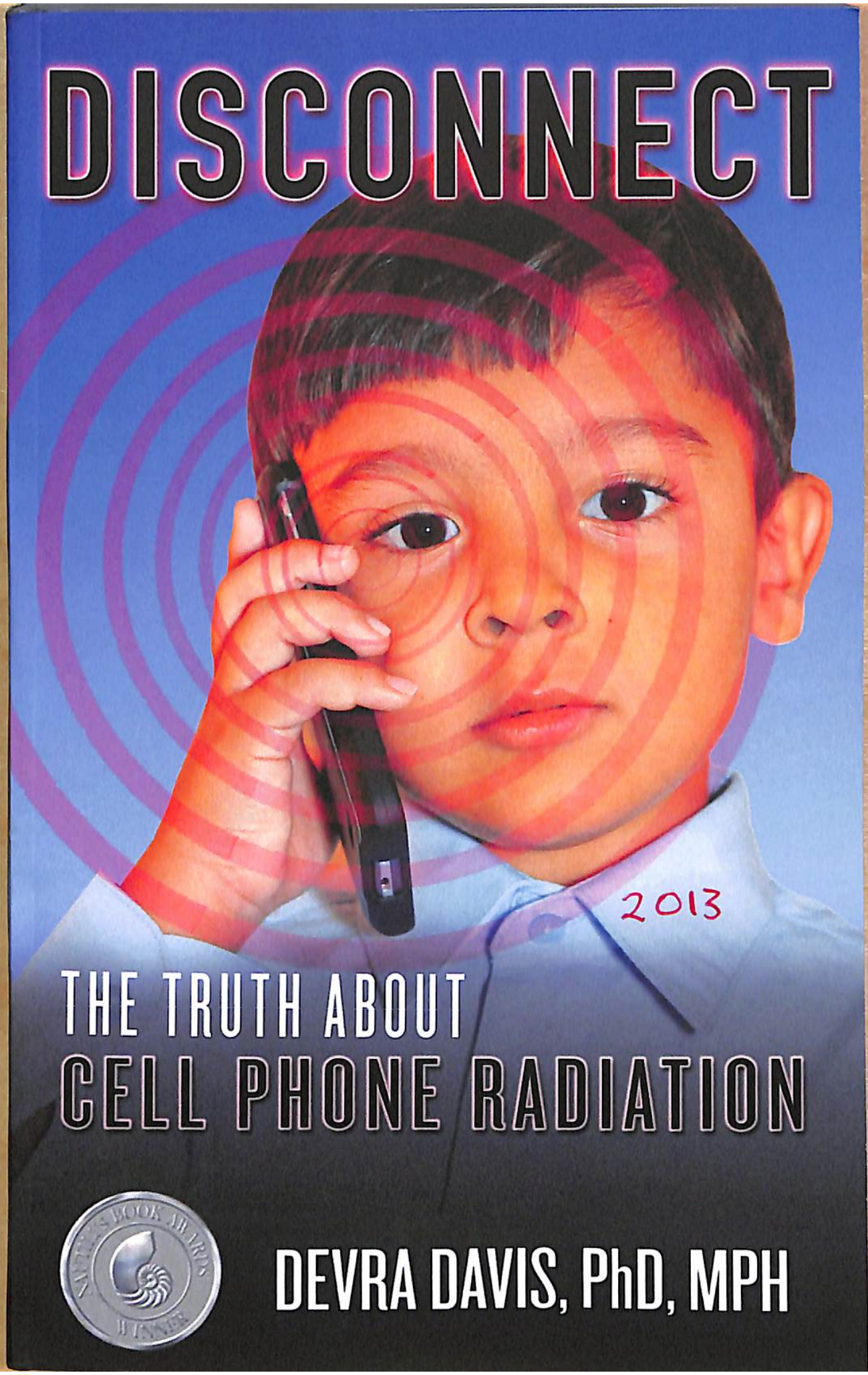
Explaining "Unexplained Illnesses"

2009

Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome, and Others

Martin L. Pall, PhD

DISCONNECT



THE TRUTH ABOUT CELL PHONE RADIATION

DEVRA DAVIS, PhD, MPH

PubMed

Abstract

Full text links

J Cell Mol Med. **2013** Aug;17(8):958-65. doi: 10.1111/jcmm.12088. Epub **2013** Jun 26.

Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects.

Pall ML[1].

Author information

[1]Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, Portland, OR, USA. martin_**pall**@wsu.edu

Abstract

The direct targets of extremely low and microwave frequency range electromagnetic fields (EMFs) in producing non-thermal effects have not been clearly established. However, studies in the literature, reviewed here, provide substantial support for such direct targets. Twenty-three studies have shown that voltage-gated **calcium** channels (VGCCs) produce these and other EMF effects, such that the L-type or other VGCC blockers block or greatly lower diverse EMF effects. Furthermore, the voltage-gated properties of these channels may provide biophysically plausible mechanisms for EMF biological effects. Downstream responses of such EMF exposures may be mediated through Ca(2+) /calmodulin stimulation of nitric oxide synthesis. Potentially, physiological/therapeutic responses may be largely as a result of nitric oxide-cGMP-protein kinase G pathway stimulation. A well-studied example of such an apparent therapeutic response, EMF stimulation of bone growth, appears to work along this pathway. However, pathophysiological responses to EMFs may be as a result of nitric oxide-peroxynitrite-oxidative stress pathway of action. A single such well-documented example, EMF induction of DNA single-strand breaks in cells, as measured by alkaline comet assays, is reviewed here. Such single-strand breaks are known to be produced through the action of this pathway. Data on the mechanism of EMF induction of such breaks are limited; what data are available support this proposed mechanism. Other Ca(2+) -mediated regulatory changes, independent of nitric oxide, may also have roles. This article reviews, then, a substantially supported set of targets, VGCCs, whose stimulation produces non-thermal EMF responses by humans/higher animals with downstream effects involving Ca(2+) /calmodulin-dependent nitric oxide increases, which may explain therapeutic and pathophysiological effects.

© **2013** The Author. Journal of Cellular and Molecular Medicine Published by Foundation for Cellular and Molecular Medicine/Blackwell Publishing Ltd.

PubMed

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov .
Get the latest research from NIH: https://www.nih.gov/coronavirus.

Full text links
DE GRUYTER FREE ACCESS

Format: Abstract

Rev Environ Health. 2015;30(2):99-116. doi: 10.1515/reveh-2015-0001.

Scientific evidence contradicts findings and assumptions of Canadian Safety Panel 6: microwaves act through voltage-gated calcium channel activation to induce biological impacts at non-thermal levels, supporting a paradigm shift for microwave/lower frequency electromagnetic field action.

Pall ML.

Abstract

This review considers a paradigm shift on microwave electromagnetic field (EMF) action from only thermal effects to action via voltage-gated calcium channel (VGCC) activation. Microwave/lower frequency EMFs were shown in two dozen studies to act via VGCC activation because all effects studied were blocked by calcium channel blockers. This mode of action was further supported by hundreds of studies showing microwave changes in calcium fluxes and intracellular calcium [Ca2+]i signaling. The biophysical properties of VGCCs/similar channels make them particularly sensitive to low intensity, non-thermal EMF exposures. Non-thermal studies have shown that in most cases pulsed fields are more active than are non-pulsed fields and that exposures within certain intensity windows have much large biological effects than do either lower or higher intensity exposures; these are both consistent with a VGCC role but inconsistent with only a heating/thermal role. Downstream effects of VGCC activation include calcium signaling, elevated nitric oxide (NO), NO signaling, peroxynitrite, free radical formation, and oxidative stress. Downstream effects explain repeatedly reported biological responses to non-thermal exposures: oxidative stress; single and double strand breaks in cellular DNA; cancer; male and female infertility; lowered melatonin/sleep disruption; cardiac changes including tachycardia, arrhythmia, and sudden cardiac death; diverse

neuropsychiatric effects including depression; and therapeutic effects. Non-VGCC non-thermal mechanisms may occur, but none have been shown to have effects in mammals. Biologically relevant safety standards can be developed through studies of cell lines/cell cultures with high levels of different VGCCs, measuring their responses to different EMF exposures. The 2014 Canadian Report by a panel of experts only recognizes thermal effects regarding safety standards for non-ionizing radiation exposures. Its position is therefore contradicted by each of the observations above. The Report is assessed here in several ways including through Karl Popper's assessment of strength of evidence. Popper argues that the strongest type of evidence is evidence that falsifies a theory; second strongest is a test of "risky prediction"; the weakest confirms a prediction that the theory could be correct but in no way rules out alternative theories. All of the evidence supporting the Report's conclusion that only thermal effects need be considered are of the weakest type, confirming prediction but not ruling out alternatives. In contrast, there are thousands of studies apparently falsifying their position. The Report argues that there are no biophysically viable mechanisms for non-thermal effects (shown to be false, see above). It claims that there are many "inconsistencies" in the literature causing them to throw out large numbers of studies; however, the one area where it apparently documents this claim, that of genotoxicity, shows no inconsistencies; rather it shows that various cell types, fields and end points produce different responses, as should be expected. The Report claims that cataract formation is produced by thermal effects but ignores studies falsifying this claim and also studies showing [Ca2+]i and VGCC roles. It is time for a paradigm shift away from only thermal effects toward VGCC activation and consequent downstream effects.

PMID: 25879308 DOI: 10.1515/reveh-2015-0001

[Indexed for MEDLINE] **Free full text**

Publication type, MeSH terms, Substance

LinkOut - more resources

PubMed

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov .
Get the latest research from NIH: https://www.nih.gov/coronavirus.

Full text links
ELSEVIER
OPEN ACCESS

Format: Abstract

J Chem Neuroanat. 2016 Sep;75(Pt B):43-51. doi: 10.1016/j.jchemneu.2015.08.001. Epub 2015 Aug 21.

Microwave frequency electromagnetic fields (EMFs) produce widespread neuropsychiatric effects including depression.

Pall ML[1].

Author information

1 Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, 638 NE 41st Avenue, Portland, OR 97232-3312, USA. Electronic address: martin_pall@wsu.edu.

Abstract

Non-thermal microwave/lower frequency electromagnetic fields (EMFs) act via voltage-gated calcium channel (VGCC) activation. Calcium channel blockers block EMF effects and several types of additional evidence confirm this mechanism. Low intensity microwave EMFs have been proposed to produce neuropsychiatric effects, sometimes called microwave syndrome, and the focus of this review is whether these are indeed well documented and consistent with the known mechanism(s) of action of such EMFs. VGCCs occur in very high densities throughout the nervous system and have near universal roles in release of neurotransmitters and neuroendocrine hormones. Soviet and Western literature shows that much of the impact of non-thermal microwave exposures in experimental animals occurs in the brain and peripheral nervous system, such that nervous system histology and function show diverse and substantial changes. These may be generated through roles of VGCC activation, producing excessive neurotransmitter/neuroendocrine release as well as oxidative/nitrosative stress and other responses. Excessive VGCC activity has been shown from genetic polymorphism studies to have roles in producing neuropsychiatric changes in humans. Two U.S. government reports from the 1970s to 1980s provide evidence for many neuropsychiatric

effects of non-thermal microwave EMFs, based on occupational exposure studies. 18 more recent epidemiological studies, provide substantial evidence that microwave EMFs from cell/mobile phone base stations, excessive cell/mobile phone usage and from wireless smart meters can each produce similar patterns of neuropsychiatric effects, with several of these studies showing clear dose-response relationships. Lesser evidence from 6 additional studies suggests that short wave, radio station, occupational and digital TV antenna exposures may produce similar neuropsychiatric effects. Among the more commonly reported changes are sleep disturbance/insomnia, headache, depression/depressive symptoms, fatigue/tiredness, dysesthesia, concentration/attention dysfunction, memory changes, dizziness, irritability, loss of appetite/body weight, restlessness/anxiety, nausea, skin burning/tingling/dermographism and EEG changes. In summary, then, the mechanism of action of microwave EMFs, the role of the VGCCs in the brain, the impact of non-thermal EMFs on the brain, extensive epidemiological studies performed over the past 50 years, and five criteria testing for causality, all collectively show that various non-thermal microwave EMF exposures produce diverse neuropsychiatric effects.

Copyright © 2015 The Author. Published by Elsevier B.V. All rights reserved.

KEYWORDS: Excessive calcium effects; Low-intensity microwave electromagnetic fields; Oxidative/nitrosative stress

PMID: 26300312 DOI: 10.1016/j.jchemneu.2015.08.001

[Indexed for MEDLINE] **Free full text**

Publication type, MeSH terms, Substance

LinkOut - more resources

Electrosmog and Autoimmune Disease

Immunology Research
February 2017; Vol. 65; No. 1; pp. 129–135

Trevor G. Marshall and Trudy J. Rumann Heil

Humans are constantly exposed to electromagnetic radiation, primarily from human-made sources such as televisions, cellular phones, and Wi-Fi, all of which use microwave frequency bands.

Recently, anti-collision vehicle radars are exposing humans to WiGig (gigahertz) radiations.

These new electromagnetic exposures have increased human exposure more than 1,000-fold. This increased exposure is termed "electrosmog." "Electrosmog" describes the electromagnetic waves surrounding us in our environment.

Human physiology operates in part via electromagnetic fields, and hence it is plausible that electrosmog would influence human biology.

KEY POINTS FROM THIS ARTICLE:

1) "Electromagnetic waves in electrosmog exert sufficient force to affect biological function."

3) Animal studies have shown that environmental electromagnetic waves tend to suppress the immune system with a potency similar to NSAIDs.

4) According to NASA:
"As you sit watching TV, not only are there visible light waves from the TV striking your eyes, but also radio waves, transmitting from a nearby station, and microwaves carrying cellphone calls and text messages, and waves from your neighbor's WiFi, and GPS units in the cars driving by. There is a chaos of waves from all across the spectrum passing through your room right now."

- "Every year, the quantity and nature of radio and microwaves contained in this Electrosmog increases."

5) "Until the 1950s, electrosmog frequencies remained out of the microwave region, but by the 1960s television channels began microwave transmissions."

6) Cellular phone technologies emerged during the 1980s; WiFi during the 1990s. Both extensively use microwave frequency bands.

7) "The recent release of WiGig and anti-collision vehicle radars in the 60 GHz region embody a 1000-fold increase in frequency, and photon energy, over the exposures mankind experienced up until the 1950s."

8) There is evidence that low-level non-ionizing electromagnetic radiation will suppress the immune response in animals.

9) "Proteins are continually in motion, responsive to electromagnetic waves."

10) Lysozyme is an antimicrobial enzyme that is unstable and non-ionizing electromagnetic radiation alters its "proper biological function."

11) The human Vitamin-D receptor (VDR) and its ligand, 1,25-dihydroxyvitamin-D, are associated with many chronic inflammatory and autoimmune diseases. "The VDR pathway exhibits a susceptibility to electrosmog."

- The primary electromagnetic range that affects the VDR is in the microwave frequency range, which is currently populated by cellphone and WiFi communication signals.

- The action of electrosmog on human proteins includes an alteration in the atoms of the VDR.

- The hydrogen bond in the VDR exhibited structural resonances at frequencies typically found in modern electrosmog.

- The VDR molecule changes shape with characteristic frequencies found in today's electrosmog.

- The VDR is even more susceptible when bound with its natural ligand, 1,25 dihydroxyvitamin-D.

12) WiFi routers comprise a significant proportion of indoor electrosmog.

13) The reported bio-effects of electromagnetic radiation from cellular towers include:

- Headaches, concentration difficulties and behavioral problems in children and adolescents.
- Sleep disturbances, headaches and concentration problems in adults.

14) Microwave shielding sleeping caps and clothing are commercially available. "This clothing typically has silver-coated polyester threads interwoven with the supporting fabric so that the garment is capable of partially blocking microwave electrosmog."

Microwave Shielding Sleeping Cap

15) These authors used 64 patients with a variety of immune diagnoses including arthritis, lupus, multiple sclerosis, Sjogrens and celiac. They had them wear protective caps with the silver threads to block the electromagnetic fields and to protect the brain from microwave electrosmog, 4 hours at night and 4 hours during the day.

- 90% reported a *definite* or *strong* change in their symptoms.

- "Follow-up reports have indicated a durable response over many months."

- When the electrosmog in a patient's environment is reduced, it changes the function of the immune system.

16) "Autoimmune patients seem predisposed to electrosmog hypersensitivity at levels currently existing in typical home and work environments, and this factor may be affecting their therapeutic response." **[Key Point]**

17) Biological molecules are constantly moving and interact with electromagnetic fields, including electrosmog.

18) "We cannot ignore the increasing body of evidence showing electromagnetic effects on the immune system."

19) The high rate of electromagnetic hypersensitivity in a healthy population "suggests that effective control of environmental electrosmog immunomodulation may soon become necessary for successful therapy of autoimmune disease." **[Important]**

COMMENTS FROM DAN MURPHY

The improvement of autoimmune disease symptoms with shielding of electrosmog may be as a consequence of its effect on the vitamin D receptor. In this study, such shielding made significant symptom changes in 90% of autoimmune patients. See:

Article Review 42-17: **Vitamin D in Autoimmunity**

PubMed

Format: Abstract

Full text links

nature publishing group PMC FREE Full text

Sci Rep. 2017 Dec 13;7(1):17541. doi: 10.1038/s41598-017-16623-8.

Exposure to Magnetic Field Non-Ionizing Radiation and the Risk of Miscarriage: A Prospective Cohort Study.

Li DK[1], Chen H[2], Ferber JR[2], Odouli R[2], Quesenberry C[2].

Author information

1 Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA, USA. dkl@dor.kaiser.org.

2 Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA, USA.

Abstract

Magnetic field (MF) non-ionizing radiation is widespread and everyone is exposed to some degree. This prospective cohort study of 913 pregnant women examined the association between high MF exposure and miscarriage risk. Cox (proportional hazards) regression was used to examine the association. After controlling for multiple other factors, women who were exposed to higher MF levels had 2.72 times the risk of miscarriage (hazard ratio = 2.72, 95% CI: 1.42-5.19) than those with lower MF exposure. The increased risk of miscarriage associated with high MF was consistently observed regardless of the sources of high MF. The association was much stronger if MF was measured on a typical day of participants' pregnancies. The finding also demonstrated that accurate measurement of MF exposure is vital for examining MF health effects. This study provides fresh evidence, directly from a human population, that MF non-ionizing radiation could have adverse biological impacts on human health.

PMID: 29235463 PMCID: PMC5727515 DOI: 10.1038/s41598-017-16623-8

Free PMC Article

Grant support

PubMed

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov .
Get the latest research from NIH: https://www.nih.gov/coronavirus.

Full text links
ELSEVIER
OPEN ACCESS

Format: Abstract

Environ Res. 2018 Jul;164:405-416. doi: 10.1016/j.envres.2018.01.035. Epub 2018 Mar 21.

Wi-Fi is an important threat to human health.

Pall ML[1].

Author information

1 Washington State University, 638 NE 41st Avenue, Portland, OR 97232-3312, USA. Electronic address: martin_pall@wsu.edu.

Abstract

Repeated Wi-Fi studies show that Wi-Fi causes oxidative stress, sperm/testicular damage, neuropsychiatric effects including EEG changes, apoptosis, cellular DNA damage, endocrine changes, and calcium overload. Each of these effects are also caused by exposures to other microwave frequency EMFs, with each such effect being documented in from 10 to 16 reviews. Therefore, each of these seven EMF effects are established effects of Wi-Fi and of other microwave frequency EMFs. Each of these seven is also produced by downstream effects of the main action of such EMFs, voltage-gated calcium channel (VGCC) activation. While VGCC activation via EMF interaction with the VGCC voltage sensor seems to be the predominant mechanism of action of EMFs, other mechanisms appear to have minor roles. Minor roles include activation of other voltage-gated ion channels, calcium cyclotron resonance and the geomagnetic magnetoreception mechanism. Five properties of non-thermal EMF effects are discussed. These are that pulsed EMFs are, in most cases, more active than are non-pulsed EMFs; artificial EMFs are polarized and such polarized EMFs are much more active than non-polarized EMFs; dose-response curves are non-linear and non-monotone; EMF effects are often cumulative; and EMFs may impact young people more than adults. These general findings and data presented earlier on Wi-Fi effects were used to assess the Foster and Moulder (F&M) review of Wi-Fi. The F&M study claimed that there

PubMed

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https:/
Get the latest research from NIH: https://www.nih.

Full text links
WILEY Full Text Article
PMC FREE Full text

Format: Abstract

Environ Mol Mutagen. 2020 Feb;61(2):276-290. doi: 10.1002/em.22343. Epub 2019 Nov 13.

Evaluation of the genotoxicity of cell phone radiofrequency radiation in male and female rats and mice following subchronic exposure.

Smith-Roe SL[1], Wyde ME[1], Stout MD[1], Winters JW[2], Hobbs CA[2], Shepard KG[2], Green AS[2], Kissling GE[3], Shockley KR[3], Tice RR[1], Bucher JR[1], Witt KL[1].

Author information

1 Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
2 Integrated Laboratory Systems, Inc., Research Triangle Park, North Carolina.
3 Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Abstract

The National Toxicology Program tested two common radiofrequency radiation (RFR) modulations emitted by **cellular** telephones in a 2-year rodent cancer bioassay that included interim assessments of additional animals for genotoxicity endpoints. Male and female Hsd:Sprague Dawley SD rats and B6C3F1/N mice were exposed from Gestation day 5 or Postnatal day 35, respectively, to code division multiple access (CDMA) or global system for mobile modulations over 18 hr/day, at 10-min intervals, in reverberation chambers at specific absorption rates of 1.5, 3, or 6 W/kg (rats, 900 MHz) or 2.5, 5, or 10 W/kg (mice, 1,900 MHz). After 19 (rats) or 14 (mice) weeks of exposure, animals were examined for evidence of RFR-associated genotoxicity using two different measures. Using the alkaline (pH > 13) comet assay, DNA damage was assessed in **cells** from three brain regions, liver **cells**, and peripheral blood leukocytes; using the micronucleus assay, chromosomal damage was

assessed in immature and mature peripheral blood erythrocytes. Results of the comet assay showed significant increases in DNA damage in the frontal cortex of male mice (both modulations), leukocytes of female mice (CDMA only), and hippocampus of male rats (CDMA only). Increases in DNA damage judged to be equivocal were observed in several other tissues of rats and mice. No significant increases in micronucleated red blood **cells** were observed in rats or mice. In conclusion, these results suggest that exposure to RFR is associated with an increase in DNA damage. Environ. Mol. Mutagen. 61:276-290, 2020.

© 2019 Wiley Periodicals, Inc.

KEYWORDS: DNA damage; Sprague Dawley; brain; comet assay; glioma; micronucleus assay

PMID: 31633839 PMCID: PMC7027901 DOI: 10.1002/em.22343

Free PMC Article

Images from this publication. See all images (3) Free text

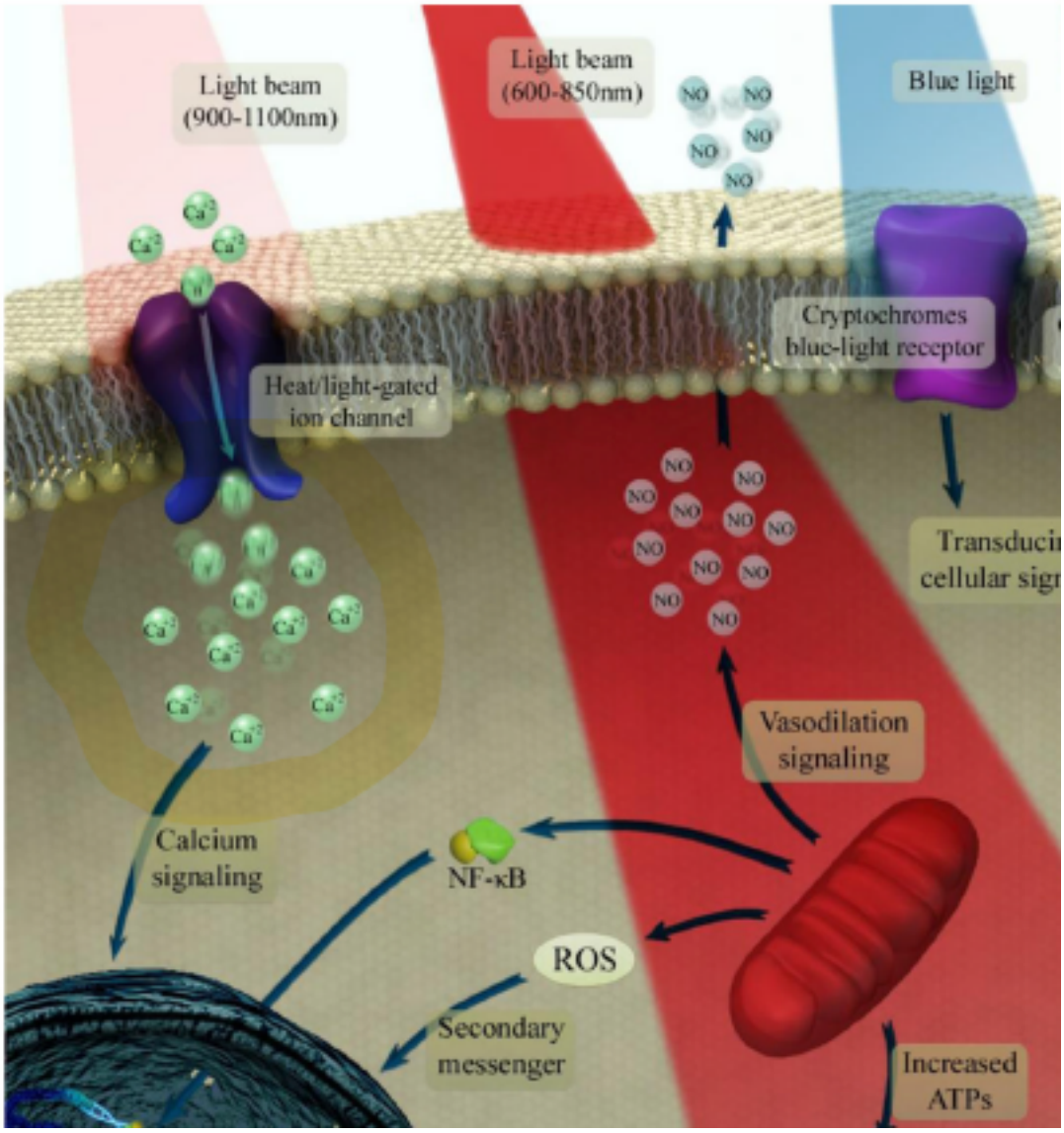
Grant support

LinkOut - more resources

HHS Public Access

Published in final edited form as:
Mol Neurobiol. 2018 August ; 55(8): 6601–6636.

Brain Photobiomodulation Therapy: A Narrative Review



areas may never see 5G. ... we still know yet.

CELL-TOWER SAFETY

The Dangers of 5G Networks

Devra Davis, PhD, MPH
Environmental Health Trust

The new 5G cell-phone network promises to be the most powerful and fastest of all time. But with that extra speed comes extra risks.

Because of the shorter length of 5G's high-frequency waves and their inability to go through walls and trees, this new network will require building about 800,000 new wireless antenna structures, many of which will be located close to houses and schools in residential neighborhoods. To put that into perspective, there were about 300,000 antennas in 2015 and half as many in 2002.

The new antennas will be able to emit 3G, 4G and 5G microwave radiation at the same time. The World Health Organization classifies this kind of radiation as a possible carcinogen, and there's evidence that it can lead to some types of brain tumors both in animal studies by the US government and in humans that have used phones regularly for a decade or longer. Recently, Sprint stopped operating a cell tower in a California school yard after four students and three teachers there developed rare cancers in the 10 years since the tower was erected. With 5G, these risks may only worsen.

The US National Toxicology Program, considered the industry gold standard for this kind of testing, reported clear evidence of rare cancers and genetic damage in animals after prolonged exposure to 2G and 3G radiation. 5G radiation is very similar, but it operates at a higher frequency and shorter range, making it potentially more dangerous.

Self-defense: The good news is that there already is a way to eliminate the damage. Hardwired fiber-optic cable can be run from a 5G tower to a home—as is regularly done in South Korea—and that means the tower can be far away from your home. Share your concerns with your local leaders, who should consider hardwiring at least the last mile with fiber-optic cable, as they did in St. Louis and Chattanooga.

Bottom Line Personal interviewed Devra Davis, PhD, MPH, president of Environmental Health Trust, a nonprofit scientific and policy think tank focusing on cell-phone radiation, Teton Village, Wyoming. She is a former senior adviser to the assistant secretary for health in the Department of Health and Human Services and a former member of the National Toxicology Program's Board of Scientific Counselors. She is author of *Disconnect: The Truth About Cell Phone Radiation.*

Photo of cell towers: Gettyimages/Mlenny

7/15/2019

THE CONTAGION MYTH

2020

Why Viruses (including "Coronavirus") Are Not the Cause of Disease

THOMAS S. COWAN, MD, and
SALLY FALLON MORELL

The INVISIBLE RAINBOW

A History of Electricity and Life

Arthur Firstenberg

2020

DR. JOSEPH MERCOLA

NEW YORK TIMES BEST-SELLING AUTHOR

EMF*D

2020

5G, Wi-Fi & Cell Phones: Hidden Harms and How to Protect Yourself

NEW YORK TIMES BESTSELLING AUTHOR OF *SLANTED*

SHARYL ATTKISSON

FOLLOW THE $CIENCE

2024

HOW BIG PHARMA MISLEADS, OBSCURES, AND PREVAILS

Photomedicine and Laser Surgery
Volume 23, Number 3, 2005
© Mary Ann Liebert, Inc.
Pp. 251–259

Biological Effects of Helium-Neon Laser Irradiation on Normal and Wounded Human Skin Fibroblasts

D. HAWKINS and H. ABRAHAMSE

ABSTRACT

Objective: **This study aimed to investigate a number of structural, cellular, and molecular responses to helium-neon (632.8 nm) laser irradiation following a single dose of 0.5, 2.5, 5, or 10 J/cm^2 on normal and wounded human skin fibroblasts.** ***Background Data:*** **Low-level laser therapy (LLLT) is a form of phototherapy, involving the application of low-power monochromatic and coherent light to injuries and lesions to stimulate healing.[1] This therapy has been successfully used for pain attenuation and to induce wound healing in nonhealing defects.[2]** ***Methods:*** **Changes in normal and wounded fibroblast cell morphology were evaluated by light microscopy. Cellular parameters evaluated cell proliferation, cell viability, and cytotoxicity while molecular parameters assessed the extent of DNA damage.** ***Results:*** **The results clearly demonstrate that LLLT has an effect on normal and wounded[3] human skin fibroblasts. The parameters showed that doses of 0.5, 2.5, 5, and 10 J/cm^2 were sufficient to produce measurable changes in fibroblast cells.** ***Conclusion:*** **A dose of 10 J/cm^2 appeared to produce a significant amount of cellular and molecular damage, which could be an important consideration for other therapies, such as photodynamic therapy.**

INTRODUCTION

ENERGY DEPOSITED IN A TISSUE is the product of the power of the laser and the length of time that the beam is in contact with the tissue. The duration of exposure of the energy is an important variable in controlling desired and unwanted effects on tissue.[4] When a laser beam is irradiated onto tissue, a local or topical primary response occurs at the cellular level; this is followed to some degree over a greater area by a systemic secondary response. Low-level laser therapy (LLLT) reactions are nonthermal since there is no immediate increase in the temperature of laser-irradiated tissue.[2] Experiments following LLLT have shown that immediate increase of heat in the target tissue is negligible (±1°C). As the law of Arndt-Schultz states, in a biological system, weak stimuli will elicit strong reactions from the system, medium stimuli will cause moderate reactions, moderately strong stimuli will slightly inhibit the system, and very strong stimuli will completely retard it.[2]

LLLT irradiation includes wavelengths from 500–1100 nm (visible to near infrared region of the spectrum). This type of radiation is a continuous wave of a constant beam of relatively low power or irradiance (0.04–50 J/cm^2), and the laser is directed at the target tissue using powers measured in milliwatts (mW).[2] A typical example of a laser used in LLLT is the helium-neon (He-Ne) laser, which emits red light at a wavelength of 632.8 nm.[5] Red light does not penetrate very effectively below the skin surface, but it is an excellent source of stimulation on a range of growth factors and is effective for wound healing or superficial condition.s[5]

He-Ne laser light can penetrate as deep as 0.5 mm into freshly excised human skin and delivers the highest relative percentage of incident energy to a certain volume of tissue. A penetration depth of even a few microns can be regarded as sufficient, because most of the relevant target cells for the induction of wound healing by LLLT—namely, fibroblasts, keratinocytes, macrophages, and endothelial cells—are located within the epidermis and upper dermis.[4]

The biostimulating effect of LLLT results in an increase in microcirculation, higher rates of ATP, RNA, and DNA synthesis, and thus improved tissue oxygenation, nutrition, and regeneration.[6] The increased activity is generally followed by a period of decreased activity, usually after several irradiations.[2] Photons enter the tissue and are readily absorbed in the mitochondria and at the cell membrane. The photonic energy is converted to chemical energy within the cell, in the form of ATP, which leads to normalization of cell function, pain relief,

Faculty of Health Sciences, Technikon Witwatersrand, Doornfontein, Johannesburg, South Africa.

levels (viability and cytotoxicity percentages and DNA damage). The Comet assay and percentage of cytotoxicity provided evidence of cellular and molecular damage and can be used together to assess the damage on the cells. The parameters could be used to measure the cellular and molecular effects of laser irradiation in other therapies such as photodynamic therapy.

Slight changes in cell morphology and cell proliferation are difficult to detect; however, at higher doses (10 J/cm^2), indicators such as debris and cell fragments showed cell lysis and cellular damage. Light microscopy was used to demonstrate a clear wound margin and confirmed that a central scratch created a successful wound environment. A clear wound margin, edge fibroblasts, and migration of fibroblasts were morphological differences that were used to distinguish wounded from normal cells. The migration rate of fibroblasts across the central scratch is a good indicator of cell proliferation. LLLT appears to stimulate wounded cells to normalize cell function, maintain viability, and increase cell proliferation so that fibroblasts migrate across the central scratch in an attempt to close the wound.

An increase in the optical density can be used to measure cell proliferation; however the optical density can also be increased if there is cell lysis, fragmentation, or cellular debris. The values obtained for optical density should be used with the LDH membrane integrity assay and percentages of cytotoxicity to assess cellular damage, and with the neutral red assay to assess cell proliferation. The Comet assay can be used with viability percentages to determine the degree of damage in viable cells.

Normal fibroblasts can be irradiated at room temperature (22°C) since normal fibroblasts incubated (22°C) for 2.5 h had similar values to the control (0 min at 22°C), indicating a minimal effect on cell proliferation and cell viability. Fibroblasts simulating total cellular damage showed a significant amount of damage at both cellular and molecular levels when compared to the normal unirradiated control. This condition was established as a positive control to confirm that the experimental tests were sensitive enough to detect structural, cellular, and molecular changes.

From the results, 2.5 J/cm^2 appeared to have a stimulatory effect by increasing cell proliferation while maintaining cell viability of normal and wounded fibroblasts without adversely increasing the amount of cellular and DNA damage. The results also revealed differences in cell proliferation, cell viability, and damage between the normal and wounded cells, with more damage for wounded cells at cellular and molecular levels. These differences can be used to distinguish and characterize normal and wounded cell responses to LLLT.

CONCLUSION

From this study distinct cellular and molecular effects of low-level laser therapy of normal and wounded skin fibroblasts could be detected. Some of the parameters complement each other and provide information about the cellular processes (proliferation and metabolic activity) of the cells following irradiation. Cell responses for irradiated normal and wounded fibroblasts at different doses could be identified and compared. This study suggests that LLLT can alter the cellular processes of normal and wounded fibroblasts following irradiation in a dose-dependent manner.

REFERENCES

1. Yuji, Y., and Kunihiko, Y. (2001). Cutaneous wound healing: an update. J Dermatol. 28, 521–534.
2. Ohshiro, T., and Calderhead, R.G. (1988). Low level laser therapy: a Practical Introduction. New York: Wiley and Sons, pp. 17, 28–30, 33, 34.
3. Rigau, J., Sun, C., Trelles, M.A., et al. (1995). Effects of the 633nm laser on the behaviour and morphology of primary fibroblasts in culture, *in:* Proceedings: effects of low power light on biological systems. T. Karu and A. Young (eds.). Barcelona: Progress in Biomedical Optics, pp. 38–42.
4. Gitomer S.J., and Jones R.D. (1990). Laser produced plasmas in medicine. SPIE 1202.
5. Schindl, A., Schindl, M., Pernerstorfer-Schon, H., et al. (1999). Diabetic neuropathic foot ulcer: successful treatment by low intensity laser therapy. Dermatology. 198, 314–317.
6. Takac, S., and Stojanovic, S. (1998). Diagnostic and biostimulating lasers. Med. Pregl. 51, 245–249.
7. Zeischegg, D.C. (2003). Low level laser therapy (LLLT) [On-line]. Ask Dr. Z. Available: www.drz.org/asp/about/index.html.
8. Pinheiro, A.L.B., Nascimento, S.C., Vieira, A.L., et al. (2002). Effects of Low level laser therapy on malignant cells: *in vitro* study. J. Clin. Laser Med. Surg. 20, 23–26.
9. Smith, K. (1991). Light and life: the photobiological basis of the therapeutic use of radiation from lasers, in: Progress in laser therapy: Selected papers from the October 1990 ILTA Congress. New York: Wiley and Sons.
10. Walsh, L.J. (1997). The current status of low level laser therapy in dentistry. Part 1. Soft tissue applications. Aus. Dent. J. 42, 247–254.
11. Walsh, L.J. (1997). The current status of low level laser therapy in dentistry. Part 2. Hard tissue applications. Aus. Dent. J. 42, 302–306.
12. Loevschall, H., and Arenholt-Bindslev, D. (1994). Effect of low level diode laser irradiation on human oral mucosa fibroblasts *in vitro.* Lasers Surg. Med. 14, 347–354.
13. Bolten, P., Young, S., and Dyson, M. (1995). The direct effect of 860nm light on cell proliferation and on succinic dehydrogenase activity of human fibroblasts *in vitro.* Laser Ther. 7, 55–60.
14. Gasparyan, L.V. (2000). Biochemical and biophysical effects of low level laser irradiation. MAL Medical Acupuncture and Lasers Congress, 28–30.9.2000. Helsinki.
15. Coombe, A.R., Ho, C.T., Darendeliler, M.A., et al. (2001). The effects of low level laser irradiation on osteoblastic cells. Clin. Orthod. Res. 4, 3–14.
16. Schindl, A., Schindl, M., Pernerstorfer-Schon, H., et al. (2000). Low intensity laser therapy: a review. J. Invest. Med. 48, 312–326.
17. Ausubel, R., Brent, R., Kingston, R.E., et al. (1994). *Short protocols in molecular cloning*, 4th ed. New York: Wiley and Sons, pp. A3–39.
18. Mossman, T.J. (1983). Principle of the MTT assay. J. Immunol. Meth. 63, 55–63.
19. Pinheiro, A.L.B., Nascimento, S.C., Vieira, A.L., et al. (2002). Effects of low level laser therapy on malignant cells: *in vitro* study. J. Clin. Laser Med. Surg. 20, 23–26.
20. Abe T., Abe Y., Aida Y., et al. (2001). Extracellular matrix regulates induction of alkaline phosphatase expression by ascorbic acid in human fibroblasts. J. Cell Physiol. 189, 144–151.
21. Sambrook, J., Fritsch, E.F., and Maniatis, T. (1989). Molecular cloning: A laboratory manual, 2nd ed. Cold Spring Harbour, NY: Cold Spring Laboratory.

Funct Neurol Rehabil Ergon 2016;6(2):97-104

ISSN: 2156-941X
© 2016 Nova Science Publishers, Inc.

Low-Level Laser Therapy for the Treatment of Chronic Neck and Shoulder Pain

#6

Gregory C. Roche[1], Daniel J. Murphy[2], Trevor S. Berry[3], and Steven Shanks[4,*]

[1]Bloomfield Laser and Cosmetic Surgery Center, Bloomfield Hills, MI, USA
[2]Auburn, CA, USA
[3]Arizona Chiropractic Neurology Center, Chandler, AZ, USA
[4]Erchonia Corporation, McKinney, TX, USA

[*] Correspondence: Steven Shanks, Erchonia Corporation, 2021 Commerce Drive, McKinney, TX 75069.
Email: SShanks@erchonia.com

Abstract

Background: Chronic neck and shoulder pain affect a large proportion of the general population. A previous randomized, double-blind study demonstrated the beneficial effects of low-level laser therapy (LLLT) for alleviating minor neck and shoulder pain. The objective of this randomized, double-blind, sham-controlled trial was to further evaluate the efficacy of LLLT for treating chronic shoulder and neck pain and improving upper body range of motion (ROM). *Methods:* Subjects were recruited from among adult patients seeking treatment of pain due osteoarthritis or degenerative joint disorders, chronic muscle spasms, or cervical or thoracic spine sprains or strains. Subjects were randomized to receive sham or active LLLT treatment with a single-head, low-level diode laser emitting a divergent 635-nm (red) laser light with an energy output of 1 mW (Erchonia® PL2000, Erchonia Corporation, McKinney, TX). Sham treatment used a similar device emitting ordinary red light. A single bilateral treatment was applied for 1 to twelve min. to the neck and shoulders. The primary outcome measure was the change in pain perception using a visual analog scale (VAS) scores immediately after treatment. The criterion for individual subject success was a 30% improvement. Overall study success was defined as ≥30% difference between treatment groups by comparing the proportion of individual successes in each group. *Results:* Among the LLLT-treated subjects (n = 43), 28 (65.1%) met the individual subject success criteria while among the sham-treated subjects (n = 43), six (11.6%) met the individual subject success criteria ($p < 0.0001$). The difference exceeded the pre-established criteria for overall study success. Mean VAS scores decreased from 60.2 to 31.2 ($p < 0.0001$) for LLLT-treated subjects *vs.* a change from 60.0 to 55.1 for sham-treated subjects (p = NS). The mean between-group difference in post-treatment VAS scores was 24.1 points ($p < 0.005$). There was a significant improvement in ROM among LLLT-treated subjects but not sham-treated subjects. There

The primary efficacy outcome measure was the change in subject VAS scores immediately after treatment.

The criterion for individual subject success was a 30% improvement.

Overall study success was defined as ≥30% difference between treatment groups by comparing the proportion of individual successes in each group.

This overall study success criterion was determined to be clinically meaningful by the U.S. Food and Drug Administration.

Subjects were randomized to receive active or sham LLLT treatment.

One investigator was responsible for administering both treatments. This investigator was the only individual present in the room during the treatment phase and did not participate in other pre- or post-treatment activities.

Another investigator was responsible for conducting pre- and post-procedure evaluations, determining the pain diagnosis and enrollment eligibility.

Patients randomized to the LLLT group were treated with a single-head, low-level diode laser emitting a divergent 635-nm (red) laser light with an energy output of 1 mW

The sham group was treated with a similar device emitting ordinary red light. **[LED]**

Among the 43 LLLT-treated subjects, 28 (65.1%) met the individual subject success criteria vs. six (11.6%) sham-treated subjects.

Among subjects in the LLLT group, 89.5% reported being Very Satisfied or Somewhat Satisfied compared to 34.3% of subjects in the sham group.

Conversely, 23.7% of sham-treated subjects were Not Very Satisfied or Not at All Satisfied compared to 2.6% of LLLT-treated subjects.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Support Care Cancer. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Support Care Cancer. 2016 June ; 24(6): 2781–2792. doi:10.1007/s00520-016-3152-z.

Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations

Judith A. E. M. Zecha[1], **Judith E. Raber-Durlacher**[1,2], **Raj G. Nair**[4], **Joel B. Epstein**[5,6], **Stephen T. Sonis**[7], **Sharon Elad**[8], **Michael R. Hamblin**[9,10,11], **Andrei Barasch**[12], **Cesar A. Migliorati**[13], **Dan M. J. Milstein**[1], **Marie-Thérèse Genot**[14], **Liset Lansaat**[15], **Ron van der Brink**[16], **Josep Arnabat-Dominguez**[17], **Lisette van der Molen**[15], **Irene Jacobi**[15], **Judi van Diessen**[18], **Jan de Lange**[1], **Ludi E. Smeele**[1,15], **Mark M. Schubert**[19], and **René-Jean Bensadoun**[20]

Judith A. E. M. Zecha: j.zecha@amc.uva.nl; Judith E. Raber-Durlacher: j.e.raberdurlacher@amc.uva.nl; Raj G. Nair: r.nair@griffith.edu.au; Joel B. Epstein: joel.epstein@cshs.org; Stephen T. Sonis: ssonis@partners.org; Sharon Elad: SElad@URMC.Rochester.edu; Michael R. Hamblin: hamblin@helix.mgh.harvard.edu; Andrei Barasch: barasaff@cs.com; Cesar A. Migliorati: migliorati@uthsc.edu; Dan M. J. Milstein: D.M.Milstein@amc.uva.nl; Marie-Thérèse Genot: mtgenot@skynet.be; Liset Lansaat: l.lansaat@nki.nl; Ron van der Brink: RVanderbrink@coh.org; Josep Arnabat-Dominguez: joseparnabat@ub.edu; Lisette van der Molen: l.vd.molen@nki.nl; Irene Jacobi: i.jacobi@nki.nl; Judi van Diessen: j.v.diessen@nki.nl; Jan de Lange: j.delange@amc.uva.nl; Ludi E. Smeele: l.smeele@nki.nl; Mark M. Schubert: mschuber@seattlecca.org

[1]Department of Oral and Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands [2]Department of Medical Dental Interaction and Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands [3]Oral Medicine Oral Pathology and Human Diseases, Menzies Health Institute Queensland, Gold Coast, QLD, Australia [4]Department of Haematology and Oncology/Cancer Services, Gold Coast University Hospital, Queensland Health, Gold Coast, QLD, Australia [5]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA [6]Division of Otolaryngology and Head and Neck Surgery, City of Hope, Duarte, CA 91010, USA [7]Division of Oral Medicine, Brigham and Women's Hospital and the Dana-Farber Cancer Institute and Biomodels LLC, Boston, MA 02115, USA [8]Division of Oral Medicine, Eastman Institute for Oral Health, and Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY 14620, USA [9]Wellman Center for Photomedicine, Massachusetts General

Correspondence to: René-Jean Bensadoun.

Disclaimer

This article is based on a narrative review of existing data and the clinical observations of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry. This article is informational in nature. As with all clinical materials, this paper should be used with the clear understanding that continued research and practice could result in new insights and recommendations. The review reflects the collective opinion and as such does not necessarily represent the opinion of any individual author. In no event shall the authors be liable for any decision made or action taken in reliance on the proposed protocols.

Conflict of interest Judith E. Raber-Durlacher, Raj G. Nair, Joel B. Epstein, Ron van der Brink, Josep Arnabat Dominguez, and Rene-Jean Bensadoun have received travel expenses and hotel accommodation from THOR Photomedicine Ltd. UK. Raj Nair has received an honorarium from THOR, UK. Michael R Hamblin was supported by US NIH grant R01AI050875. All the other authors declare that they have no conflict of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

Low level laser therapy; Low level light therapy; Photobiomodulation; Mucositis; Orofacial complications; Chemotherapy; Radiation therapy; Head and neck cancer; Safety; LLLT and PBM

Introduction

Nearly all patients with advanced head and neck cancer (HNC) suffer complications from treatment with radiation therapy (RT) or chemoradiotherapy (CRT) [1]. CRT is currently the standard of care with or without surgery in advanced HNC. An increased frequency and severity of side effects is seen, particularly when chemotherapy (CT) is combined with accelerated or hyperfractionated RT regimens. It is now recognized that organ preservation in HNC treatment is not synonymous with function preservation, and effects on quality of life (QoL) must be considered in cancer treatment planning and extending survival [2, 3].

RT to the head and neck, with or without CT, damages adjacent tissues within the radiation field despite continuing efforts to minimize these effects [1]. Furthermore, targeted therapies administered as single agents, and combined with RT or CRT, may generate additional symptoms [4–6]. Acute complications include oral mucositis (OM), pain, dysphagia, infections, salivary changes, dysgeusia, and dermatitis. Common chronic complications include hyposalivation and xerostomia, mucosal infections, mucosal atrophy, neuropathies including mucosal pain, dysgeusia, tooth demineralization and rampant caries, progression of periodontitis, soft tissue and/or bone necrosis, mucocutaneous and muscular fibrosis, dysphagia, trismus, lymphedema, dermatitis, and voice and speech alterations [7]. These complications are associated with morbidity and mortality, increased use of health care resources and costs, and may compromise patient adherence to cancer therapy protocols resulting in suboptimal outcomes.

Among the few supportive care measures available, low level laser or light therapy (LLLT) has shown significant promise. LLLT refers to light therapy that may stimulate tissue regeneration, reduce inflammation, and control pain. These treatments were originally referred to as “low level laser” because the light is of low intensity compared with other forms of medical laser treatment, which are used for ablation, cutting, and coagulation. At the 2014 joint North American Association for Laser Therapy (NAALT) and World Association for Laser Therapy (WALT) conference, photobiomodulation (PBM) was accepted as the preferred name with the following definition: “The therapeutic use of light [e.g. visible, near infrared (NIR), infrared (IR)] absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic, biological reactions through photochemical or photophysical events, leading to physiological changes” [8].

The potential utility of PBM in the management of side-effects of chemoradiation therapy in head and neck cancer

Although the biological mechanisms underlying the therapeutic effects of PBM have not been fully elucidated, studies suggest that PBM enhances wound healing [9], significantly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

reduces inflammation, and prevents fibrosis [10–15]. Moreover, PBM reduces pain and improves function [16–19]. These photobiological reactions have been shown to occur in various tissues.

Systematic reviews have suggested efficacy of PBM for OM management in hematopoietic stem cell transplant (HSCT) recipients and in HNC patients [20–25]. Whereas in most studies, PBM is applied intra-orally on the oral mucosal tissues, studies indicate that it may also be administered extra-orally, with a resultant effect on structures at risk for OM transcutaneously, thereby enhancing the ease of delivery and possibly the efficacy of treatment [23, 26].

In addition, new generation PBM devices consisting of a cluster of laser or light-emitting diode (LED) beams, instead of a single laser point, provide exposure of larger fields. Monochromatic high-quality LED beams have the same properties as diode lasers with the same wavelength, but their light beam is less coherent. LED specifics need to be carefully matched to PBM using lasers when considering LED arrays.

When used with appropriate parameters, the light is able to penetrate into tissues sufficiently to activate cellular processes [27]. This finding suggests that extra-oral administration of PBM (with or without concurrent use of intra-orally administered PBM) enables the light to reach other anatomical structures of the head and neck at risk for RT- and CRT-induced complications. This may broaden the range of indications for PBM for the prevention and treatment of cancer treatment-induced complications.

Goals of this work

A task force consisting of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry was formed. The mission of this group is to aid in the design of PBM study protocols, identify validated outcome measures, and test the efficacy and safety of PBM for the management of complications related to cancer therapy.

In this paper, we review and discuss PBM mechanisms of action, dosimetry, and safety considerations. In a subsequent paper (part 2), we (i) identify selected oral, oropharyngeal, facial, and neck complications of treatment for HNC, in which PBM may have potential for prophylaxis and/or treatment; (ii) propose PBM parameters for prophylaxis and therapy to mitigate these complications based on current evidence and knowledge; and (iii) discuss directions of future research related to the use of PBM in HNC.

PBM mechanisms of action and therapeutic effects

The conclusion that PBM effectively modulates biological function is supported by a plethora of clinical and laboratory studies [17, 28]. Despite variations in instrumentation and dosing parameters, since its introduction in 1967, PBM has been shown to enhance wound repair and tissue regeneration by influencing different phases of injury resolution including the following: (i) the inflammatory phase, in which immune cells migrate to the site of tissue injury, ii) the proliferative phase, which includes stimulation of fibroblasts and macrophages

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

as well as other repair components, and iii) the remodeling phase, consisting of collagen deposition and rebuilding of the extracellular matrix at the wound site [29].

Although the complex biological mechanisms underlying the therapeutic effects of PBM have not been completely elucidated and may vary among different cell types and tissue states (healthy versus stressed or hypoxic), laboratory and clinical studies suggest that PBM significantly reduces inflammation and prevents fibrosis [10–15]. It has become increasingly clear that PBM's biological effects are closely dose-related. In fact, the historical lack of dosing consistency has been a confounder in the comprehensive interpretation of PBM activity. Nonetheless, confirmatory studies have contributed to a fundamental understanding of PBM biology.

Current data suggest that PBM acts predominantly on cytochrome c oxidase (CcO) in the mitochondrial respiratory chain by facilitating electron transport resulting in an increased transmembrane proton gradient that drives adenosine triphosphate (ATP) production [30]. ATP is the universal energy source in living cells essential for all biologic reactions, and even a small increase in ATP levels can enhance bioavailability to power the functions of cellular metabolism [31]. In addition, the absorption of red or NIR light may cause a short, transient burst of reactive oxygen species (ROS) that is followed by an adaptive reduction in oxidative stress. This action, impairment of ROS production, has been shown to favorably mitigate radiation-induced injury and mimics the activity of molecular agents that attenuate tissue damage (examples include amifostine, N-acetyl cysteine, and superoxide dismutase).

Low concentrations of ROS impact many cellular processes, including activation of key transcription factors such as nuclear factor kappa B (NF-κB). This results in the expression of stimulatory and protective genes [32], which generate growth factors belonging to the fibroblast growth factor family, pro-inflammatory cytokines, and chemokines that are involved in tissue repair.

In hypoxic or otherwise stressed cells, mitochondria produce nitric oxide (mtNO), which binds to CcO and displaces oxygen [33]. This binding results in inhibition of cellular respiration, decreased ATP production, and increased oxidative stress (a state that develops when the levels of ROS exceed the defense mechanisms), leading to the activation of intracellular signaling pathways, including several transcription factors [34]. These include redox factor-1 (Ref-1), activator protein-1 (AP-1), NF-κB, p53, activating transcription factor/cAMP-response element–binding protein (ATF/CREB), hypoxia-inducible factor (HIF)-1, and HIF-like factor [35]. These transcription factors induce downstream production of both inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6, cyclooxygenase (COX)-2, and prostaglandin E2 (PGE-2) [34, 36, 37] and anti-inflammatory mediators [transforming growth factor (TGF)-beta, IL-10]. There is evidence suggesting that when PBM is administered with appropriate parameters to stressed cells, NO is dissociated from its competitive binding to CcO, ATP production is increased, and the balance between prooxidant and antioxidant mediators is restored, resulting in a reduction of oxidative stress [38]. For example, PBM has been shown to attenuate the production of ROS by human neutrophils [39]. Silveira et al. [40] reported that PBM reduced ROS in an animal model of traumatic tissue injury, whereas a study in a model of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of 830 nm [85]. PBM (808 nm; 5.85 and 7.8 J/cm^2) had an inhibitory effect on the proliferation of a human hepatoma cell line [86], and Sroka et al. [87] reported that glioblastoma/astrocytoma cells exhibited a slightly decreased mitotic rate after PBM at 805 nm and 5–20 J/cm^2. Similarly, 808-nm laser irradiation with an energy density of more than 5 J/cm^2 inhibited cell proliferation of glioblastoma cells in vitro [88]. Moreover, Al Watban et al. [89] observed growth inhibition of cancer cell lines at relatively high cumulative PBM doses. This prompted Crous and Abrahamse [90] to hypothesize that PBM may have a therapeutic potential in lung cancer.

Protective effects of PBM against cytotoxic therapy

There are no data to suggest that PBM may protect cancer cells against the cytotoxic effects of RT. On the contrary, Schartinger et al. [91] observed a pro-apoptotic effect of PBM in head and neck SCC cells, whereas no anti-apoptotic effects occurred that might promote tumor cell resistance to cancer therapy. Increased apoptosis of human osteosarcoma cells was also induced by the administration of NIR (810 nm, continuous wave, 20 mW/cm^2, 1.5 J/cm^2) prior to NPe6-mediated photodynamic therapy as a result of increased cellular ATP and a higher uptake of the photosensitizer [92]. Recently, it was reported that PBM administered to normal human lymphoblasts and leukemia cells prior to RT, resulted in a differential response of normal versus malignant cells suggesting that PBM does not confer protection and may even sensitize cancer cells to RT-induced killing [93]. Nevertheless, in vivo and clinical studies are warranted before firm conclusions can be drawn.

Carcinogenic effects of PBM on normal cells

It seems unlikely that PBM has carcinogenic effects on normal cells. The non-ionizing wavelengths of the red and NIR spectrum used in PBM are far longer than the safety limit of 320 nm for DNA damage [94]. No signs of malignant transformation in non-malignant epithelial cells and fibroblasts were observed following exposure to PBM with a wavelength of 660 nm, 350 mW for 15 min during 3 consecutive days [91]. In addition, no malignant transformation of normal breast epithelial cells was detected in an in vitro study comparing the effects of different doses and wavelengths of PBM during multiple exposures [84].

Data derived from in vivo and clinical studies

PBM (660 nm, 30 mW, 424 mW/cm^2, 56.4 J/cm^2, 133 s, 4 J), applied to chemically induced SCC in hamster cheek pouch tissue, increased tumor growth [95]. PBM at a dose of 150 J/cm^2 appeared safe, with only minor effects on B16F10 melanoma cell proliferation in vitro, and had no significant effect on tumor growth in vivo. Only a high power density (2.5 W/cm^2) combined with a very high dose of 1050 J/cm^2 could induce melanoma tumor growth in vivo [96]. In a mouse model to study PBM effects on UV-induced skin tumors, the experimental mice received full body 670 nm PBM delivered twice a day at 5 J/cm^2 for 37 days, whereas controls received sham PBM [97]. No enhanced tumor growth was observed, whereas there was a small but significant reduction in tumor area in the PBM group, potentially related to a local photodynamic effect or PBM-induced antitumor immune activity.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Schaffer et al. [98] observed that PBM increased the locoregional blood flow that contributed to better local oxygenation and hypothesized that PBM applied shortly before cancer treatment might enhance the effect of ionizing RT and local delivery of chemotherapy. A recent randomized controlled trial in which PBM was administered for prevention of OM during CRT in HNC patients (diagnosed with SCC of the nasopharynx, oropharynx, or hypopharynx) reported that at a median follow-up of 18 months (range 10–48 months), patients treated with PBM had better locoregional disease control and improved progression-free or overall survival [99].

Current evidence suggests that PBM in the red or NIR spectrum, with an energy density of 1–6 J/cm^2 is safe and effective. However, as with drug-based therapies for comparable indications, disciplined follow-up studies in which subject cohorts large enough to represent the HNC tumor population with respect to gender, tobacco and alcohol use, human papilloma virus (HPV) status, primary stage, tumor therapy, and variations in PBM dose and fields are needed to definitely conclude that PBM fails to negatively impact survival and progression-free survival.

Discussion and concluding remarks

PBM mechanisms have not been fully elucidated, but based on its recognized therapeutic effects, PBM may have utility in a broad range of oral, oropharyngeal, facial, exocrine glands, and neck complications of HNC treatment.

Titrating adequate doses and defining the other required PBM parameters according to evidence gathered in a systematic way for each indication is a prerequisite for a successful use of this technique. Without standardization in beam measurement, dose calculation, and the correct reporting of these parameters, studies will not be reproducible, and outcomes will not be consistent.

There are no known significant adverse side effects for PBM (administered with parameters discussed in more detail in part 2) in HNC patients. However, the potential effect on residual and new dysplastic and malignant cells has not been definitively resolved. Virtually, all studies have focused on cell-based assays rather than conventional xenograft or orthotopic animal models. And the results of in vitro investigations have been largely dependent on the experimental design and selection of target cells.

The lack of consistent findings and/or the latitude of interpretation of the clinical significance of molecular biology findings hamper meaningful conclusions. Continuing research addressing the molecular pathways affected by PBM is necessary.

It seems unlikely that PBM has carcinogenic effects on normal cells or protects to cytotoxic effects of RT; there is even some evidence suggesting that PBM may enhance treatment response.

Studies indicate that different tumor cells have distinct responses to specific PBM parameters and doses. In part, these differences may be also explained by variations in the cellular microenvironment, since these have been shown to affect cellular signal transduction

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Support Care Cancer. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Support Care Cancer. 2016 June ; 24(6): 2793–2805. doi:10.1007/s00520-016-3153-y.

Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols

Judith A. E. M. Zecha[1], **Judith E. Raber-Durlacher**[1,2], **Raj G. Nair**[3], **Joel B. Epstein**[4,5], **Sharon Elad**[6], **Michael R. Hamblin**[7,8,9], **Andrei Barasch**[10], **Cesar A. Migliorati**[11], **Dan M. J. Milstein**[1], **Marie-Thérèse Genot**[12], **Liset Lansaat**[13], **Ron van der Brink**[5], **Josep Arnabat-Dominguez**[15], **Lisette van der Molen**[13], **Irene Jacobi**[13], **Judi van Diessen**[14], **Jan de Lange**[1], **Ludi E. Smeele**[1,13], **Mark M. Schubert**[16], and **René-Jean Bensadoun**[17]

Judith A. E. M. Zecha: j.zecha@amc.uva.nl; Judith E. Raber-Durlacher: j.e.raberdurlacher@amc.uva.nl; Raj G. Nair: r.nair@griffith.edu.au; Joel B. Epstein: joel.epstein@cshs.org; Sharon Elad: SElad@URMC.Rochester.edu; Michael R. Hamblin: hamblin@helix.mgh.harvard.edu; Andrei Barasch: barasaff@cs.com; Cesar A. Migliorati: migliorati@uthsc.edu; Dan M. J. Milstein: D.M.Milstein@amc.uva.nl; Marie-Thérèse Genot: mtgenot@skynet.be; Liset Lansaat: l.lansaat@nki.nl; Ron van der Brink: RVanderbrink@coh.org; Josep Arnabat-Dominguez: joseparnabat@ub.edu; Lisette van der Molen: l.vd.molen@nki.nl; Irene Jacobi: i.jacobi@nki.nl; Judi van Diessen: j.v.diessen@nki.nl; Jan de Lange: j.delange@amc.uva.nl; Ludi E. Smeele: l.smeele@nki.nl; Mark M. Schubert: mschuber@seattlecca.org; René-Jean Bensadoun: renejean.bensadoun@che-nice.com

[1]Department of Oral and Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105, AZ Amsterdam, The Netherlands [2]Department of Medical Dental Interaction and Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University, P.O. Box 22660 1100 DD, Amsterdam, the Netherlands [3]Oral Medicine Oral Pathology and Human Diseases, Menzies Health Institute Queensland and Oral Medicine Consultant, Department of Haematology and Oncology/Cancer Services, Gold Coast University Hospital, Queensland Health, Queensland, Australia [4]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA [5]Division of Otolaryngology and Head and Neck Surgery, City of Hope, Duarte, CA 91010, USA [6]Division of Oral Medicine, Eastman Institute for Oral Health, and Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY 14620, USA [7]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA 02114, USA [8]Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA [9]Harvard-MIT Division of Health Science and Technology, Cambridge, MA 02139, USA [10]Division of Oncology, Weill Cornell

Correspondence to: René-Jean Bensadoun, renejean.bensadoun@che-nice.com.

Disclaimer This article is based on a narrative review of existing data and the clinical observations of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry. This article is informational in nature. As with all clinical materials, this paper should be used with the clear understanding that continued research and practice could result in new insights and recommendations. The review reflects the collective opinion and as such does not necessarily represent the opinion of any individual author. In no event shall the authors be liable for any decision made or action taken in reliance on the proposed protocols.

Disclosures Judith A.E.M. Zecha, Andrei Barasch, Sharon Elad, Steven Sonis, Cesar A. Migliorati, Marie-Thérèse Genot, Dan M.J. Milstein, Liset Lansaat, Irene Jacobi, Judi van Diessen, Jan. de Lange, Ludi E. Smeele and Mark M. Schubert have no disclosures relevant to this work to report.

Judith E. Raber-Durlacher, Raj G. Nair, Joel B. Epstein, Ron van der Brink, Josep Arnabat Dominguez, and Rene-Jean Bensadoun have received travel expenses and hotel accommodation for the founding meeting of iGLOB from THOR Photomedicine Ltd., UK. Raj Nair has received an honorarium from THOR, UK. Michael R Hamblin was supported by US NIH grant R01AI050875.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Medical Center, New York, NY, USA [11]Department of Diagnostic Sciences and Oral Medicine, Director of Oral Medicine, College of Dentistry, University of Tennessee Health Science Center, 875 Union Ave. Suite N231, Memphis, TN 38163, USA [12]Laser Therapy Unit, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium [13]Antoni van Leeuwenhoek Department of Head and Neck Oncology and Surgery, Netherlands Cancer Institute, Amsterdam, the Netherlands [14]Antoni van Leeuwenhoek Department of Radiation Oncology, Amsterdam, Netherlands Cancer Institute, Amsterdam, the Netherlands [15]Department of Oral Surgery, Faculty of Dentistry, University of Barcelona, Barcelona, Spain [16]Seattle Cancer Care Alliance (SCCA), Oral Medicine, 825 Eastlake Ave E Ste G6900, Seattle, WA 98109, USA [17]World Association for Laser Therapy (WALT) Scientific Secretary, Centre de Haute Energie (CHE), 10 Bd Pasteur, 06000 Nice, France

Abstract

Purpose—There is a large body of evidence supporting the efficacy of low-level laser therapy (LLLT), more recently termed photobiomodulation (PBM) for the management of oral mucositis (OM) in patients undergoing radiotherapy for head and neck cancer (HNC). Recent advances in PBM technology, together with a better understanding of mechanisms involved and dosimetric parameters may lead to the management of a broader range of complications associated with HNC treatment. This could enhance patient adherence to cancer therapy, and improve quality of life and treatment outcomes. The mechanisms of action, dosimetric, and safety considerations for PBM have been reviewed in part 1. Part 2 discusses the head and neck treatment side effects for which PBM may prove to be effective. In addition, PBM parameters for each of these complications are suggested and future research directions are discussed.

Methods—Narrative review and presentation of PBM parameters are based on current evidence and expert opinion.

Results—PBM may have potential applications in the management of a broad range of side effects of (chemo)radiation therapy (CRT) in patients being treated for HNC. For OM management, optimal PBM parameters identified were as follows: *wavelength*, typically between 633 and 685 nm or 780–830 nm; *energy density*, laser or light-emitting diode (LED) output between 10 and 150 mW; *dose*, 2–3 J (J/cm^2), and no more than 6 J/cm^2 on the tissue surface treated; *treatment schedule*, two to three times a week up to daily; *emission type*, pulsed (<100 Hz); and *route of delivery*, intraorally and/or transcutaneously. To facilitate further studies, we propose potentially effective PBM parameters for prophylactic and therapeutic use in supportive care for dermatitis, dysphagia, dry mouth, dysgeusia, trismus, necrosis, lymphedema, and voice/speech alterations.

Conclusion—PBM may have a role in supportive care for a broad range of complications associated with the treatment of HNC with CRT. The suggested PBM irradiation and dosimetric parameters, which are potentially effective for these complications, are intended to provide guidance for well-designed future studies. It is imperative that such studies include elucidating the effects of PBM on oncology treatment outcomes.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

Low-level laser therapy; Low-level light therapy; Photobiomodulation; Mucositis; Orofacial complications; Chemotherapy; Radiation therapy; Head and neck cancer; LLLT; PBM

Introduction

Nearly all patients with advanced head and neck cancer (HNC) suffer orofacial, oropharyngeal, and neck complications from treatment with radiation therapy (RT) or chemoradiotherapy (CRT) [1].

The severity of complications varies depending upon the type and site of the tumor, mode and intensity of therapies involved, and individual patient characteristics. Nevertheless, in most patients, complications are associated with significant morbidity and mortality resulting in increased use of health-care resources and may compromise patient adherence to cancer therapy protocols resulting in suboptimal outcomes. Most patients develop multiple complications, which result in a significant burden of illness with negative impact on quality of life (QoL) [1–5].

Supportive care addressing these complications must continue from initial diagnosis of HNC, through treatment and survival. However, many interventions have limitations and are primarily palliative in nature [6].

Among the presently available supportive care measures, the use of photobiostimulation (PBM) has shown significant promise. PBM refers to various light energies such as low-level laser therapy (LLLT) and light-emitting diode (LED) and visible light (see part 1).

Systematic reviews have suggested efficacy of PBM for oral mucositis (OM) management in myeloablative hematopoietic stem cell transplant (HSCT) recipients and in HNC patients [7–12]. However, recent advances in PBM application and PBM devices, together with a better understanding of the pathobiology of HNC treatment-induced complications, may lead to a broader range of indications for PBM in the management of these problems.

A task force consisting of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry was formed. The mission of this group is to identify potential indications for PBM in the management of side effects of cancer therapy, design of PBM study protocols, identify validated outcome measures, and test the efficacy and safety of proposed protocols for the management of complications related to cancer therapy.

Part 1 of this review addressed mechanisms of action, dosimetric, and safety considerations. This paper (part 2) discusses the following: (i) selected oral, oropharyngeal, facial, and neck complications of treatment for HNC, in which PBM may have potential for prophylaxis and/or treatment; (ii) PBM parameters for prophylaxis and therapy to mitigate these complications based on current evidence and knowledge; and (iii) directions of future research related to the use of PBM in HNC.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

PBM for the management of orofacial and neck complications of cancer therapy

The following paragraphs summarize selected acute and chronic complications associated with HNC therapy and the literature relevant to the use of PBM for the management of these complications.

For each of these complication, we propose prophylactic and therapeutic PBM protocols based on evidence derived from the literature and expert opinion (Table 1). These protocols are intended to provide clinical guidance and to serve as a starting point for continuing research. Please see part 1 of this review for discussion of mechanism of action and of safety of PBM.

Oral mucositis

Oral mucositis affects virtually all patients undergoing CRT for HNC. Clinically, the manifestations of OM form a continuum, with erythematous mucosal changes when mild, and, ulcerative lesions that expose the submucosa when severe. The detrimental effects of OM upon QoL and functional status are significant [2].

The current understanding of the pathogenesis of OM is largely based on animal models, which document the multi-factorial nature of this inflammatory condition and have implicated a cascade of interrelated events in multiple tissue compartments. These observations lead to the five-phase model of OM, based on the sequence of events following cytotoxic treatment [13]. Inflammation induced by the formation of excessive reactive oxygen species (ROS) and activation of nuclear factor kappa B (NF-κB) are the key factors in its pathobiology [14]. Subsequent studies implicated microvascular injury, formation of proinflammatory cytokines, host–microbiome interactions, and extracellular matrix alterations in mucositis pathogenesis [15]. In addition, epidermal growth factor receptor (EGFR) inhibitors and tyrosine kinase receptor inhibitors (TKI) administered as single drugs or combined with CRT may enhance OM or cause additional symptoms [16, 17]. Effective management options for OM are limited [18], and pain control is typically inadequate [2].

A Cochrane meta-analysis concluded that PBM may prevent severe OM [7]. A systematic review and meta-analysis of 11 randomized controlled trials (RCTs) in HNC patients treated with (chemo)radiation therapy concluded that there was consistent evidence that PBM applied with doses of 1–6 J per point reduced OM prevalence, severity, and duration, and its associated pain [9]. Another meta-analysis including RCTs in various cancer treatment settings showed that PBM reduced OM risk and decreased its severity and duration [10]. The efficacy appeared to be similar for red [630–670 nm] and NIR (780–830 nm) light, although the optimal doses may vary between these wavelengths. Similarly, a systematic review and meta-analysis including 18 RCTs reported that prophylactic PBM reduced severe OM and associated pain in patients treated for HNC or undergoing HSCT [12]. The Clinical Practice Guidelines of the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) Mucositis Study Group found evidence to recommend PBM for the prevention of OM in HSCT recipients conditioned with high-dose

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

chemotherapy, with or without total body irradiation, and to suggest a role for patients treated with RT for HNC [11, 18]. Evidence was derived from high-quality studies using specific PBM parameters, and the authors noted that there remains a need to identify optimal PBM parameters per cancer treatment modality.

Based on this evidence and on our experience, we propose the following regimen for the management of OM and mucositis affecting the oropharynx: wavelength of 633–685 or 780–830 nm; power output of between 10 and 150mW; *energy density* 2–3 J/cm^2, and no more than 6 J/cm^2 on the tissue surface treated; administered two to three times a week up to daily; and using successive intraoral applications on single spots on the mucosa, rather than a scanning motion over the entire mucosal surface. The upper safety limit was set as a precaution since no clinical data defining a safe upper limit are currently available. *Emission type*, continuous or pulsed (<100 Hz) as low-frequency pulsed light may be superior to continuous wave light for wound healing or the prevention of injury. Extraorally administered PBM may be effective for the management of OM of the buccal mucosa, vestibule, and inner epithelial surfaces of the lips which could be applied in combination with an intraoral device.

Dermatitis

Radiation dermatitis occurs in the majority of patients with locoregionally advanced HNC treated with RT.

The pathobiology of acute radiation dermatitis is complex and partially overlaps that of OM. Irradiation of the skin leads to direct tissue injury and inflammatory cell recruitment, involving damage to epidermal basal cells and connective tissue including endothelial cells and vascular components [19]. Radiation-induced generation of free radicals induces DNA injury and release of inflammatory cytokines [mainly interleukin (IL)-1 and IL-6] [20, 21]. This process leads to the development of erythema, edema, and possible ulceration. Late RT-induced changes involving skin are characterized by the loss of follicular structures, an increase in collagen and damage to elastic fibers in the dermis, and a fragile epidermal covering [22]. Transforming growth factor beta (TGF-β) is considered to play a central role in mediating RT-induced tissue fibrosis [23–25].

The severity of skin reactions is dependent on the total radiation dose, the dose per fraction, the overall treatment time, beam type and energy, the surface area of the skin exposed to radiation, the use of combined chemoradiotherapy with or without targeted therapies, and individual risk factors [20]. The severity of acute reactions has been shown to predict late effects. Radiation dermatitis impacts adversely on cosmesis and function and reduces QoL, especially in patients who develop secondarily infected dermatitis [19].

Patients with head and neck squamous cell carcinoma (HNSCC) treated with an epithelial growth factor receptor (EGFR) inhibitor may develop an acneiform skin rash in addition to radiation dermatitis [17, 22].

Based on the effects of PBM on the epidermis and dermis (reduced inflammation and improved wound healing), and on the shared similarities in pathobiology with OM, it seems

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

any alteration in muscle or tissue properties of these structures. Although voice and speech dysfunctions significantly affect QoL, these complications have received little attention and are likely underreported in efforts to preserve organ function after cancer therapy [117–119].

Currently, there is limited information on the prevalence of speech and voice dysfunction in advanced HNC patients treated with RT or CRT. Prospective studies are needed, including baseline measurements and standardized multidimensional assessment of functional aspects of voice and speech [118].

The etiology of voice and speech problems resembles that of dysphagia and may include neuromuscular weakness as a result of tumor invasion. Dependent on the dose tolerance of the critical organs involved, CRT-induced voice and/or speech dysfunction can result from mucositis of the soft palate, tongue and laryngeal soft tissues, edema, fibrosis, or atrophy of the vocal folds, pharyngeal and oral tissues, and altered saliva or hyposalivation [120–122].

New RT delivery techniques designed to spare these structures may prevent functional impairment.

A study using an animal model of reflux laryngitis (a condition including hoarseness, voice fatigue, globus, chronic cough, throat pain, and dysphagia) suggested that the anti-inflammatory effects of PBM may play in the management of this condition [123].

We are not aware of any studies on the effect of PBM on the quality of speech and voice in HNC patients. Since PBM may preserve function of the anatomical structures involved by its anti-inflammatory effects and may have indirect benefits by stimulating the salivary flow, future studies are warranted.

Conclusion

Acute and chronic complications induced by RT and CRT in patients with HNC represent a significant clinical challenge [1]. There are similarities with respect to pathophysiology across different complications, and patients may suffer from multiple concurrent and interrelated problems [13]. There is anecdotal evidence suggesting that the inflammation associated with acute complications is a harbinger for chronic complications. This observation suggests that preventive approaches starting before, and in the early phases of treatment with RT and CRT, may not only reduce the risk for developing acute problems but may also have an impact on the risk for late complications.

PBM has shown effectiveness in the management of OM and elicits several potentially beneficial effects, including reduction of inflammation and pain, promotion of tissue repair, reduction of fibrosis, and protection and regeneration of nerves. Therefore, there is a clear motivation for studies on the application of PBM for the prevention and treatment of a broad range of acute and chronic complications associated with RT or CRT in HNC patients.

The purpose of this article is to serve as a basis for establishing a platform for facilitating future collaborations among clinicians and researchers, in order to create firm scientific evidence for the use of PBM in patients with HNC. PBM protocols should be administered

Case Report ISSN 2768-6647

Medical and Clinical Case Reports

Impact of Red and Violet Laser Therapy on Peripheral Arterial Disease: Case Series

Andrzej Eberhardt[1] and Travis Sammons[2*]

[1]*General surgery and Vascular, Vascular Surgery and Phlebology in Femmed Clinic, Warsaw, Poland.*

[2]*Erchonia Corporation, Melbourne, FL, USA.*

[*]Correspondence:
Travis M. Sammons, Erchonia Corporation, 112 Southchase Blvd., Fountain Inn, SC 29644, Tel: 888-242-0571, Fax: 321.473.1608.

Received: 29 Nov 2023; **Accepted:** 26 Dec 2023; **Published:** 02 Jan 2024

Citation: Andrzej Eberhardt, Travis Sammons. Impact of Red and Violet Laser Therapy on Peripheral Arterial Disease: Case Series. Med Clin Case Rep. 2024; 4(1): 1-4.

Keywords
Peripheral arterial diseases, Red and violet Laser therapy, Surgery.

Introduction

Peripheral arterial disease (PAD) is a manifestation of atherosclerotic disease impacting the lower section of the aorta, along with its primary offshoots and the arteries that provide blood to the limbs. The range of clinical manifestations associated with PAD encompasses individuals with symptomless conditions, those who undergo intermittent claudication (IC), and those exhibiting more serious signs of critical limb ischemia. PAD is a common condition that affects a large proportion of the adult population worldwide. The condition occurs predominantly in individuals between the ages of 45 and 70 years and present much more frequently in males than in females [1]. The estimated prevalence of claudication ranges from 0.4% to 14.4%. The occurrence of symptomless conditions identified through noninvasive examinations is notably greater, varying from 0.9% to 22%. The proportion of symptomatic cases to symptomless cases ranges from 1:0.9 to 1:6.

Factors that elevate the risk of atherosclerosis, such as advancing age, smoking, diabetes, dyslipidemia, and hypertension, enhance the probability of developing PAD in the lower extremities [2]. Individuals often report experiencing limb pain consistent with intermittent claudication, along with walking difficulties. Eventually, they may also encounter rest pain, notably at night, which can be described as sensations of coldness, burning, heightened sensitivity, and tingling [3].

Low-level laser therapy (LLLT) is a promising non-invasive physiotherapeutic method. The primary objective of this research was to investigate the impact of low-level laser therapy on the blood circulation to the lower extremities.

Material and Methods

Thirty-six (n=36) individuals treated in Warsaw Outpatient Clinics of Vascular Surgery were qualified for the study. All individuals had symptoms of intermittent claudication. The claudication distance was not less than 200 meters (Fontaine's stages II B). Segmental or total occlusion of the superficial femoral artery was found in ultrasound examination in all individuals. The duration of symptoms ranged from 6 to 27 months. All individuals had pharmacological therapy in accordance with the TASC II guidelines and walking training (3 times a week from 3-6 kilometers). All individuals underwent a Doppler ultrasound examination of the popliteal artery with flow measured in cm/sec performed once a week for 12 weeks. Each individuals received an application with Erchonia EVRL device, which emits a red laser (635 nm) and blue/violet laser (405 nm) both at 7.5mW. The laser procedure was performed once a week for 15 minutes. The area on the thigh was irradiated to the height of the occluded artery. Each individual provided written informed consent prior to participating in any study-related activity.

Results

All thirty-six (n=36) individuals completed the study. The age ranges from 41–80 years, with 24 men (67%) and 12 women. Among the respondents, there were 21 finger smokers, which constituted 58% of the study group and 15 people with diabetes, which constituted 42% of the study group. 10 subjects (28%) were both smokers and had diabetes.

Intervertebral Disk Nutrition: A Review of Factors Influencing Concentrations of Nutrients and Metabolites

Thijs Grunhagen, DPhil[a,b], Aboulfazl Shirazi-Adl, PhD[c], Jeremy C.T. Fairbank, MA, MD, FRCS[d], Jill P.G. Urban, PhD[a,*]

KEYWORDS

• Oxygen • Glucose • Diffusion • pH • End plate
• Calcification • Intervertebral • Disk

The normal adult human disk is virtually avascular. Nutrients, principally glucose and oxygen, necessary for survival and activity of disk cells are transported from blood vessels at its margins to the cells deep within the disk matrix, mainly by diffusion; products of metabolism, principally lactic acid, are removed by the reverse route. Loss of adequate nutrient supply has long been associated with the development and progression of disk degeneration because it adversely affects activity and even the viability of disk cells. Although the disk has only a small number of cells, these cells play a vital role. Such cells are responsible for making and maintaining the macromolecules of the disk matrix and, hence, ultimately govern the disk's biomechanical functioning.

Here the authors discuss some of the factors that determine the rate at which nutrients can reach the disk cells. The authors review how these change with degeneration and age. The authors also discuss how the balance between rate of nutrient supply and rate of demand influences the nutrient-metabolite milieu of disk cells and, hence, their activity and survival. Finally, the authors assess the role of nutrient supply in developing successful biologic treatments for disk degeneration.

FACTORS INFLUENCING RATE OF SUPPLY OF NUTRIENTS TO THE DISK CELLS

Blood Supply to the Disks

The adult human disk is virtually avascular apart from a small number of capillaries that penetrate only a few millimeters into the outermost annulus. The disk is, thus, nourished by blood vessels at its margins.[1,2] Those arising in the vertebral bodies feed most of the disk; only the outer annulus is nourished by blood vessels in the soft tissues at the annulus periphery.[3,4] The supply through the vertebral bodies is, thus, critical for disk health.[4] The blood supply to the vertebral column has

The authors thank the European Community's Seventh Framework Program (FP7, 2007–2013) under grant agreement HEALTH-F2-2008-201626 for support.

[a] Department of Physiology, Anatomy and Genetics, Oxford University, Le Gros Clark Building, South Parks Road, Oxford OX1 3QX, UK
[b] Philips Research, High Tech Campus 5, 5656 AE, Eindhoven, The Netherlands
[c] Génie mécanique, École Polytechnique, Montréal, Québec, Canada H3C 3A7
[d] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, OX3 7LD, UK
* Corresponding author.
E-mail address: jill.urban@dpag.ox.ac.uk

Orthop Clin N Am 42 (2011) 465–477
doi:10.1016/j.ocl.2011.07.010
0030-5898/11/$ – see front matter © 2011 Elsevier Inc. All rights reserved.

An official website of the United States government
Here's how you know

Randomized Controlled Trial Lasers Surg Med. 2022 Mar;54(3):342-347.
doi: 10.1002/lsm.23480. Epub 2021 Sep 16.

HeaLED: Assessment of skin healing under light-emitting diode (LED) exposure-A randomized controlled study versus placebo

Florence Le Duff [1], Eric Fontas [2], Davide Guardoli [1], Jean-Philippe Lacour [1], Thierry Passeron [1 3]

Affiliations

Affiliations

1 Dermatology Department, Archet Hospital-CHU, University Côte d'Azur, Nice, France.
2 Délégation à la Recherche Clinique et à l'innovation (DRCI), Université Côte D'Azur, CHU Nice, Nice, France.
3 INSERM U 1065, C3M, University Côte d'Azur, Nice, France.

PMID: 34529859 DOI: 10.1002/lsm.23480

Abstract

Background: Light-emitting diodes (LEDs) in the visible or near-infrared spectrum have been reported to promote wound healing. However, despite being frequently proposed in daily clinical practice, the efficacy of photobiomodulation treatment after a laser procedure relies on very limited clinical data.

Objective: To compare the relative efficacy of LED versus placebo treatment in decreasing erythema and transepidermal water loss (TEWL) after a fractional CO_2 session.

Methods: We conducted an open prospective intraindividual randomized controlled study with 10 healthy volunteers. An ablative fractional laser was performed on the seven forearm areas. Three consecutive daily sessions of LED (590, 630, and 850 nm [two tested irradiances each] and placebo) were applied after randomization. Physical measures (colorimetry, TEWL), photography, and clinical evaluation were performed on Days 1, 2, 3, 7, and 21. The main criterion of evaluation was the variation of parameter a* (erythema) at 72 hours for each LED parameter compared to placebo treatment.

Results: No significant differences in the variation of the parameter a* or any of the other studied parameters were found for the different LEDs compared to the placebo area.

Conclusion: Photobiomodulation failed to improve healing after laser ablation compared to placebo.

Keywords: CO2 laser; ablative fractional laser; healing; light-emitting diode; photobiomodulation.

© 2021 Wiley Periodicals LLC.

PubMed Disclaimer

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 30 August 2022
DOI 10.3389/fonc.2022.927685

Check for updates

OPEN ACCESS

EDITED BY
Dwight E. Heron,
Bon Secours Health System,
United States

REVIEWED BY
Vinagolu K. Rajasekhar,
Memorial Sloan Kettering Cancer Center, United States
Avraham Eisbruch,
University of Michigan, United States

*CORRESPONDENCE
René-Jean Bensadoun
renejean.bensadoun@che-nice.com

SPECIALTY SECTION
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

RECEIVED 24 April 2022
ACCEPTED 28 July 2022
PUBLISHED 30 August 2022

CITATION
Robijns J, Nair RG, Lodewijckx J, Arany P, Barasch A, Bjordal JM, Bossi P, Chilles A, Corby PM, Epstein JB, Elad S, Fekrazad R, Fregnani ER, Genot M-T, Ibarra AMC, Hamblin MR, Heiskanen V, Hu K, Klastersky J, Lalla R, Latifian S, Maiya A, Mebis J, Migliorati CA, Milstein DMJ, Murphy B, Raber-Durlacher JE, Roseboom HJ, Sonis S, Treister N, Zadik Y, Bensadoun R-J and "Cancer Supportive Care" WALT Working Group (2022) Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. *Front. Oncol.* 12:927685. doi: 10.3389/fonc.2022.927685

Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022

Jolien Robijns[1], Raj G. Nair[2], Joy Lodewijckx[1], Praveen Arany[3], Andrei Barasch[4], Jan M. Bjordal[5], Paolo Bossi[6], Anne Chilles[7], Patricia M. Corby[8], Joel B. Epstein[9], Sharon Elad[10], Reza Fekrazad[11], Eduardo Rodrigues Fregnani[12], Marie-Thérèse Genot[13], Ana M. C. Ibarra[14], Michael R. Hamblin[15], Vladimir Heiskanen[16], Ken Hu[17], Jean Klastersky[18], Rajesh Lalla[19], Sofia Latifian[20], Arun Maiya[21], Jeroen Mebis[1], Cesar A. Migliorati[22], Dan M. J. Milstein[23], Barbara Murphy[24], Judith E. Raber-Durlacher[25], Hendrik J. Roseboom[25], Stephen Sonis[26], Nathaniel Treister[26], Yehuda Zadik[27], René-Jean Bensadoun[28]*
and "Cancer Supportive Care" WALT Working Group

[1]UHasselt, Faculty of Medicine and Life Sciences, Diepenbeek, Belgium, [2]Oral Medicine, Oral Pathology and Oral Oncology, Griffith University, Department of Haematology and Oncology, Gold Coast University Hospital, Gold Coast, QL, Australia, [3]School of Dental Medicine, Oral Biology and Biomedical Engineering, University at Buffalo, Buffalo, NY, United States, [4]Harvard School of Dental Medicine, Division of Oral Medicine and Dentistry, Boston, MA, United States, [5]Physiotherapy Research Group, IGS, University of Bergen, Bergen, Norway, [6]Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy, [7]Radiotherapy Department, Institut Curie, Paris, France, [8]New York University College of Dentistry, Bluestone Center for Clinical Research, New York, NY, United States, [9]City of Hope Duarte, CA and Cedars-Sinai Health System, Los Angeles, CA, United States, [10]Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, United States, [11]Department of Periodontology, Dental Faculty – Radiation Sciences Research Center, Laser Research Center in Medical Sciences, AJA University of Medical Sciences, Tehran, Iran, [12]Oral Medicine Department, Hospital Sírio-Libanês, São Paulo, Brazil, [13]Laser Therapy Unit, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium, [14]Postgraduate Program on Biophotonics Applied to Health Sciences, Nove de Julho University, São Paulo, Brazil, [15]Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [16]Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland, [17]Department of Radiation Oncology, NYU Langone Health, New York, NY, United States, [18]Medical Oncology, Institut Jules Bordet, Brussels, Belgium, [19]Section of Oral Medicine, University of Connecticut School of Dental Medicine, Farmington, CT, United States, [20]Department of Medicine, Institut Jules Bordet, Universiteí Libre de Bruxelles, Brussels, Belgium, [21]Manipal College of Health Professions, MAHE, Manipal, India, [22]Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry, Gainesville, Florida, United States, [23]Oral and Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [24]Department of Oncology, Vanderbilt University Medical Center, Nashville, TN, United States, [25]Department of Oral and Maxillofacial Surgery, Amsterdam UMC, University of Amsterdam, Department of Oral Medicine, Academic Centre for Dentistry Amsterdam, University of Amsterdam and VU University, Amsterdam, Netherlands, [26]Division of Oral Medicine and Dentistry, Brigham and Women's Hospital; Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine; Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, MA, United States, [27]Department of Military Medicine, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, and Department of Oral Medicine, Sedation and Maxillofacial Imaging, Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel, [28]Department of Radiation Oncology, Centre de Haute Energie, Nice, France

Disclaimer: This article is based on recommendations from the 12th WALT Congress, Nice, October 3-6, 2018, and a follow-up review of the existing data and the clinical observations of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry. This article is informational in nature. As with all clinical materials, this paper should be used with a clear understanding that continued research and practice could result in new insights and recommendations. The review reflects the collective opinion and, as such, does not necessarily represent the opinion of any individual author. In no event shall the authors be liable for any decision made or action taken in reliance on the proposed protocols.

Objective: This position paper reviews the potential prophylactic and therapeutic effects of photobiomodulation (PBM) on side effects of cancer therapy, including chemotherapy (CT), radiation therapy (RT), and hematopoietic stem cell transplantation (HSCT).

Background: There is a considerable body of evidence supporting the efficacy of PBM for preventing oral mucositis (OM) in patients undergoing RT for head and neck cancer (HNC), CT, or HSCT. This could enhance patients' quality of life, adherence to the prescribed cancer therapy, and treatment outcomes while reducing the cost of cancer care.

Methods: A literature review on PBM effectiveness and dosimetry considerations for managing certain complications of cancer therapy were conducted. A systematic review was conducted when numerous randomized controlled trials were available. Results were presented and discussed at an international consensus meeting at the World Association of photobiomoduLation Therapy (WALT) meeting in 2018 that included world expert oncologists, radiation oncologists, oral oncologists, and oral medicine professionals, physicists, engineers, and oncology researchers. The potential mechanism of action of PBM and evidence of PBM efficacy through reported outcomes for individual indications were assessed.

Results: There is a large body of evidence demonstrating the efficacy of PBM for preventing OM in certain cancer patient populations, as recently outlined by the Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Building on these, the WALT group outlines evidence and prescribed PBM treatment parameters for prophylactic and therapeutic use in supportive care for radiodermatitis, dysphagia, xerostomia, dysgeusia, trismus, mucosal and bone necrosis, lymphedema, hand-foot syndrome, alopecia, oral and dermatologic chronic graft-versus-host disease, voice/speech alterations, peripheral neuropathy, and late fibrosis amongst cancer survivors.

Conclusions: There is robust evidence for using PBM to prevent and treat a broad range of complications in cancer care. Specific clinical practice guidelines or evidence-based expert consensus recommendations are provided. These recommendations are aimed at improving the clinical utilization of PBM therapy in supportive cancer care and promoting research in this field. It is anticipated these guidelines will be revised periodically.

KEYWORDS

photobiomodulation (PBM), cancer supportive care, guidelines, recommendations, mucositis, dermatitis, cancer-treatment side effects

1 Introduction

Despite the ongoing improvements in cancer therapy, it is still associated with severe life-impairing side effects. Both treatment- and patient-related risk factors determine the severity of the complications. Moreover, they negatively impact the patients' quality of life (QoL) and daily activities. Therefore, effective supportive care strategies are necessary (1). The biological effects of photobiomodulation (PBM) therapy were discovered by Endre Mester in 1965 (2). Currently, PBM is defined as: "the use of non-ionizing optical radiation in the visible and near-infrared spectral range is absorbed by endogenous chromophores to elicit photophysical and photochemical events at various biological scales without eliciting thermal damage, leading to physiological changes and therapeutic benefits" (3). There is a considerable body of evidence supporting the efficacy of PBM for the prevention of oral mucositis (OM) in patients undergoing radiotherapy (RT) for head and neck cancer (HNC), chemotherapy (CT), or hematopoietic stem cell transplantation (HSCT) (4). Recent advances in understanding the mechanisms of action of PBM and dosimetry parameters of PBM have resulted in examining other oncology-related conditions that may lead to effective management of a broader range of complications associated with cancer treatment. This could improve overall QoL, adherence to cancer treatment regimens, and their outcomes while reducing cost of care (5).

2 Methods

This position paper was developed based on reviewing existing literature on PBM in supportive cancer care. For oral mucositis, a systematic review was feasible. For all other indications, expert consensus opinions are based on a narrative review of the literature and the personal experiences of contributing experts. A level of evidence was assigned to these indications based on the Somerfield criteria based on the type and design of the study (6). The level of evidence for each intervention is then translated into a guideline recommendation where Level I or II evidence is achieved by at least one well-designed randomized controlled trial (RCT). A suggestion was possible for lower-level evidence, but only when consistent evidence from multiple studies and panel consensus on the interpretation of this evidence. Thus, to enable maximal, practical clinical use and promote future research for PBM in supportive cancer care, WALT makes recommendations in two categories as clinical practice guidelines and consensus expert opinion. We strongly recommend clinical judgment of the provider and individual patient scenario be carefully éaccounted for in interpreting and applying these WALT PBM recommendations.

3 Results

The reader is referred to comprehensive reviews in these WALT series for a detailed discussion of PBM parameters. A brief review of critical PBM parameters is presented below.

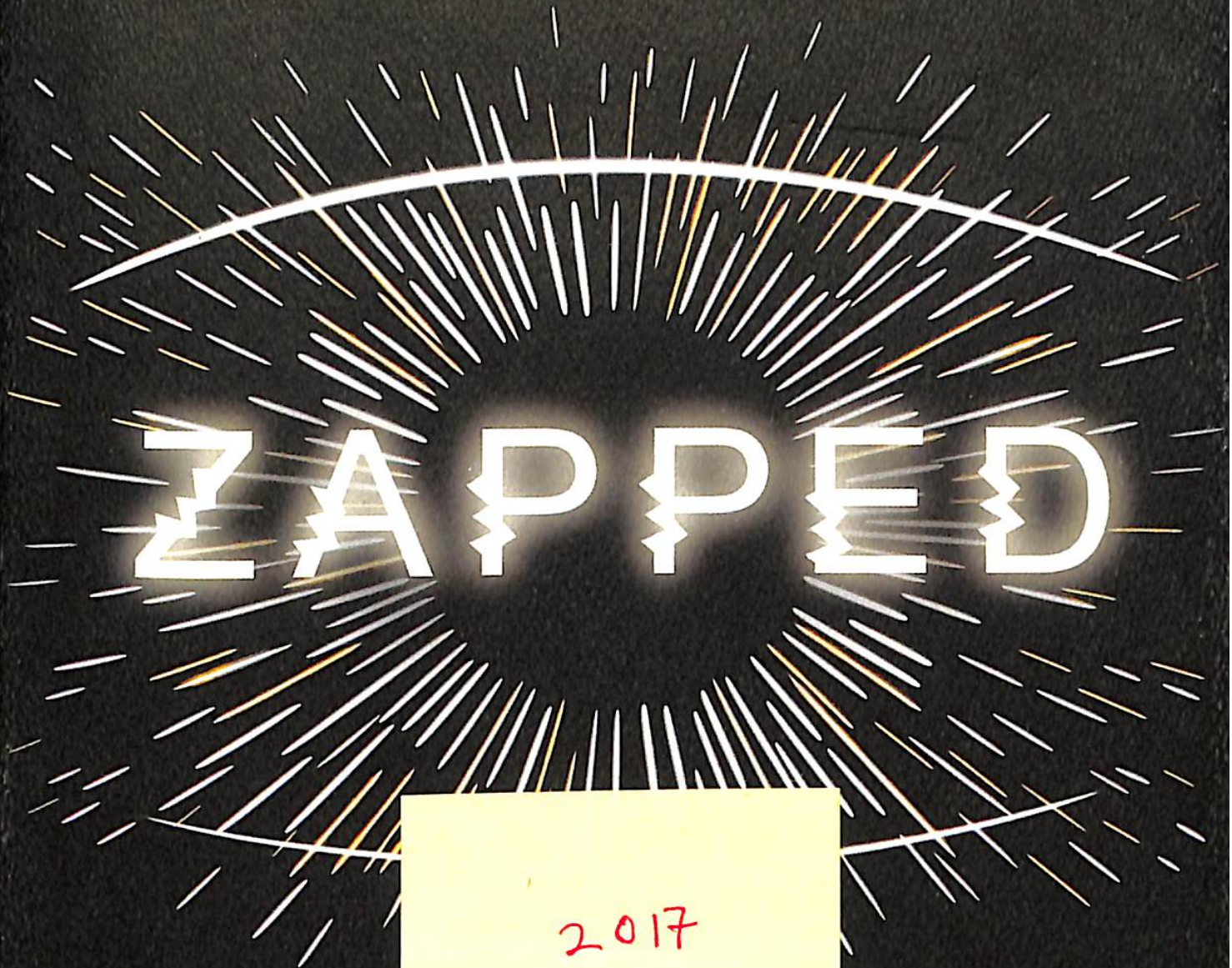
3.1 PBM parameters

PBM parameters using low-level lasers or light-emitting diodes (LEDs) in cancer supportive care (summarized in Table 1) are usually within the red and near-infrared (NIR) wavelength range between 600 nanometers (nm) and around 1,000 nm, with a power density from 5 (mW)/cm^2 to 150 mW/cm^2 (7). The duration of application varies according to the site, but it may well be within 30 - 60 seconds per point. While shorter efficacious treatment times have been used (2-10sec per point, multiple spots that are clinically laborious), this could be attributed to cumulative PBM dose effects. The therapeutic dosage is depicted as the energy density measured in Joules as J/cm^2 and varies between 0.1 to 12 J/cm^2 as per current literature. Low-level laser systems used include helium-neon (HeNe), neodymium-doped yttrium aluminum garnet (Nd : YAG), gallium aluminum arsenide (GaAlAs) diode lasers, indium gallium aluminum phosphorus (InGaAlP), and non-thermal, non-ablative carbon dioxide (CO_2) lasers (8). In recent years, LEDs with wavelengths in the red or NIR regions have become increasingly common due to their safety, low cost, and suitability for home use (8, 9).

The biological effects of PBM on the exposed tissues depend upon a number of variables, including the location of the cells in the field of exposure, cell type, molecular and redox state of the cell, the tissue microenvironment, PBM parameters such as wavelength, power density, type of delivery as in pulsing or continuous, beam or spot size, and duration of exposure (10, 11). It is well known that PBM therapy exhibits a biphasic dose-response that warrants optimal tissue-specific irradiation dose parameters. In other words, doses lower than the optimal value may have a diminished effect, while doses higher than optimal can have no beneficial or even adverse therapeutic outcomes (12, 13). The effect of such a phenomenon has been consistently evident in published data on the effectiveness and particular disparity of PBM therapy in cancer complications.

Titrating adequate doses and defining the essential PBM parameters as per evidence gathered in a systematic way for each indication is a prerequisite for the successful use of this treatment modality. Without standardization in beam measurement, dose calculation, and the correct reporting of these parameters, studies will not be reproducible, and outcomes will not be consistent. A common misconception is that energy (in J) or energy density (J/cm^2) is all that is necessary to replicate a successful treatment, irrespective of the original power, power

From Infrared to X-rays,
the Curious History of Invisible Light



ZAPPED

2017

BOB BERMAN

AUTHOR OF ZOOM

Zapped
From Infrared to X-rays, the Curious History of Invisible Light

Bob Berman
2017

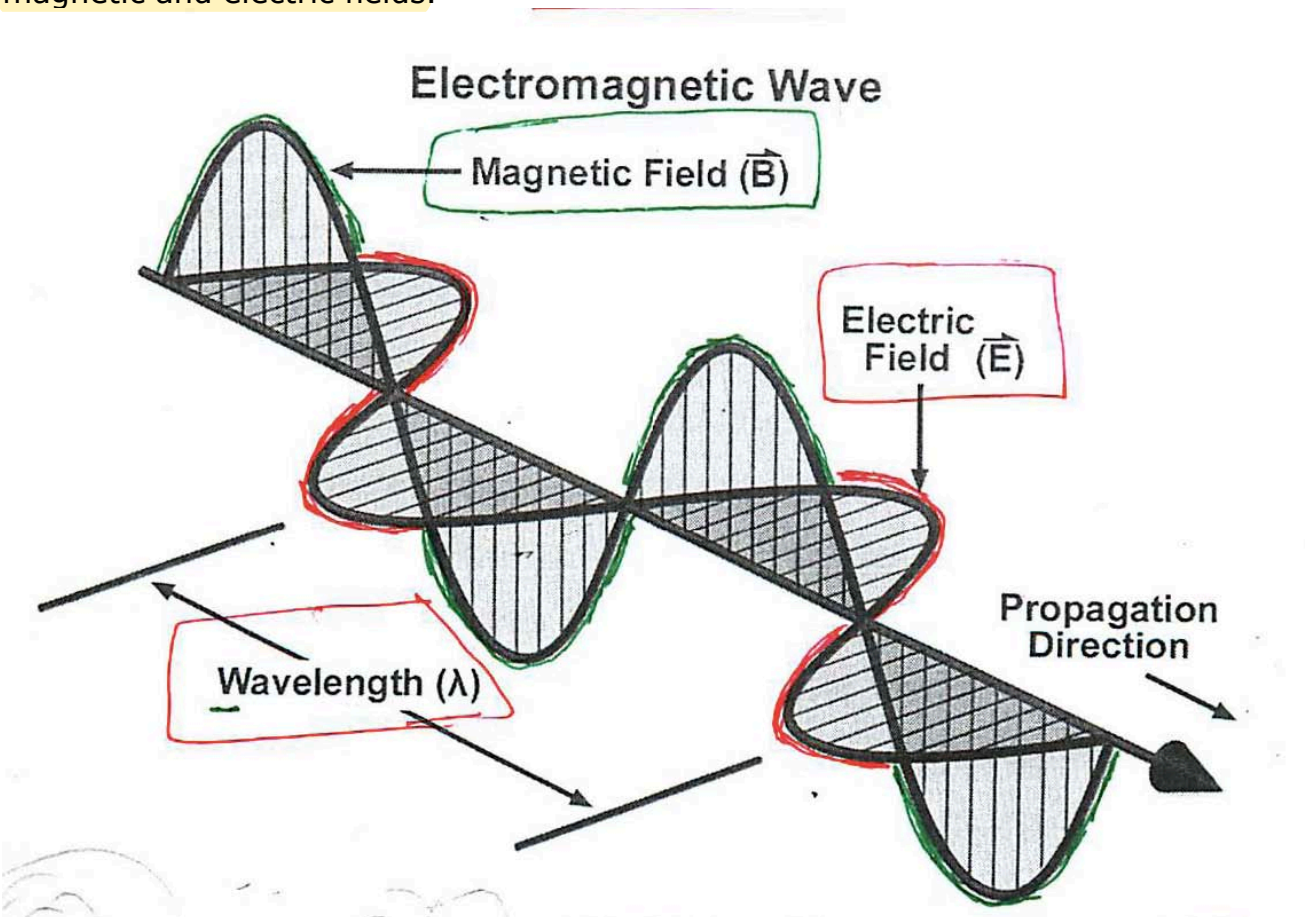
There is a "whole world of light outside our range of vision."

"Photons constitute 99.9999999 percent of everything."

"Light is made up of intertwined magnetic and electrical fields." Yet, "neither magnetism nor electricity is visible to our eyes."

All light consists of a dual wave:
a *magnetic pulse* accompanied by an *electric pulse* positioned at a ninety-degree angle to it. Therefore, light is an electromagnetic phenomenon.

Light is a "manifestation of magnetism and electricity." Light is the unification of magnetic and electric fields.

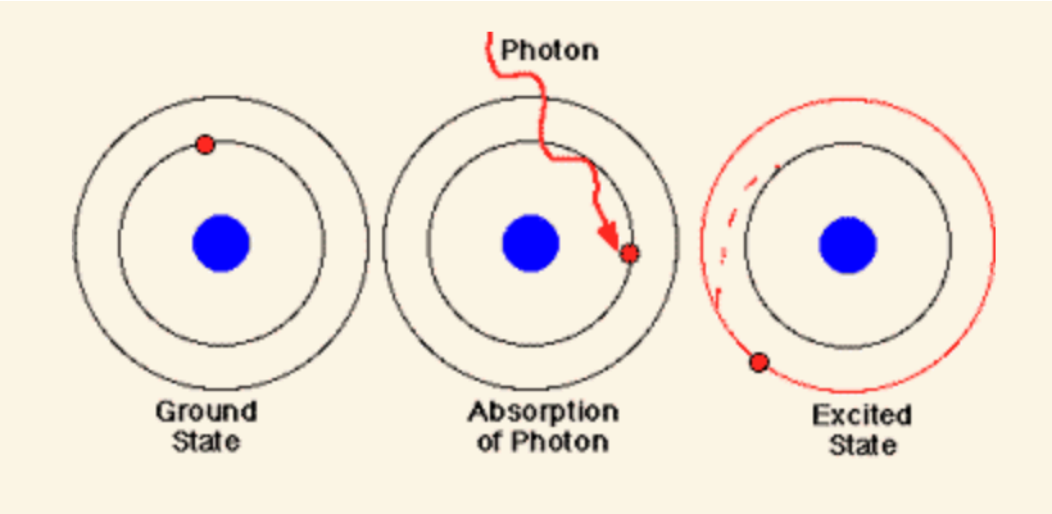


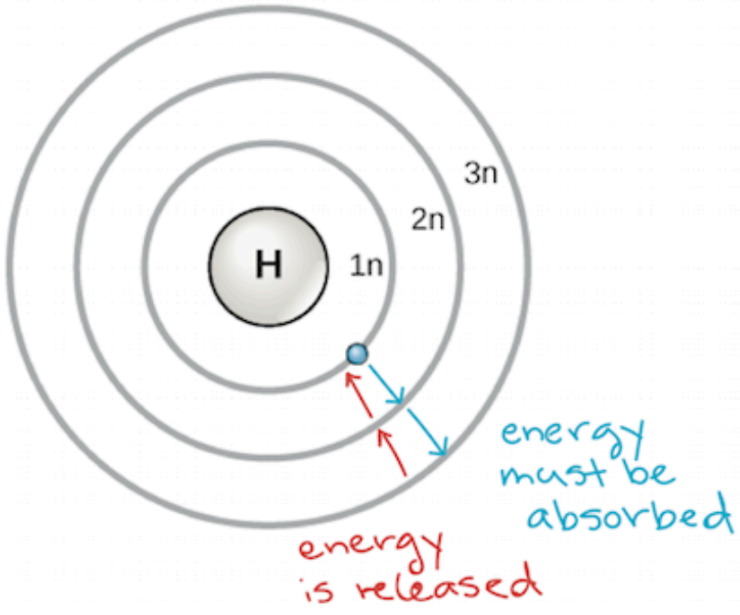
All light consists of a dual wave. A magnetic pulse is accompanied by an electric pulse positioned at a ninety-degree angle to it. *(Molecular Expressions at*

The energy of the photon is absorbed, and the photon disappears.

Photon absorption boosts an electron from ground state to a higher orbit, in an all-or-none fashion.

An "excited state" pigment is produced, with a higher energy level than the ground state pigment, but this excited state is very short-lived, about a billionth of a second.

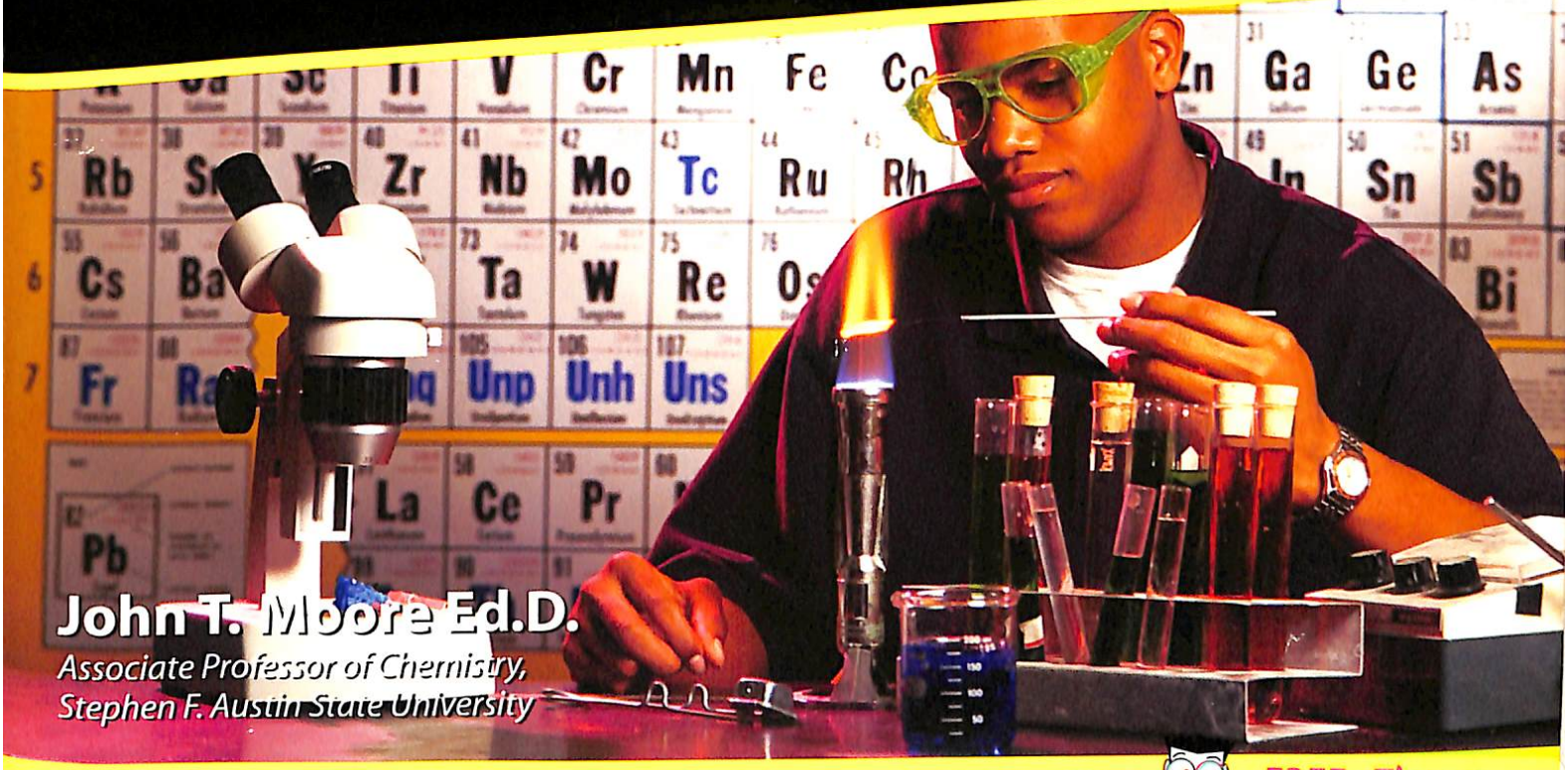




Discover how easy it is to grasp the basics of chemistry

2003

Chemistry FOR DUMMIES®



John T. Moore Ed.D.
Associate Professor of Chemistry,
Stephen F. Austin State University

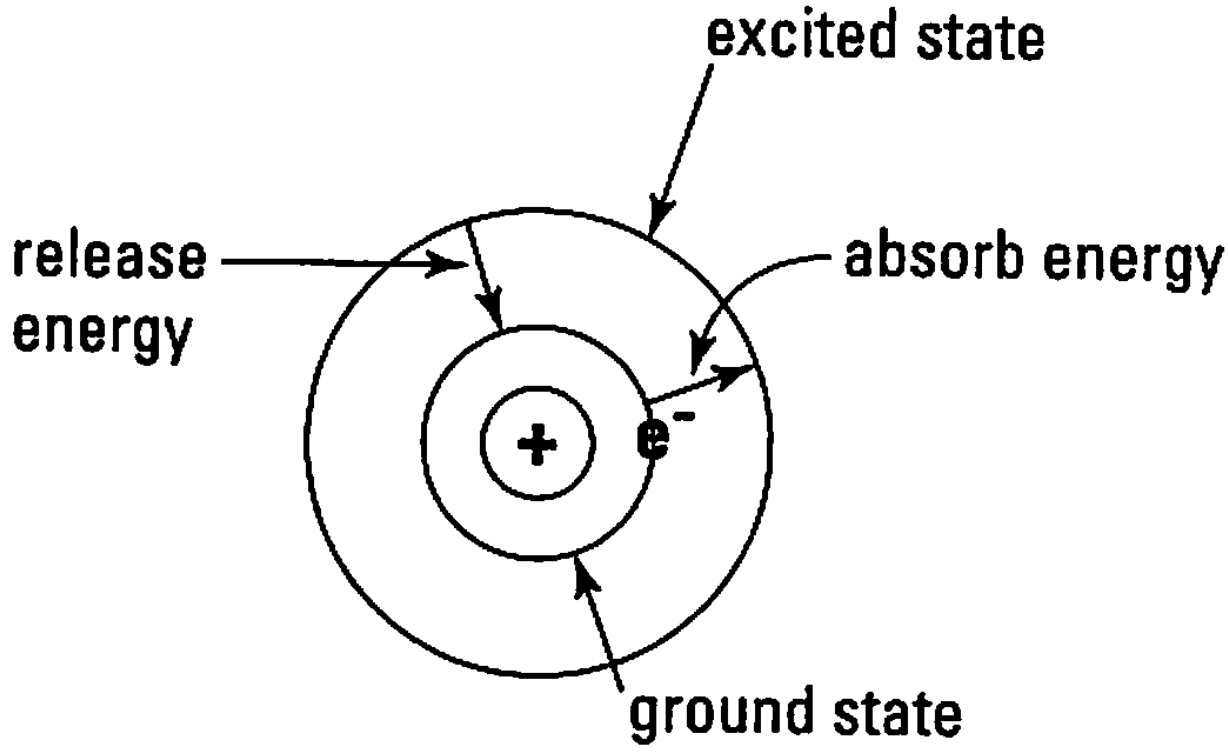
A Reference for the Rest of Us!™

FREE eTips at dummies.com®

Niels Bohr (1885-1962, Nobel Prize 1922), a Danish Physicists, showed that electrons in atoms orbit around the nucleus at different energy levels (shells).

The energy level an electron normally occupies is called its *ground state*. An electron can move to a higher-energy, less stable level (shell) by absorbing energy. This higher-energy, less stable state is called the electron's *excited state*.

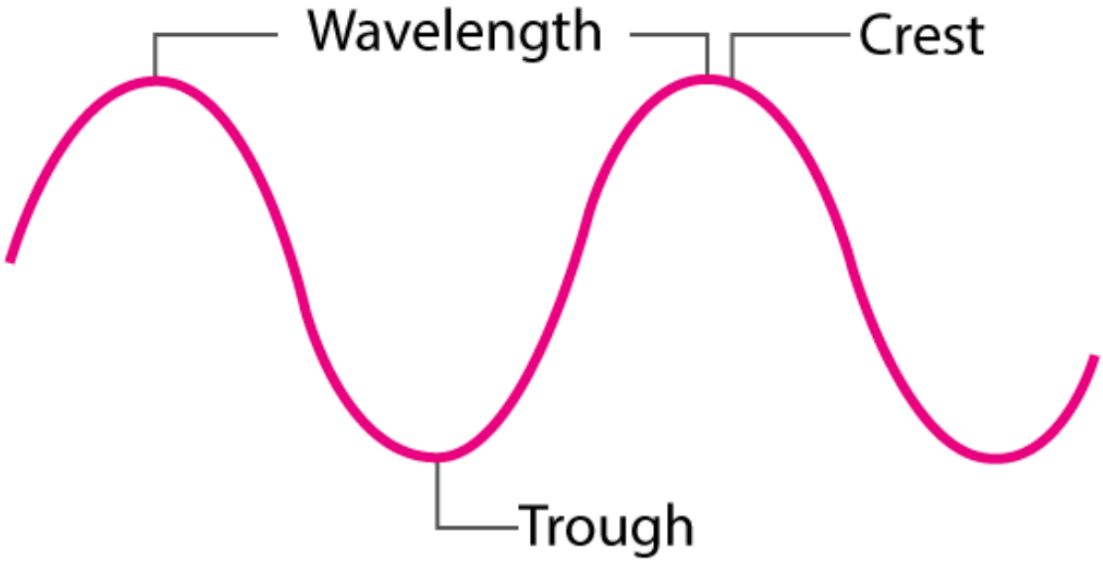
When an excited electron returns to its original ground state, energy is released, and this energy becomes the *electromagnetic spectrum*.



"Chemical reactions depend on the loss, gain, or sharing of electrons."

When photons of visible light energy strike certain atoms, that energy may push an electron from that atom to a higher energy level where it can be picked up by an electron acceptor in the mitochondrial electron transport chain.

To allow electrons to move to higher orbit, the wavelength must be between 380 nm to 683 nm.



The Key Concept

Energy = (Planck's Constant) X (Frequency)

(Wavelength) X (Frequency) = 186,282 miles/second

Increase Wavelength *Must* Decrease Frequency
and
Therefore Decreases Energy

Decrease Wavelength *Must* Increase Frequency
and
Therefore Increases Energy

Shorter Wavelengths:	***Longer Wavelengths:***
Have *More* Energy	Have *Less* Energy
Have *Higher* Frequencies (Hertz)	Have *Lower* Frequencies (Hertz)
Do *Not* Penetrate as Deep	Penetrate Deeper
Do *Not* Generate Heat	Increase Molecular Motion and thus Generate Heat

The Electronvolt

The Electron Volt

Dan Murphy, DC

Photon energy is the energy carried by a *single* photon.

The *shorter* the photon's *wavelength* the *higher* the photon's *frequency*, and the *higher* its *energy*.

Absorption of high energy (shorter wavelengths, approximately 400-700 nm) photons results in elevation of electrons to higher energy levels (shells). **[photochemistry]**

Absorption of low energy (longer wavelengths, > 800 nm) photons results in absorption by water molecules, increased molecular vibration, and heat generation. **[photophysical]**

Lasers are a source of energetic photons.

Laser literature frequently measures laser energy in joules.

Photon energy can be expressed using any unit of energy; the unit commonly used to denote photon energy is the ***electronvolt (eV)***.

Joules are too large to appropriately measure the energy of photons.
(It would be like measuring your shoe size in miles).

Consequently, the preferred method for measuring the energy from a single photon by physicists and solid-state chemists is by using the *electron volt.*

Wavelengths below 400nm (like x-rays) have so much energy that they eject electrons away from atoms. This is called ionization, and it damages tissue, and can even cause cancer. This was first established in experiments by Albert Einstein.

Wavelengths between 400nm to 660nm have less energy, they do not eject electrons, they do not cause ionization, and do not damage tissue.

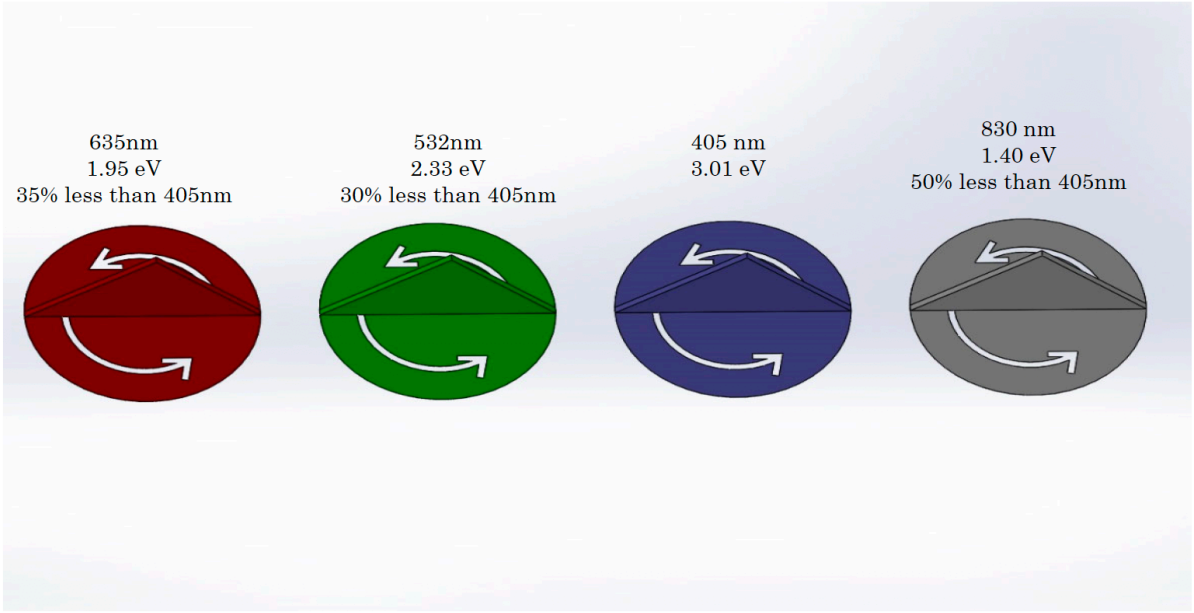
However, wavelengths between 400nm to 660nm have sufficient energy to displace electrons in atoms to a higher energy state (level). This is desirable because the higher energy level electron is now more available for donation, expediting the efficiency of ***all*** human physiological processes.

The electrons influenced by the laser will in turn influence adjacent electrons, creating the cascade of systemic influence that has been documented in laser physiology. This is known as the ***London Dispersion effect***.

Importantly, the brightness of the laser light (milliwatts / watts) is irrelevant.

Longer wavelengths (above 660nm) penetrate deeper, but at a cost of reduced electron volt ability to displace electrons to a higher energy state. Just because there is deeper penetration does not mean that it excites electrons to a higher energy level

Jcm2 for each circle would be the same but the energy per photon is vastly different



Photon Energy is measured in Electron Volt (eV)

The shorter the wavelength, the higher the Electron Volt (eV)

- 405nm = 3.06 eV
- 532nm = 2.33 eV
- 635nm = 1.95 eV
- 830nm = 1.49 eV

405 nm has 70% more energy per photon than 830nm

Ionization requires 10 eV to 1,000 eV

What does increasing power change?

- By adding power to the laser/LED more photons will be emitted.
- Changing the power does not change the energy (eV) of the photon.
- Increasing the power does not increase "depth of penetration"

Laser Basics

Laser
is
MONOCHROMATIC

This means it is of a single wavelength.

Background environmental light is a combination of all wavelengths.

Laser eliminates all wavelengths but one.

Laser
is
COHERENT

This means that the light is not scattered.

All of the light is brought to a single point.

An Overview of Laser Principle, Laser-Tissue Interaction Mechanisms and Laser Safety Precautions for Medical Laser Users

International Journal of Pharmacology
2011; Vol. 7; No. 2; pp 149-160

Laser can now be regarded as practical and economical tool with unique properties that has been utilized effectively in several applications.

Medical, dental, biological and various chemical and physical investigations use lasers due to their advantages. The medical laser systems offer the physician and the dentist not only a window, but also a door into this high technology which facilitate a lot of clinical and therapeutic applications.

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation.

The history of laser development should be traced as far back as 1917 when Albert Einstein showed that the process of stimulated emission must exist.

Coherence means the electromagnetic rays of light are in phase with each other. "Coherence is the most fundamental property of laser and distinguishes it from the light from other sources." "A laser may be defined as a source of coherent light."

Monochrome means that all the photons have the same wavelength.

- This contrasts greatly with a typical incandescent light bulb which emits wavelengths through the entire visible spectrum.

"**Wavelength** is the most important determinant in how light affects tissue."

- "Wavelength determines the quality of type of interaction between the laser and the tissue."

"In biological tissue, either water molecules or macromolecules such as proteins and pigments mainly cause absorption."

- "The absorption of infrared light can be attributed to water molecules."
- UV and visible light are absorbed by proteins and pigments.
- The absorbed portion of the laser radiation can produce ***photochemical*** (visible light) and/or ***photothermal*** (infrared wavelengths) effects.

Photothermal:

- "As the temperature is raised, the large, specially configured molecules necessary for life are shaken open."

- Most proteins, DNA, RNA, membranes and their integral structures start to unwind or melt at temperatures beginning at 40° C (104°F).

    - "The result is denaturation or loss of function."

Photochemical:

- "Photochemical reactions generally do not result in a significant rise in temperature."

- "Photochemical interaction mechanisms take place at very low power densities (typically, 1 W cm^2)."

- "In most cases, wavelengths in the visible range are used because of their high optical penetration depths."

- **Biostimulation** using light is a *photochemical effect*.

    - The *photochemical—biostimulation* process uses "low energy, low light, soft, cold laser and low intensity, low power therapy with the application of monochromatic red-light energy close to infrared wavelengths to stimulate growth factor cells and improve wound/soft tissue healing."

    - "To many scientists and clinicians, the idea is that low intensity light energy can promote and upgrade metabolic processes that result in tissue repair and pain relief which is unbelievable."

    - "Reports from almost every region of the world indicate that low intensity lasers promote the repair process of skin, tendons, ligaments, bone and cartilage in experimental animals as well as wounds from various etiologies in humans."

Dose-Response, 7:358–383, 2009
Formerly Nonlinearity in Biology, Toxicology, and Medicine
Copyright © 2009 University of Massachusetts
ISSN: 1559-3258
DOI: 10.2203/dose-response.09-027.Hamblin

International Dose-Response Society
www.Dose-Response.org

BIPHASIC DOSE RESPONSE IN LOW LEVEL LIGHT THERAPY

Ying-Ying Huang □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Aesthetic and Plastic Center of Guangxi Medical University, Nanning, P.R. China

Aaron C.-H. Chen □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Boston University School of Medicine, Graduate Medical Sciences, Boston, MA

James D. Carroll □ THOR Photomedicine Ltd, 18A East Street, Chesham, HP5 1HQ, UK

Michael R. Hamblin □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA

□ The use of low levels of visible or near infrared light for reducing pain, inflammation and edema, promoting healing of wounds, deeper tissues and nerves, and preventing cell death and tissue damage has been known for over forty years since the invention of lasers. Despite many reports of positive findings from experiments conducted in vitro, in animal models and in randomized controlled clinical trials, LLLT remains controversial in mainstream medicine. The biochemical mechanisms underlying the positive effects are incompletely understood, and the complexity of rationally choosing amongst a large number of illumination parameters such as wavelength, fluence, power density, pulse structure and treatment timing has led to the publication of a number of negative studies as well as many positive ones. A biphasic dose response has been frequently observed where low levels of light have a much better effect on stimulating and repairing tissues than higher levels of light. The so-called Arndt-Schulz curve is frequently used to describe this biphasic dose response. This review will cover the molecular and cellular mechanisms in LLLT, and describe some of our recent results in vitro and in vivo that provide scientific explanations for this biphasic dose response.

1. INTRODUCTION

1.1. Brief history

Low level laser therapy (LLLT) is the application of light (usually a low power laser or LED in the range of 1mW – 500mW) to a pathology to promote tissue regeneration, reduce inflammation and relieve pain. The light is typically of narrow spectral width in the red or near infrared

Address correspondence to Professor Michael R. Hamblin, BAR 414, Wellman Center for Photomedicine, Massachusetts General Hospital, 40 Blossom Street, Boston, MA 02114; Phone: 617-726-6182, Fax: 617-726-8566, E-mail: hamblin@helix.mgh.harvard.edu

(NIR) spectrum (600nm – 1000nm), with a power density (irradiance) between 1mw-5W/cm^2. It is typically applied to the injury for a minute or so, a few times a week for several weeks. Unlike other medical laser procedures, LLLT is not an ablative or thermal mechanism, but rather a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change.

The phenomenon was first published by Endre Mester at Semmelweis University, Budapest, Hungary in 1967 a few years after the first working laser was invented (Mester *et al.* 1967). Mester conducted an experiment to test if laser radiation might cause cancer in mice. He shaved the hair off their backs, divided them into two groups and irradiated one group with a low powered ruby laser (694-nm). The treatment group did not get cancer and to his surprise, the hair grew back more quickly than the untreated group. He called this "Laser Biostimulation".

1.2. Evidence for effectiveness of LLLT

Since 1967 over 100 phase III, randomized, double-blind, placebo-controlled, clinical trials (RCTs) have been published and supported by over 1,000 laboratory studies investigating the primary mechanisms and the cascade of secondary effects that contribute to a range of local tissue and systemic effects.

RCTs with positive outcomes have been published on pathologies as diverse as osteoarthritis (Bertolucci and Grey 1995; Ozdemir *et al.* 2001; Stelian *et al.* 1992), tendonopathies (Bjordal *et al.* 2006b; Stergioulas *et al.* 2008; Vasseljen *et al.* 1992), wounds (Caetano *et al.* 2009; Gupta *et al.* 1998; Ozcelik *et al.* 2008; Schubert *et al.* 2007), back pain (Basford *et al.* 1999), neck pain (Chow *et al.* 2006; Gur *et al.* 2004), muscle fatigue (Leal Junior *et al.* 2008a; Leal Junior *et al.* 2008b), peripheral nerve injuries (Rochkind *et al.* 2007) and strokes (Lampl *et al.* 2007; Zivin *et al.* 2009); nevertheless results have not always been positive. This failure in certain circumstances can be attributed to several factors including dosimetry (inadequate or too much energy delivered, inadequate or too much irradiance, inappropriate pulse structure, irradiation of insufficient area of the pathology), inappropriate anatomical treatment location and concurrent patient medication (such as steroidal and non-steroidal anti-inflammatories which can inhibit healing) (Aimbire *et al.* 2006; Goncalves *et al.* 2007).

1.3. The medicine and the dose

As with other forms of medication, LLLT has its active ingredients or "medicine" (irradiation parameters) and a "dose" (the irradiation time). Table 1 lists the key parameters that define the medicine and Table 2 defines the dose. It is beyond the scope of this paper to exhaustively list and discuss every conceivable aspect of laser radiation or other light

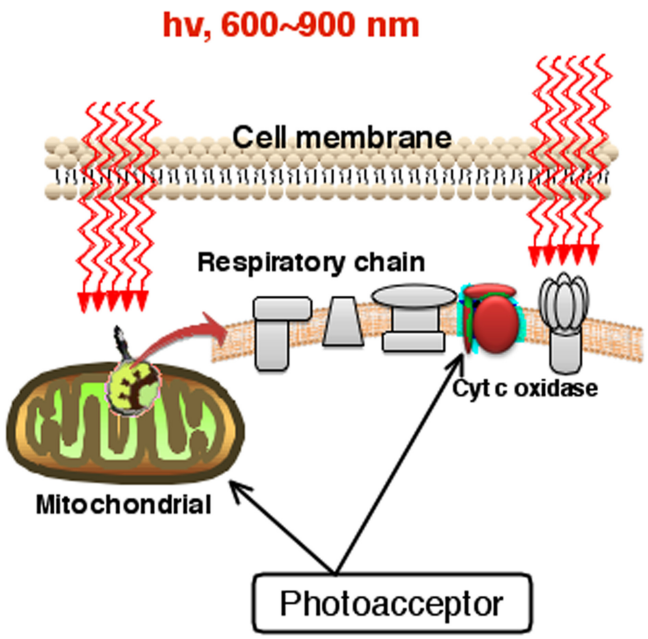


FIGURE 1. Schematic diagram showing the absorption of red and NIR light by specific cellular chromophores or photoacceptors localized in the mitochondrial respiratory chain

tissue penetration of light is maximized. This optical window runs approximately from 650 nm to 1200 nm. (Figure 2). The absorption and scattering of light in tissue are both much higher in the blue region of the spectrum than the red, because the principle tissue chromophores (hemoglobin and melanin) have high absorption bands at shorter wavelengths, tissue scattering of light is higher at shorter wavelengths, and furthermore water strongly absorbs infrared light at wavelengths greater than 1100-nm. Therefore the use of LLLT in animals and patients almost exclusively involves red and near-infrared light (600-1100-nm) (Karu and Afanas'eva 1995).

Phototherapy is characterized by its ability to induce photobiological processes in cells. Exact action spectra are needed for determination of photoacceptors as well as for further investigations into cellular mechanisms of phototherapy. The action spectrum shows which specific wavelength of light is most effectively used in a specific chemical reaction (Karu and Kolyakov 2005). The fact that defined action spectra can be constructed for various cellular responses confirms the first law of photobiology described above (light absorption by specific molecular chromophores).

2.3. Mitochondrial Respiration and ATP

Current research about the mechanism of LLLT effects inevitably involves mitochondria. Mitochondria play an important role in energy generation and metabolism. Mitochondria are sometimes described as

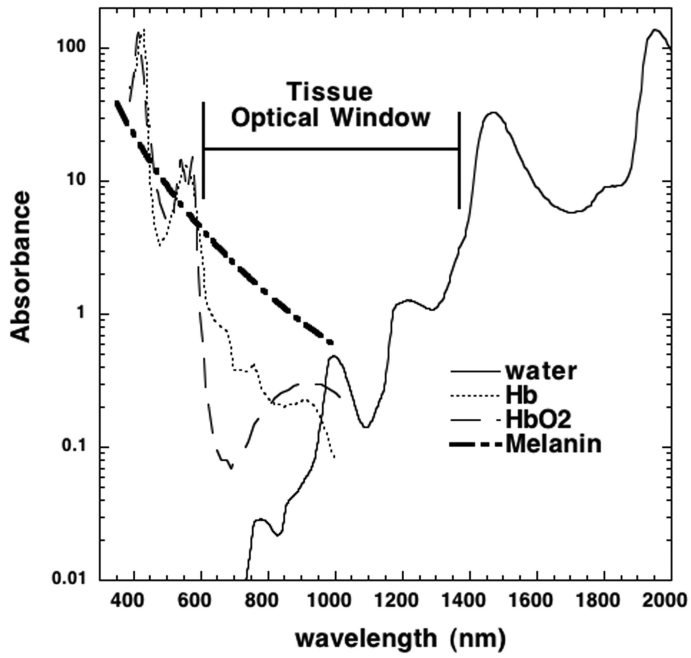


FIGURE 2. Absorption spectra of the main chromophores in living tissue on a log scale showing the optical window where visible and NIR light can penetrate deepest into tissue.

"cellular power plants", because they convert food molecules into energy in the form of ATP via the process of oxidative phosphorylation (see Figure 3 for an illustartion of the mitochondrial respiratory chain).

The mechanism of LLLT at the cellular level has been attributed to the absorption of monochromatic visible and NIR radiation by components of the cellular respiratory chain (Karu 1989). Several pieces of evidence suggest that mitochondria are responsible for the cellular response to red visible and NIR light. The effects of HeNe laser and other illumination on mitochondria isolated from rat liver, have included increased proton electrochemical potential, more ATP synthesis (Passarella *et al.* 1984), increased RNA and protein synthesis (Greco *et al.* 1989) and increases in oxygen consumption, membrane potential, and enhanced synthesis of NADH and ATP.

2.4. Cytochrome c oxidase and nitric oxide release

Absorption spectra obtained for cytochrome c oxidase (Cox) in different oxidation states were recorded and found to be very similar to the action spectra for biological responses to light (Karu and Kolyakov 2005). Therefore it was proposed that Cox is the primary photoacceptor for the red-NIR range in mammalian cells (Karu and Kolyakov 2005).

Nitric oxide produced in the mitochondria can inhibit respiration by binding to Cox and competitively displacing oxygen, especially in stressed

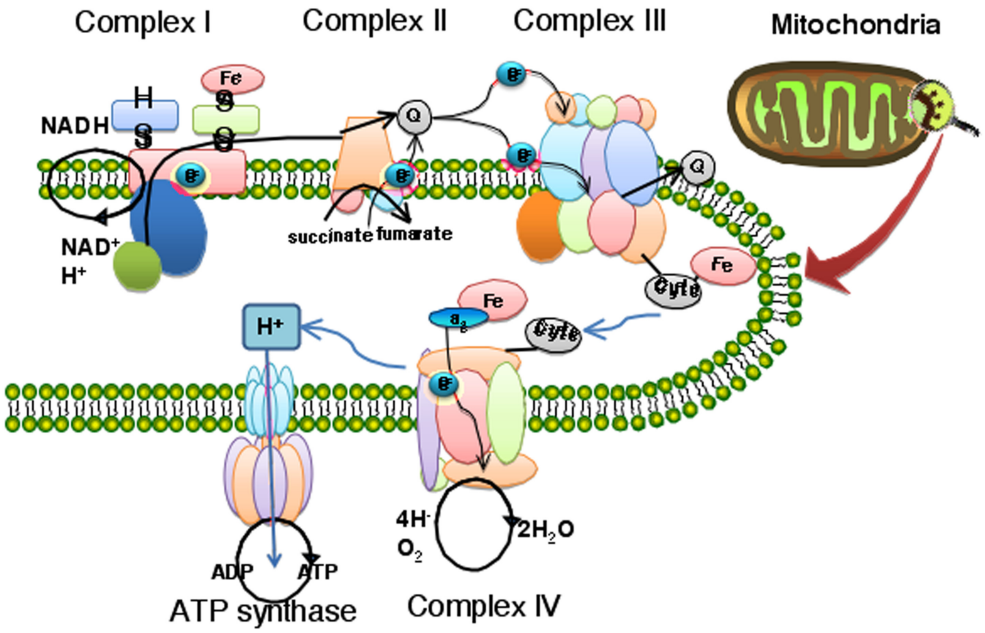


FIGURE 3. Mitochondrial respiratory chain consisting of contains five complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), cytochrome c oxidase (Complex IV), and ATP synthase (ComplexV).

or hypoxic cells (Brown 2001). Increased nitric oxide (NO) concentrations can sometimes be measured in cell culture or in animals after LLLT due to its photo release from the mitochondria and Cox. It has been proposed that LLLT might work by photodissociating NO from Cox, thereby reversing the mitochondrial inhibition of respiration due to excessive NO binding (Lane 2006). Figure 4 illustrates the photodissociation of NO from its binding sites on the heme iron and copper centers where it cometively inhibits oxygen binding and reduces necessary enzymic activity, thus allowing an immediate influx of oxygen and resumption of respiration and generation of reactive oxygen species.

2.5. NO signaling

In addition to NO being photodissociated from Cox as described, it may also be photo-released from other intracellular stores such as nitrosylated hemoglobin and nitrosylated myoglobin (Shiva and Gladwin 2009). Light mediated vasodilation was first described in 1968 by R F Furchgott, in his nitric oxide research that lead to his receipt of a Nobel Prize thirty years later in 1998 (Mitka 1998). Later studies conducted by other researchers confirmed and extended Furchgott's early work and demonstrated the ability of light to influence the localized production or release of NO and stimulate vasodilation through the effect NO on cyclic guanine

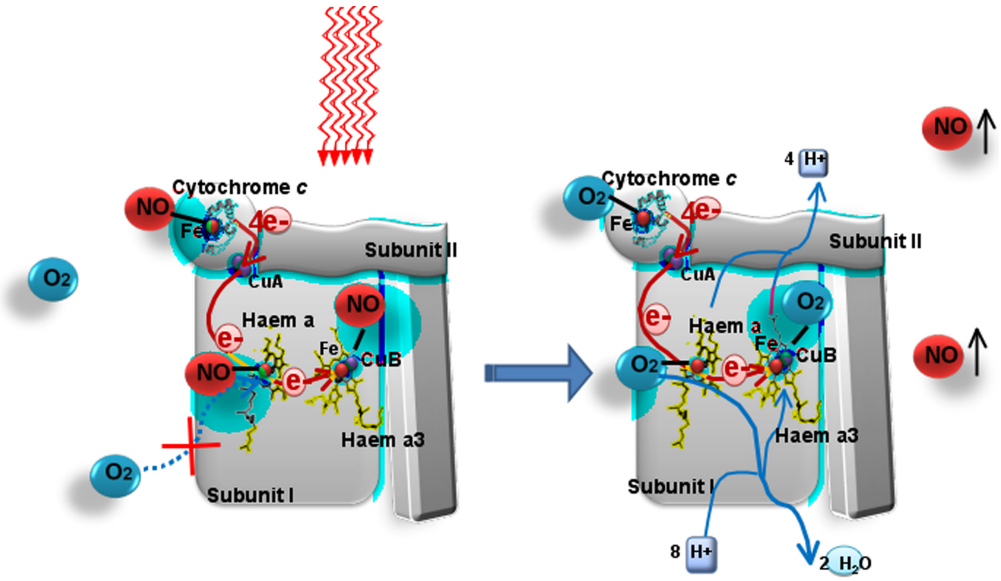


FIGURE 4. When NO is released from its binding to heme iron and copper centers in cytochrome c oxidase by the action of light, oxygen is allowed to rebind to these sites and respiration is restored to its former level leading to increased ATP synthesis.

monophosphate (cGMP). This finding suggested that properly designed illumination devices may be effective, noninvasive therapeutic agents for patients who would benefit from increased localized NO availability

2.6. Reactive oxygen species and gene transcription

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are involved in the signaling pathways from mitochondria to nuclei. Reactive oxygen species (ROS) are very small molecules that include oxygen ions such as superoxide, free radicals such as hydroxyl radical, and hydrogen peroxide, and organic peroxides. They are highly with biological molecules such as proteins, nucleic acids and unsaturated lipids. ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling (Storz 2007), regulating nucleic acid synthesis, protein synthesis, enzyme activation and cell cycle progression (Brondon *et al.* 2005). LLLT was reported to produce a shift in overall cell redox potential in the direction of greater oxidation (Karu 1999) and increased ROS generation and cell redox activity have been demonstrated (Alexandratou *et al.* 2002; Chen *et al.* 2009b; Grossman *et al.* 1998; Lavi *et al.* 2003; Lubart *et al.* 2005; Pal *et al.* 2007; Zhang *et al.* 2008). These cytosolic responses may in turn induce transcriptional changes. Several transcription factors are regulated by changes in cellular redox state. But the most important one is nuclear factor B (NF-B). Figure 5 illustrates the effect of redox-sensitive transcription factor NF-κB

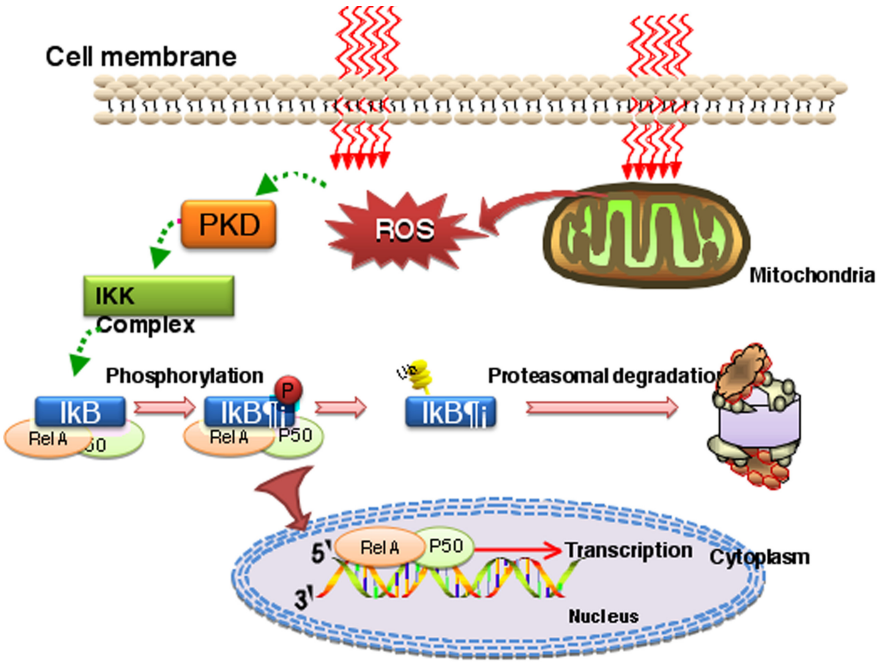


FIGURE 5. Reactive oxygen species (ROS) formed as a result of LLLT effects in mitochondria may activate the redox-sensitive transcription factor NF-κB (relA-p50) via protein kinase D (PKD).

activated after LLLT and is instrumental in causing transcription of protective and stimulatory gene products.

2.7. Downstream cellular response

Although the underlying mechanism of LLLT are still not completely understood, in vitro studies, animal experiments and clinical studies have all tended to indicate that LLLT delivered at low doses may produce a better result when compared to the same light delivered at high doses. LLLT can prevent cell apoptosis and improve cell proliferation, migration and adhesion at low levels of red/NIR light illumination (see Figure 6).

LLLT at low doses has been shown to enhance cell proliferation in vitro in several types of cells: fibroblasts (Lubart *et al.* 1992; Yu *et al.* 1994), keratinocytes (Grossman *et al.* 1998), endothelial cells (Moore *et al.* 2005), and lymphocytes (Agaiby *et al.* 2000; Stadler *et al.* 2000). The mechanism of proliferation was proposed to involve photostimulatory effects in mitochondria processes, which enhanced growth factor release, and ultimately led to cell proliferation (Bjordal *et al.* 2007). Kreisler et al showed (Kreisler *et al.* 2003) that the attachment and proliferation of human gingival fibroblasts were enhanced by LLLT in a dose-dependent manner. LLLT modulated matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells (Gavish *et al.* 2006). Shefer at el. showed (Shefer *et al.* 2002) that LLLT could activate skeletal

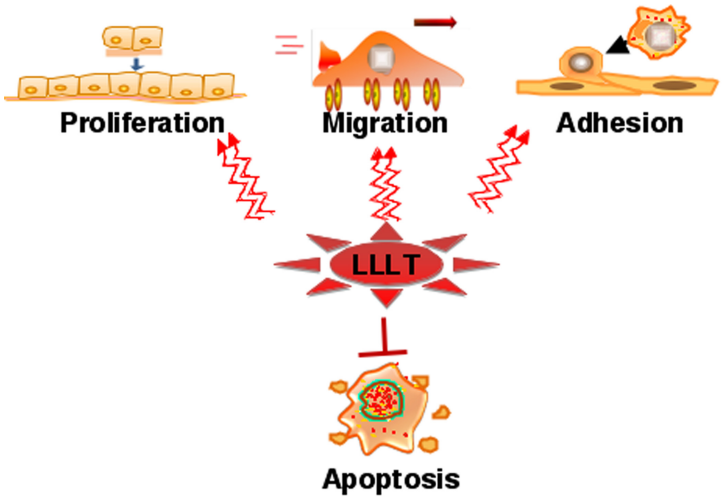


FIGURE 6. The downstream cellular effects of LLLT signaling include increases in cell proliferation, migration and adhesion molecules. Cell survival is increased and cell death reduced by expression of proteins that inhibit apoptosis.

muscle satellite cells, enhancing their proliferation, inhibiting differentiation and regulating protein synthesis.

2.8. Downstream tissue response

There have been a large number of both animal model and clinical studies that demonstrated highly beneficial LLLT effects on a variety of diseases, injuries, and has been widely used in both chronic and acute conditions (see Figure 7). LLLT may enhance neovascularisation, promote angiogenesis and increase collagen synthesis to promote healing of acute (Hopkins *et al.* 2004) and chronic wounds (Yu *et al.* 1997). LLLT provided acceleration of cutaneous wound healing in rats with a biphasic dose response favoring lower doses (Corazza *et al.* 2007). LLLT can also stimulate healing of deeper structures such as nerves (Gigo-Benato *et al.* 2004), tendons (Fillipin *et al.* 2005), cartilage (Morrone *et al.* 2000), bones (Weber *et al.* 2006) and even internal organs (Shao *et al.* 2005). LLLT can reduce pain (Bjordal *et al.* 2006a), inflammation (Bjordal *et al.* 2006b) and swelling (Carati *et al.* 2003) caused by injuries, degenerative diseases or autoimmune diseases. Oron reported beneficial effect of LLLT on repair processes after injury or ischemia in skeletal and heart muscles in multiple animal models in vivo (Ad and Oron 2001; Oron *et al.* 2001a; Oron *et al.* 2001b; Yaakobi *et al.* 2001). LLLT has been used to mitigate damage after strokes (in both animals (Lapchak *et al.* 2008) and humans (Lampl *et al.* 2007)), after traumatic brain injury (Oron *et al.* 2007) and after spinal cord injury (Wu *et al.* 2009).

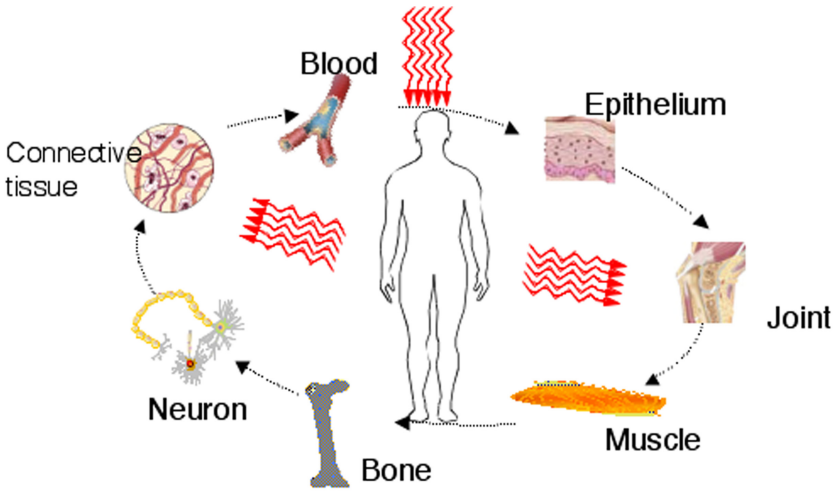


FIGURE 7. Beneficial tissue effects of LLLT can include almost all the tissues and organs of the body.

3. REVIEW OF BIPHASIC DOSE RESPONSES IN LLLT

3.1. Dose dependence and dose rate effects—the biphasic curve

A biphasic response has been demonstrated many times in LLLT research (Lanzafame *et al.* 2007; Oron *et al.* 2001a) and the "Arndt-Schulz Law" is frequently quoted as a suitable model to describe dose dependent effects of LLLT (Chow *et al.* 2006; Hawkins and Abrahamse 2006a; Hawkins and Abrahamse 2006b; Lubart *et al.* 2006; Sommer *et al.* 2001). The concept of the Arndt-Schulz Law dates from the years around the end of the nineteenth century, when H. Schulz published a series of papers that examined the activity of various kinds of poisons (iodine, bromine, mercuric chloride, arsenious acid, etc.) on yeast, showing that almost all these agents have a slightly stimulatory effect on the yeast metabolism when given in low doses (Schulz 1877; Schulz 1888). He then came into contact with the psychiatrist R. Arndt and together they developed a principle that later became known as the 'Arndt-Schulz law', stating that weak stimuli slightly accelerate vital activity, stronger stimuli raise it further, but a peak is reached and even stronger stimuli suppress it, until a negative response is finally achieved (Martius 1923). In 1960 Townsend and Luckey surveyed the field of classic medical pharmacology and published a list of 100 substances known to be capable of causing an inhibition at high concentrations and stimulation at low concentrations and termed the phenomenon "hormoligosis" (Townsend and Luckey 1960). The modern term "hormesis" was first used by Stebbing in 1982 (Stebbing 1982) and has been thoroughly reviewed by Calabrese (Calabrese 2001b; Calabrese 2002; Calabrese 2004a; Calabrese 2004b; Calabrese 2005).

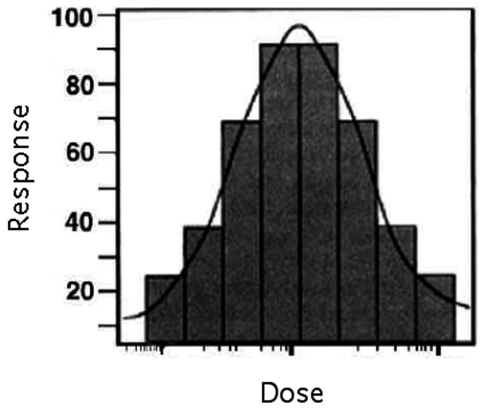


FIGURE 8. Idealized biphasic dose response curve (often termed Arndt-Schulz curve) typically reported in LLLT studies.

In the context of LLLT the increasing "stimulus" may be irradiation time or increased irradiance. This non-linear effect contradicts the Bunsen-Roscoe rule of reciprocity (which was originally formulated for visual detection of light by photoreceptors (Brindley 1952)), which predicts that if the products of exposure time in seconds and irradiance in mW/cm^2 are equal, i.e. the energy density is the same, then the changes in biological endpoint will be equal. This inverse linear relationship between irradiance and time has frequently failed in LLLT research (Karu and Kolyakov 2005; Lubart *et al.* 2006).

A "biphasic" curve can be used to illustrate the expected dose response to light at a subcellular, cellular, tissue or clinical level. Simply put, it suggests that if insufficient energy is applied there will be no response (because the minimum threshold has not been met), if more energy is applied the then a threshold is crossed and biostimulation is achieved but when too much energy is applied then the stimulation disappears and is replaced by bioinhibition instead. An idealized illustration (Figure 8) similar to that suggested by Sommer (Sommer *et al.* 2001) helps understand the concept.

3.2. Biphasic Response—irradiance

As early as 1978 Endre Mester observed a "threshold phenomenon" after laser irradiation of lymphocytes in vitro (Mester *et al.* 1978). Peter Bolton in 1991 irradiating macrophages with two different irradiances (W/cm^2) but the same energy density (J/cm^2) recorded different results (Bolton *et al.* 1991). Karu (Karu and Kolyakov 2005) found a dependence of stimulation of DNA synthesis rate on light intensity at a constant energy density 0.1 J/cm^2 with a clear maximum at 0.8 mW/cm^2. In another study (Karu *et al.* 1997) the same group found no less than seven maxima in the dose vs. biological effect curves using a pulsed 810-nm diode laser.

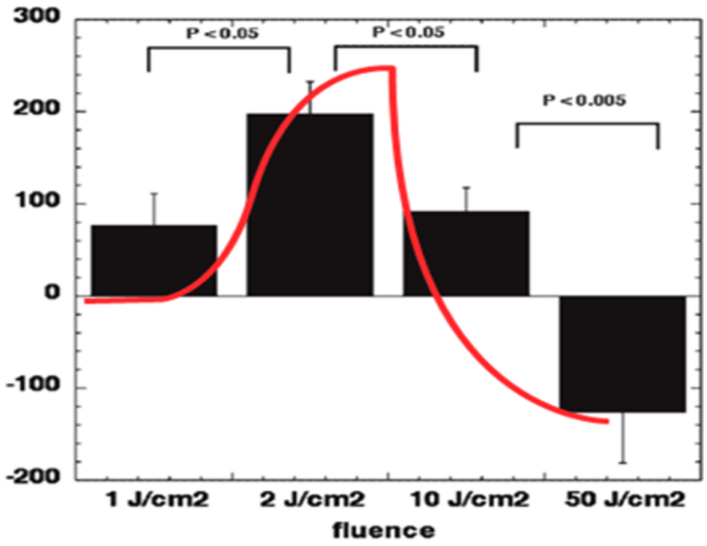


FIGURE 11. Biphasic dose response in measured difference in integrated area under the curve of time course of wound size compared to no treatment control, with a clear maximum seen at 2 J/cm^2, and the high dose of 50 J/cm^2 gave a worsening of the wound healing time curve.

sic dose response with positive effects (difference in integrated area under the curve of time course of wound size compared to no treatment control) seen in low doses with a clear maximum seen at 2 J/cm^2, and the high dose of 50 J/cm^2 actually gave a worsening of the wound healing time curve i.e. there was a greater expansion of the wound compared with non-treated controls.

4.3. Rat arthritis

In another in vivo study (Castano *et al.* 2007) we investigated whether LLLT using an 810-nm laser could have a therapeutic effect in a rat model of inflammatory arthritis caused by zymosan injected into their knee joints. In this model the severity of the arthritis is quantified by measuring the diameter of the swollen joint every day and plotting a time course for each joint. We compared illumination regimens consisting of a high and low fluence (3 and 30 J/cm^2), delivered at high and low irradiance (5 and 50 mW/cm^2) using 810-nm laser light daily for 5 days, with the positive control of conventional corticosteroid (dexamethasone) therapy.

As shown in Figure 12 three of the illumination regimens were effective in reducing the mean integrated knee swelling almost as much as the positive control of the powerful steroid, dexamathasone; these were 3 J/cm^2 delivered at 5 mW/cm^2 and 30 J/cm^2 delivered at 50 mW/cm^2 both of which took 10 minutes, and 30 J/cm^2 delivered at 5 mW/cm^2 which took 100 minutes. The only ineffective dose regimen was 3 J/cm^2

ROS mediated activation of NF-κB in MEF cells presented in 4.1 provides additional support for this hypothesis (Chen *et al.* 2009a). It is well-accepted that ROS can have both beneficial and harmful effects (Huang and Zheng 2006). Hydrogen peroxide is often used to kill cells in vitro (Imlay 2008). Other ROS such as singlet oxygen (Klotz *et al.* 2003) and hydroxyl radicals (Pryor *et al.* 2006) are thought to be harmful even at low concentrations. The concept of biphasic dose response in fact is well established in the field of oxidative stress (Day and Suzuki 2005). If the generation of ROS can be shown to be dose dependent on the delivered energy fluence this may provide an explanation for the stimulation and inhibition observed with low and high light fluences.

5.2. Excessive NO

The other mechanistic hypothesis that is put forward to explain the cellular effects of LLLT relates to the photolysis of nitrosylated proteins that releases free NO (see section 2.6). Again the literature has many papers that discuss the so-called two-faced or "Janus" molecule NO (Anggard 1994; Lane and Gross 1999). NO can be either protective or harmful depending on the dose and particularly on the cell or tissue type where it is generated (Calabrese 2001a).

5.3. Activation of a cytotoxic pathway

The third hypothesis to explain the biphasic dose response of LLLT is the idea that the protective and stimulatory effects of light occur at low doses, but there is an additional pathway that leads to damaging effects of light that only occurs at high doses, and effectively overwhelms the beneficial effects of low doses of light. Work from South China Normal University provides some support for this hypothesis. Low doses of LLLT were found to phosphorylate hepatocyte growth factor receptor (c-Met), and initiate signaling via cyclic AMP and Jun kinase and Src (Gao and Xing 2009). By contrast, high dose LLLT was found to induce apoptosis via a mitochondrial caspase-3 pathway and cytochrome c release was attributed to opening of the mitochondrial permeability transition pore caused by high-level intracellular reactive oxygen species (ROS) generation (Wu *et al.* 2009). A secondary signaling pathway through Bax activation was observed (Wu *et al.* 2009).

6. SUMMARY AND CONCLUSION

LLLT delivered at low doses tends to work better than the same wavelength delivered at high levels, which illustrates the basic concept of biphasic dose response or hormesis (Calabrese 2001b). In general, fluences of red or NIR as low as 3 or 5 J/cm^2 will be beneficial in vivo, but a large dose

like 50 or 100 J/cm^2 will lose the beneficial effect and may even become detrimental. The molecular and cellular mechanisms LLLT suggest that photons are absorbed by the mitochondria; they stimulate more ATP production and low levels of ROS, which then activates transcription factors, such as NF-κB, to induce many gene transcript products responsible for the beneficial effects of LLLT. ROS are well known to stimulate cellular proliferation of low levels, but inhibit proliferation and kill cells at high levels. Nitric oxide is also involved in LLLT, and may be photo-released from its binding sites in the respiratory chain and elsewhere. It is possible that NO release in low amounts by low dose light may be beneficial, while high levels released by high dose LLLT may be damaging. The third possibility is that LLLT may activate transcription factors, upregulating protective proteins which are anti-apoptotic, and generally promote cell survival. In contrast, it is entirely possible that different transcription factors and cell-signaling pathways, that promote apoptosis, could be activated after higher light exposure. We believe that further advances in the mechanistic understanding of LLLT will continue to be made in the near future. These advances will lead to greater acceptance of LLLT in mainstream medicine and may lead to LLLT being used for serious diseases such as stroke, heart attack and degenerative brain diseases. Nevertheless the concept of biphasic dose response or LLLT hormesis (low levels of light are good for you, while high levels are bad for you) will remain.

ACKNOWLEDGMENTS

Research in the Hamblin laboratory is supported by the US NIH (grants R01CA/AI838801 and R01AI050875 to MRH).

REFERENCES

Ad N and Oron U. 2001. Impact of low level laser irradiation on infarct size in the rat following myocardial infarction. Int J Cardiol 80:109-16.

Agaiby AD, Ghali LR, Wilson R, and Dyson M. 2000. Laser modulation of angiogenic factor production by T-lymphocytes. Lasers Surg Med 26:357-63.

Aimbire F, Albertini R, Pacheco MT, Castro-Faria-Neto HC, Leonardo PS, Iversen VV, Lopes-Martins RA, and Bjordal JM. 2006. Low-level laser therapy induces dose-dependent reduction of TNFalpha levels in acute inflammation. Photomed Laser Surg 24:33-7.

al-Watban FA and Andres BL. 2001. The effect of He-Ne laser (632.8 nm) and Solcoseryl in vitro. Lasers Med Sci 16:267-75.

Alexandratou E, Yova D, Handris P, Kletsas D, and Loukas S. 2002. Human fibroblast alterations induced by low power laser irradiation at the single cell level using confocal microscopy. Photochem Photobiol Sci 1:547-52.

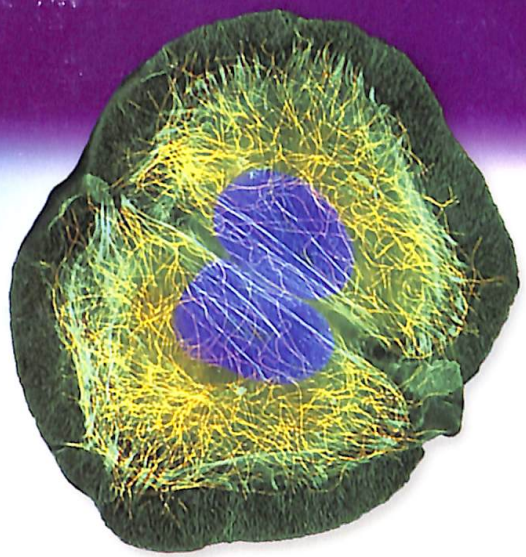
Anders J, Romanczyk T, Moges H, Ilev I, Waynant R, and Longo L. 2007. Light Interaction With Human Central Nervous System Progenitor Cells. NAALT conference proceedings. 2007

Anggard E. 1994. Nitric oxide: mediator, murderer, and medicine. Lancet 343:1199-206.

Basford JR, Sheffield CG, and Harmsen WS. 1999. Laser therapy: a randomized, controlled trial of the effects of low-intensity Nd:YAG laser irradiation on musculoskeletal back pain. Arch Phys Med Rehabil 80:647-52.

Bertolucci LE and Grey T. 1995. Clinical analysis of mid-laser versus placebo treatment of arthralgic TMJ degenerative joints. Cranio 13:26-9.

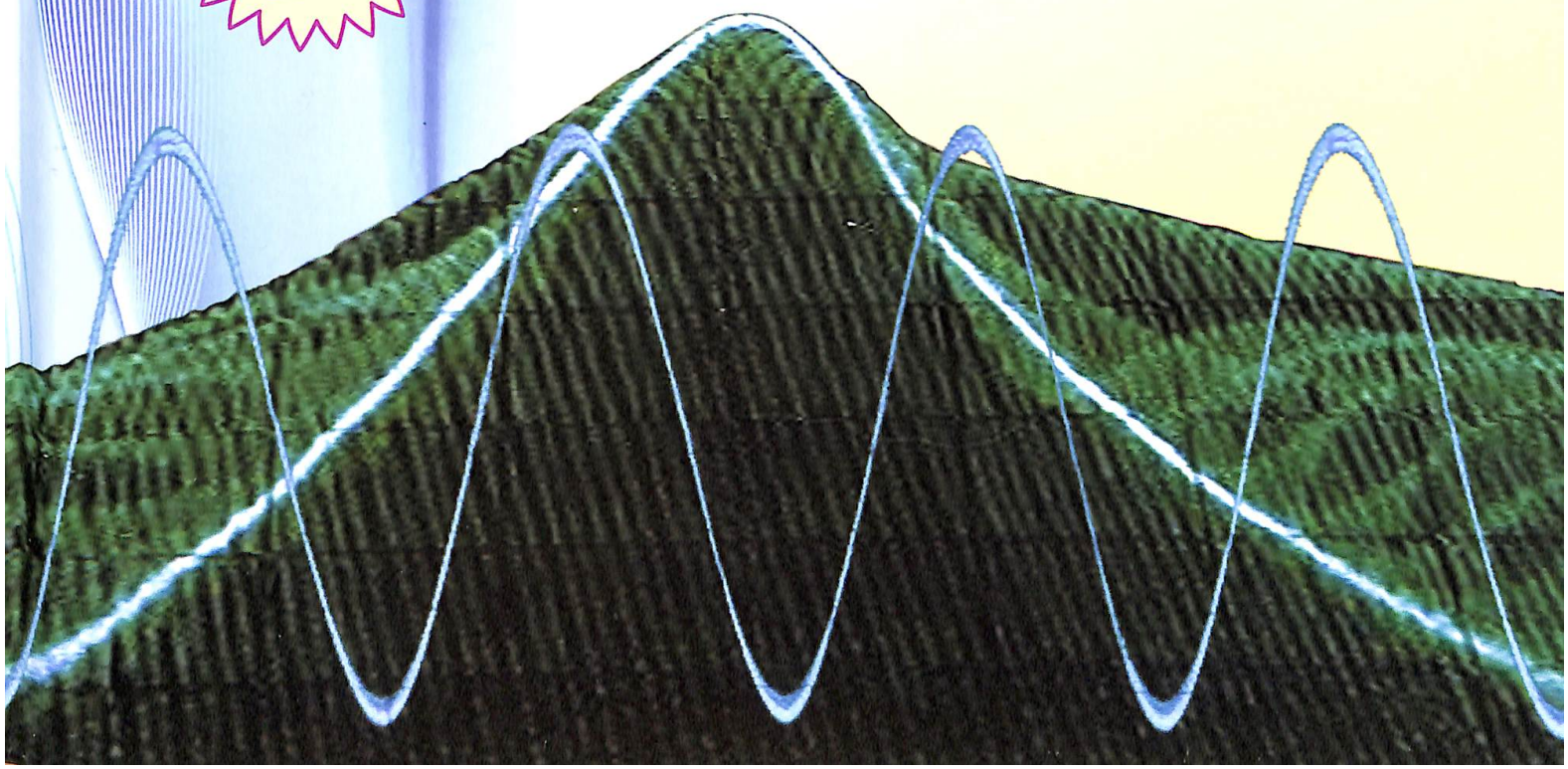
Nenah Sylver, PhD



The Rife Handbook

of Frequency Therapy and Holistic Health

REVISED 2011 EDITION



PERFORMANCE
CHIROPRACTIC & WELLNESS

The Complete

Erchonia EVRL, GVL & Base Station

A-Z Protocol Manual

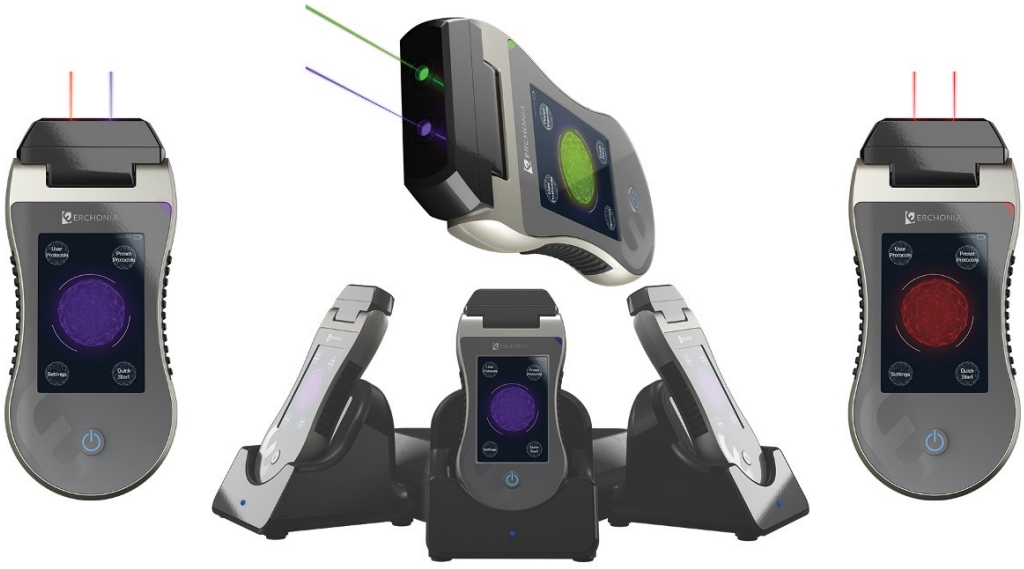
for

Low Level Laser Therapy

By

Jerome Rerucha D.C., B.S., C.S.C.S., C.H.P.S.

Certified Human Performance Specialist (C.H.P.S.)®



performancepractic.com

PubMed

Format: Abstract

Altern Ther Health Med. 2017 Oct 2. pii: AT5647. [Epub ahead of print]

Review of Literature on Low-level Laser Therapy Benefits for Nonpharmacological Pain Control in Chronic Pain and Osteoarthritis.

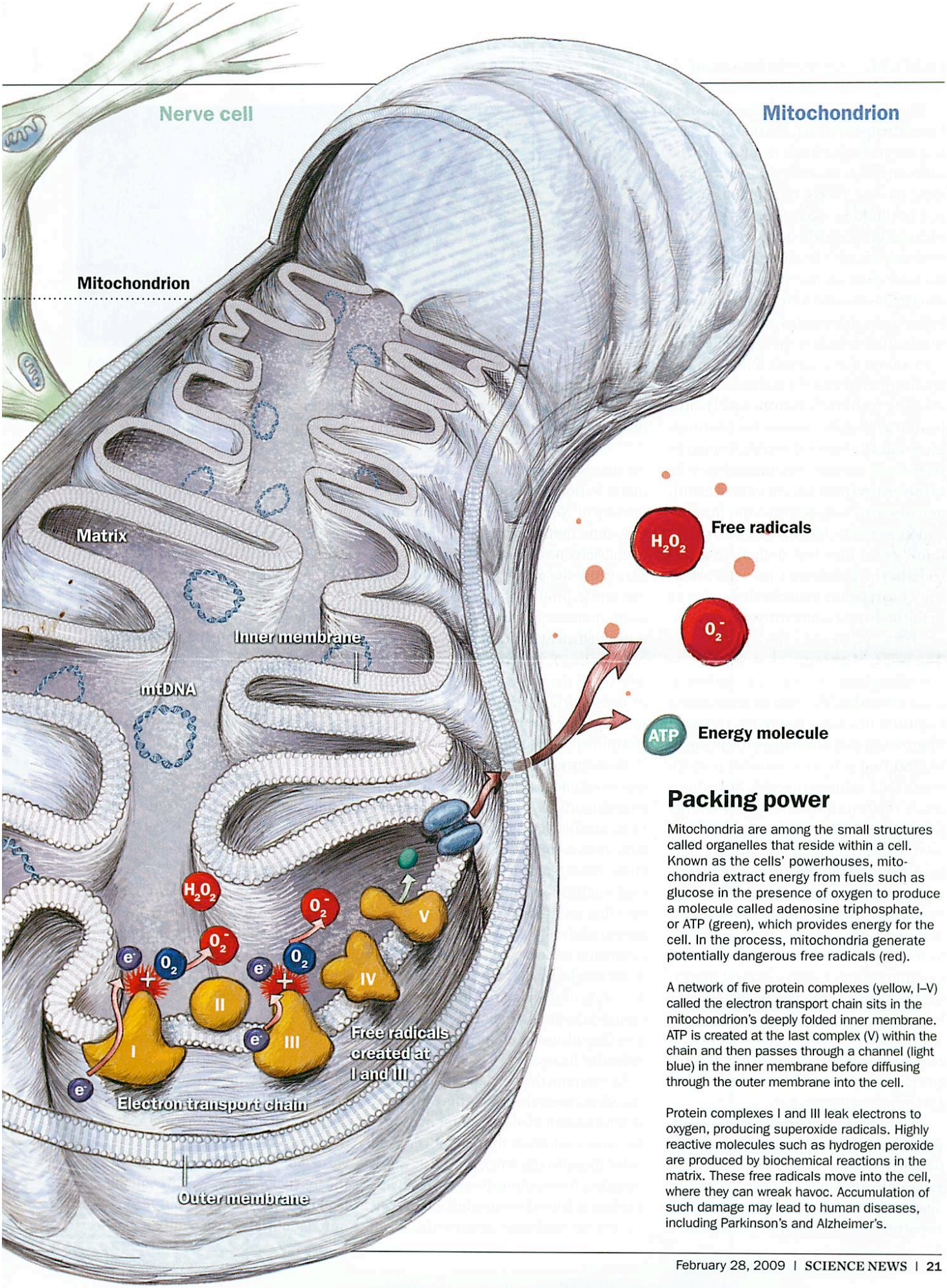
Dima R, Tieppo Francio V, Towery C, Davani S.

Abstract

Introduction • Low-level **laser** therapy (LLLT) is a form of light therapy that triggers biochemical changes within cells. Photons are absorbed by cellular photoreceptors, triggering chemical alterations and potential biochemical benefits to the human body. LLLT has been used in pain management for years and is also known as cold **laser** therapy, which uses low-frequency continuous **laser** of typically 600 to 1000 nm wavelength for pain reduction and healing stimulation. Many studies have demonstrated analgesic and anti-inflammatory effects provided by photobiomodulation in both experimental and clinical trials. Objective • The purpose of this research article was to present a summary of the possible pain management benefits of LLLT. Results • In cold **laser** therapy, coherent light of wavelength 600 to 1000 nm is applied to an area of concern with hope for photo-stimulating the tissues in a way that promotes and accelerates healing. This is evidenced by the similarity in absorption spectra between oxidized **cytochrome c oxidase** and action spectra from biological responses to light. LLLT, using the properties of coherent light, has been seen to produce pain relief and fibroblastic regeneration in clinical trials and laboratory experiments. LLLT has also been seen to significantly reduce pain in the acute setting; it is proposed that LLLT is able to reduce pain by lowering the level of biochemical markers and oxidative stress, and the formation of edema and hemorrhage. Many studies have demonstrated analgesic and anti-inflammatory effects provided by photobiomodulation in both experimental and clinical trials. Conclusion • Based on current research, the utilization of LLLT for pain management and osteoarthritic conditions may be a complementary strategy used in clinical practice to provide symptom management for patients suffering from osteoarthritis and chronic pain.

PMID: 28987080

Mitochondria



Packing power

Mitochondria are among the small structures called organelles that reside within a cell. Known as the cells' powerhouses, mitochondria extract energy from fuels such as glucose in the presence of oxygen to produce a molecule called adenosine triphosphate, or ATP (green), which provides energy for the cell. In the process, mitochondria generate potentially dangerous free radicals (red).

A network of five protein complexes (yellow, I–V) called the electron transport chain sits in the mitochondrion's deeply folded inner membrane. ATP is created at the last complex (V) within the chain and then passes through a channel (light blue) in the inner membrane before diffusing through the outer membrane into the cell.

Protein complexes I and III leak electrons to oxygen, producing superoxide radicals. Highly reactive molecules such as hydrogen peroxide are produced by biochemical reactions in the matrix. These free radicals move into the cell, where they can wreak havoc. Accumulation of such damage may lead to human diseases, including Parkinson's and Alzheimer's.

Mitochondria Gone Bad
Problems in the cell's energy factories power new ideas on disease and aging

Laura Bell
Science News
February 28, 2009

"Mitochondria might even be the biological epicenter of aging itself."

"Mitochondrial metabolism is the key to aging."

"People are only as young as their mitochondria."

Anna Gvozdjáková
Editor

Mitochondrial Medicine

Mitochondrial Metabolism, Diseases, Diagnosis and Therapy

Springer

LEE KNOW, ND

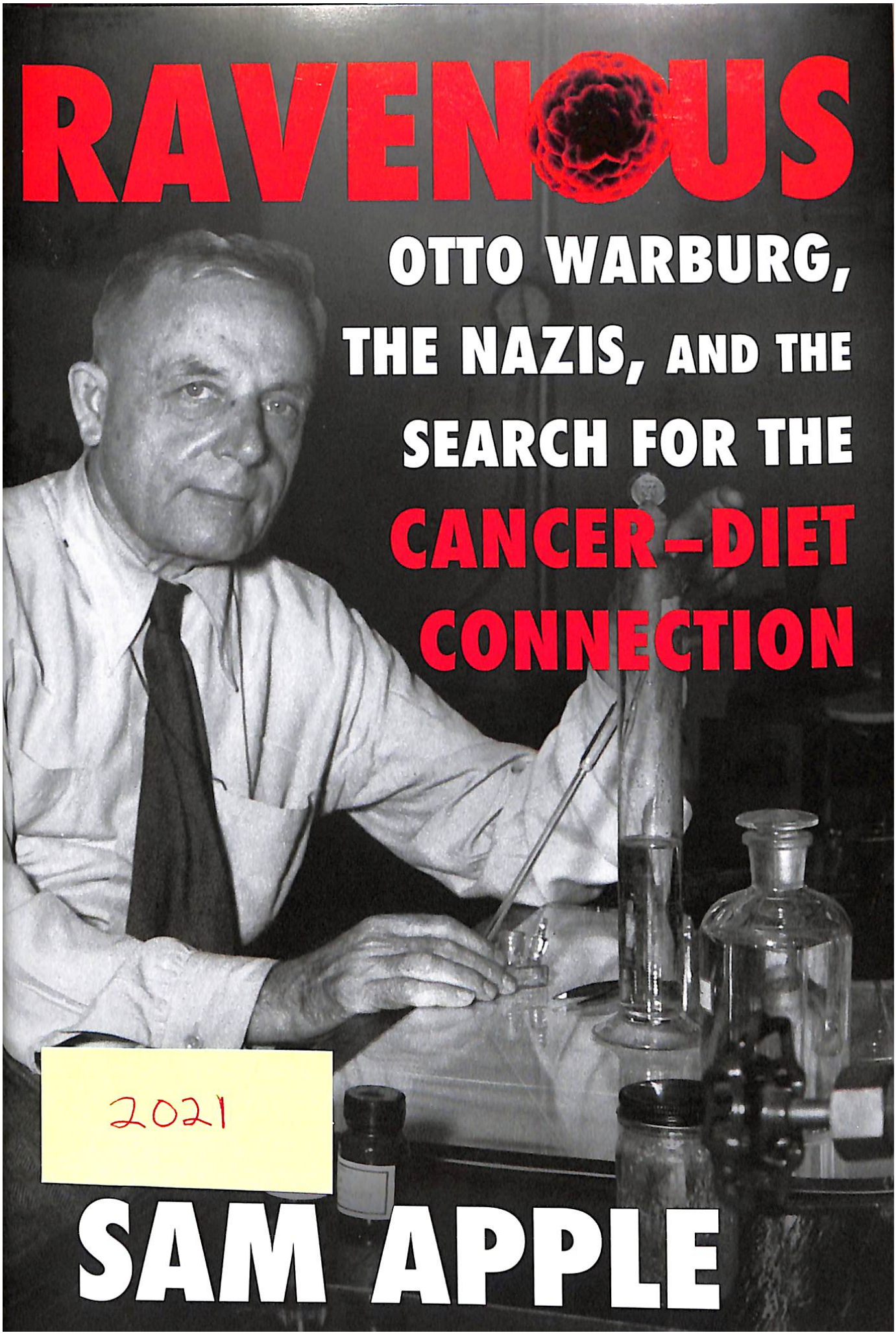
MITOCHONDRIA AND THE FUTURE OF MEDICINE

The Key to Understanding Disease, Chronic Illness, Aging, and Life Itself

2018

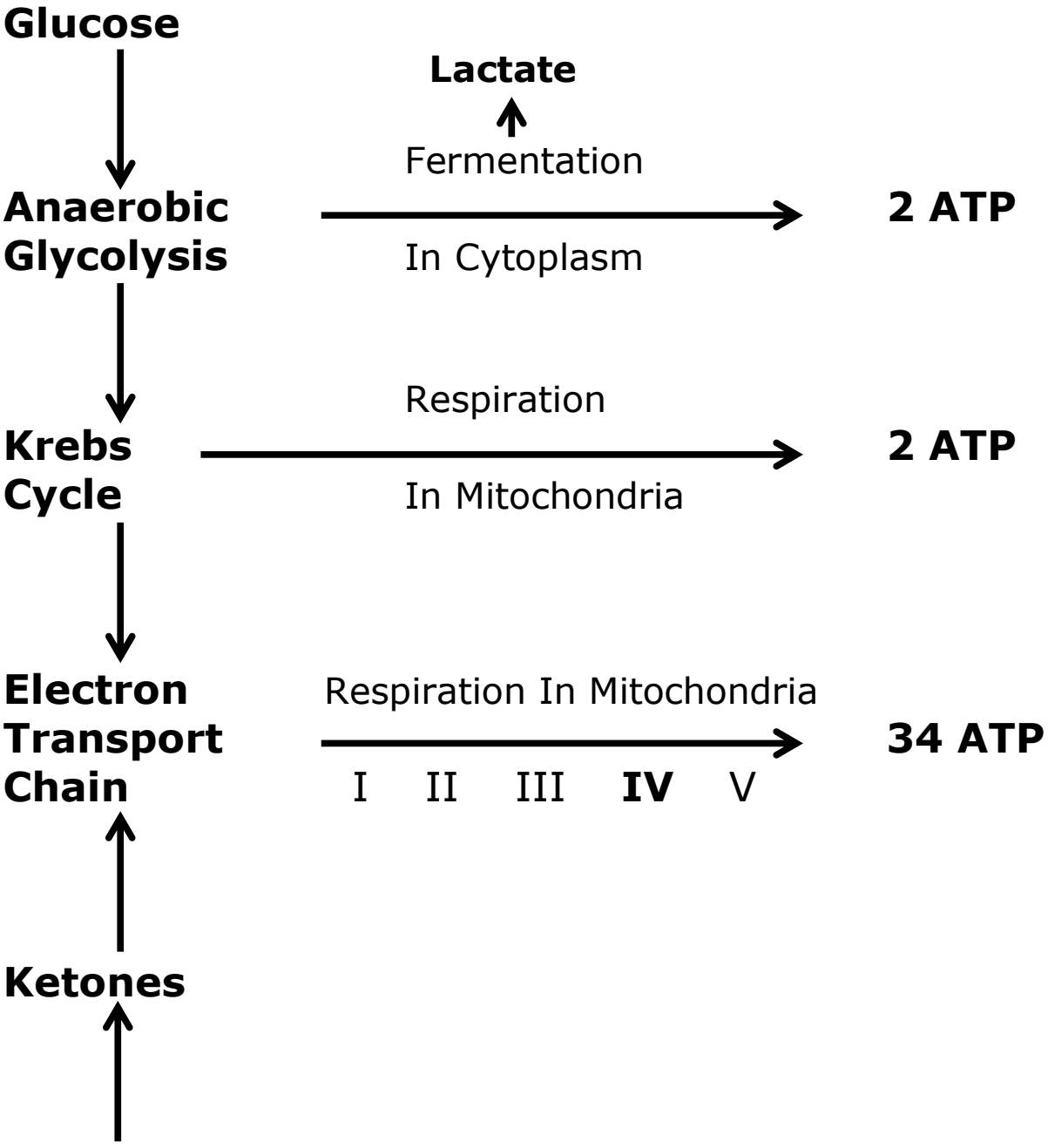
RAVENOUS

OTTO WARBURG, THE NAZIS, AND THE SEARCH FOR THE CANCER–DIET CONNECTION



2021

SAM APPLE



IV = Cytochrome c Oxidase (ATP)
III = Cytochrome c Reductase (O_2^-= Superoxide)

Fermentation may occur with or *without* oxygen
Respiration *requires* oxygen

2022

TRANSFORMER

The Deep Chemistry of Life and Death

NICK LANE

The experiment for which Warburg won the Nobel Prize in 1931 was just so beautiful I have to tell you about it.

Warburg knew he could block respiration by using the gas carbon monoxide (CO), which in cells binds to metal atoms in the catalyst that converts oxygen to water.

The binding of CO therefore halts the final step of respiration.

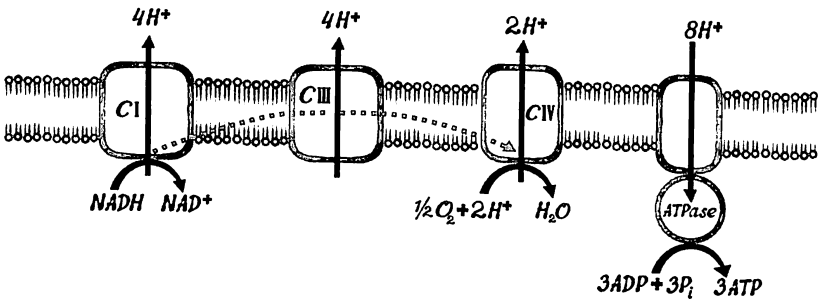
Here's the clever bit. CO can be detached from the catalyst through the absorption of light. That kick-starts respiration and oxygen consumption over again.

But not all wavelengths of light worked equally; some were absorbed by the catalyst, which then releases its bound CO, while other wavelengths just bounce off, leaving the CO bound.

Warburg used light sources that emitted photons with specific wavelengths, ... By measuring the rate of respiration at different wavelengths of light, he could reconstitute the absorption spectrum for the catalyst, showing that it was a heme pigment, closely related to hemoglobin, the pigment that transports oxygen in our own red blood cells..."

"The heme protein that Warburg discovered is now called "cytochrome oxidase.'"

Transformer



A grossly simplified schematic of the respiratory chain. The transfer of electrons from NADH to oxygen is shown by the dotted line. These electrons pass through three great protein complexes embedded in the membrane (complex I, III and IV; we'll meet complex II in Chapter 4). This current of electrons powers the extrusion of ten protons across the membrane, generating a combined electrical charge and concentration difference (the proton-motive force) that drives ATP synthesis from ADP (adenosine diphosphate) and inorganic phosphate (P_i). In humans, eight protons pass through the ATP synthase for one turn of it

Otto Warburg
The Oxygen-transferring Ferment of Respiration
Nobel Lecture, December 10, 1931

The Effect of Light on Inhibition of Cellular Respiration by Carbon Monoxide

Not only cellular respiration but also simpler iron catalyses are reversibly inhibited by carbon monoxide and prussic acid.

●●●

But it would never have been possible to reach a definite conclusion if Nature had not endowed the iron compounds of carbon monoxide with the remarkable property of becoming dissociated - with splitting off from the carbon monoxide – under the action of light.

●●●

By using monochromatic light and comparing the amount of light energy absorbed with the amount of carbon monoxide set free, it is found that Einstein's law of photochemical equivalence is very exactly fulfilled.

●●●

If then this is exposed to monochromatic light of various wavelengths and of measured quantum intensity, and the effect of light W measured the increase in the rate of catalysis - it is found that the effects of the light are proportional to the quanta absorbed.

●●●

The respiration of living cells was inhibited by carbon monoxide.

We then irradiated with monochromatic light of various wavelengths and of measured quantum intensity, and the increase of respiration measured together with the relative absorption spectrum.

Feel Incredible, Avoid Disease, and Age Well

"A tour de force."
—Mark Hyman, MD

2024

GOOD ENERGY

The Surprising Connection Between Metabolism and Limitless Health

CASEY MEANS, MD
WITH CALLEY MEANS

An official website of the United States government
Here's how you know

FULL TEXT LINKS

Review > Nat Rev Rheumatol. 2011 Mar;7(3):161-9. doi: 10.1038/nrrheum.2010.213.
Epub 2011 Jan 4.

The role of mitochondria in osteoarthritis

Francisco J Blanco [1], Ignacio Rego, Cristina Ruiz-Romero

Affiliations
PMID: 21200395 DOI: 10.1038/nrrheum.2010.213

Abstract

Mitochondria are important regulators of cellular function and survival that may have a key role in aging-related diseases. Mitochondrial DNA (mtDNA) mutations and oxidative stresses are known to contribute to aging-related changes. Osteoarthritis (OA) is an aging-associated rheumatic disease characterized by articular cartilage degradation and elevated chondrocyte mortality. Articular cartilage chondrocytes survive and maintain tissue integrity in an avascular, low-oxygen environment. Recent ex vivo studies have reported mitochondrial dysfunction in human OA chondrocytes, and analyses of mitochondrial electron transport chain activity in these cells show decreased activity of Complexes I, II and III compared to normal chondrocytes. This mitochondrial dysfunction may affect several pathways that have been implicated in cartilage degradation, including oxidative stress, defective chondrocyte biosynthesis and growth responses, increased cytokine-induced chondrocyte inflammation and matrix catabolism, cartilage matrix calcification, and increased chondrocyte apoptosis. Mitochondrial dysfunction in OA chondrocytes may derive from somatic mutations in the mtDNA or from the direct effects of proinflammatory mediators such as cytokines, prostaglandins, reactive oxygen species and nitric oxide. Polymorphisms in mtDNA may become useful as biomarkers for the diagnosis and prognosis of OA, and modulation of serum biomarkers by mtDNA haplogroups supports the concept that mtDNA haplogroups may define specific OA phenotypes in the complex OA process.

Related information

MedGen

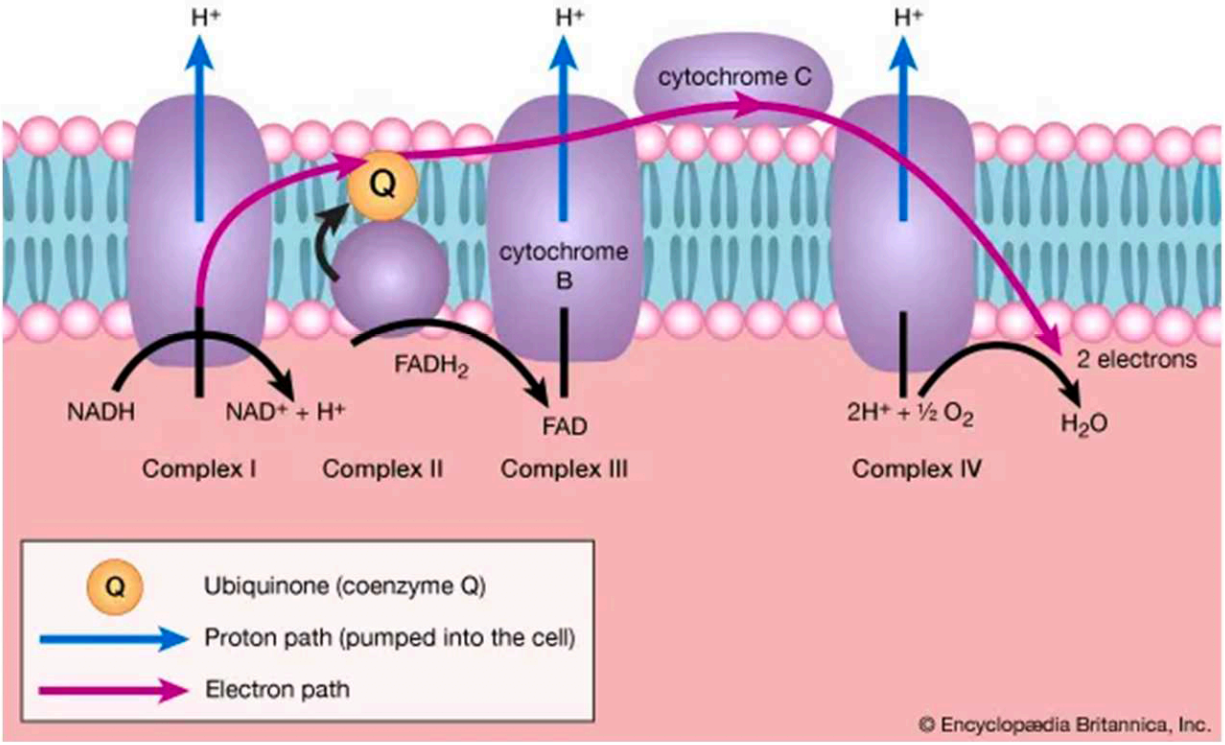
LinkOut - more resources

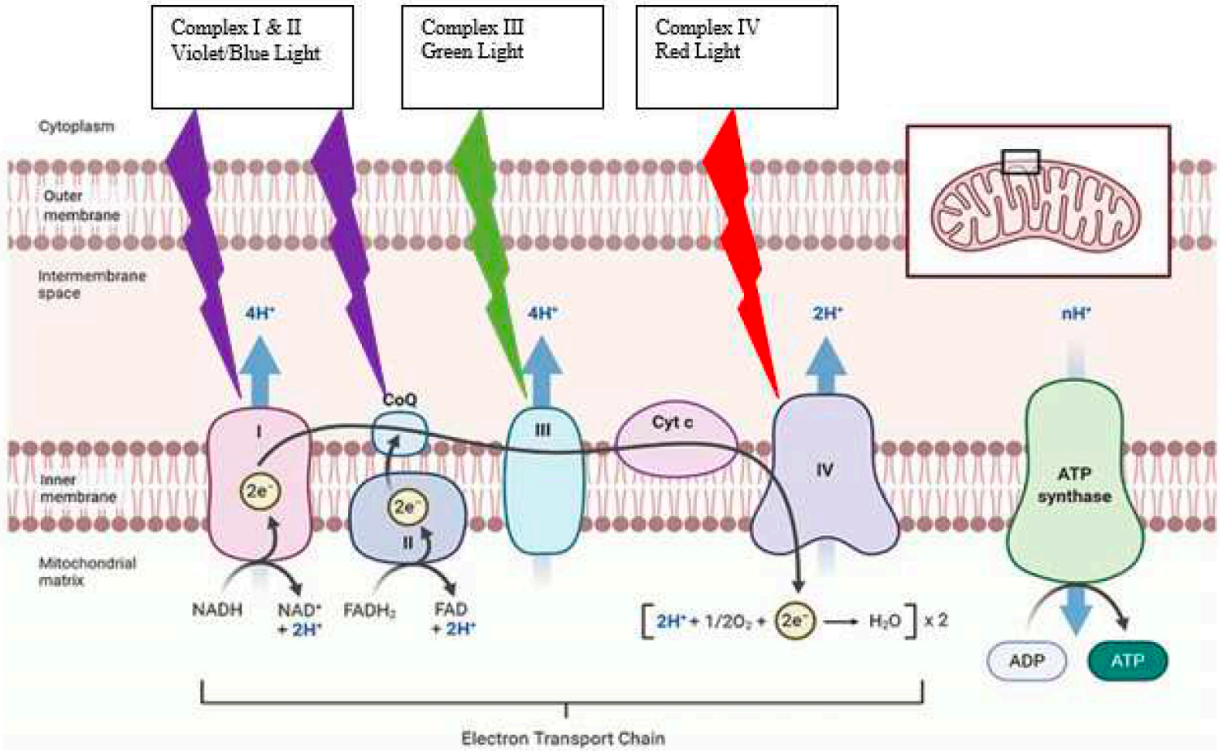
Full Text Sources
Nature Publishing Group
Ovid Technologies, Inc.

Other Literature Sources
The Lens - Patent Citations

Medical
MedlinePlus Health Information

Electron transport chain





Mitochondrial

Vitamins

Minerals

Supplements

All nutrients affect mitochondrial physiology directly or indirectly. These are the most important ones that affect the mitochondria directly.

CoQ-10

Pyrroloquinoline Quinone = PQQ

Magnesium = Mg++

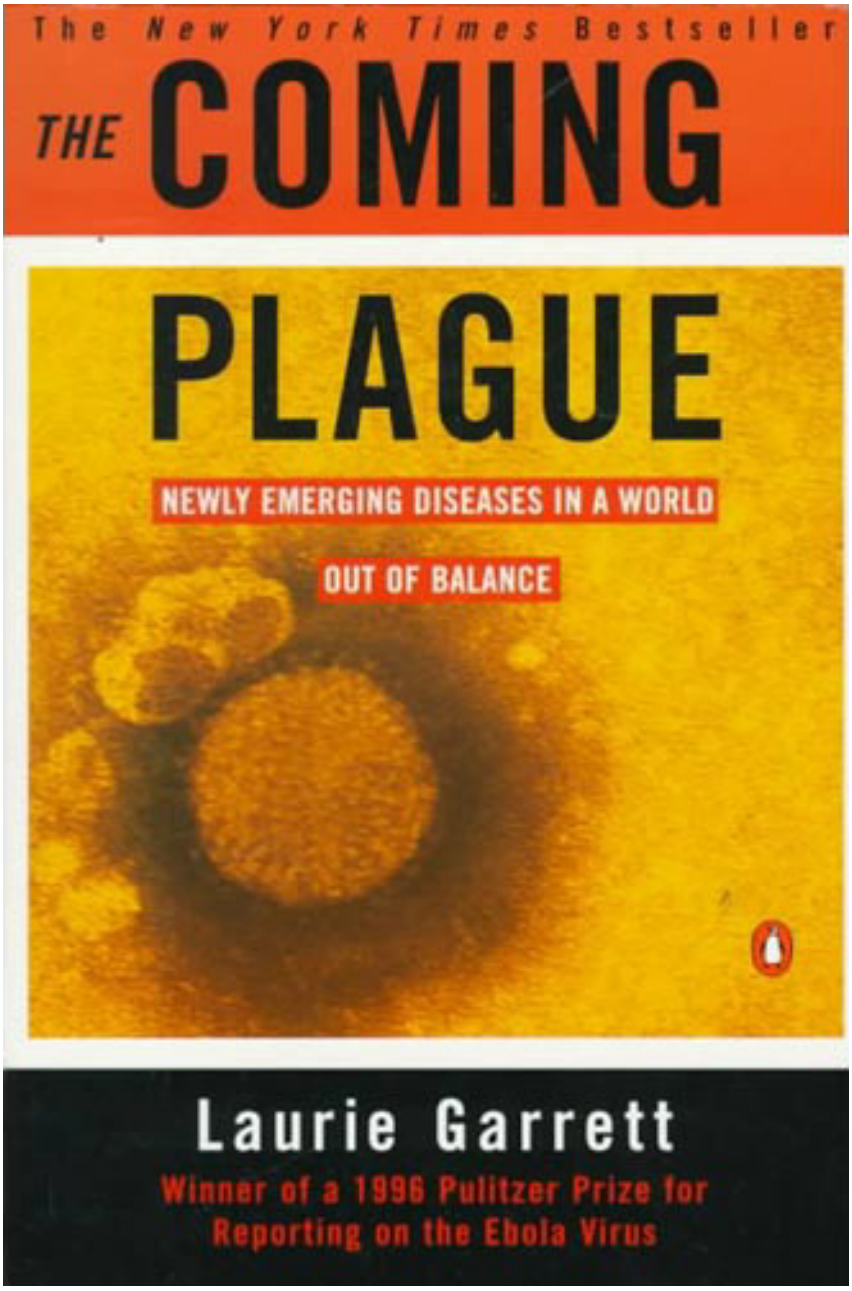
Acetyl-l-carnitine

Alpha-lipoic acid

Vitamin B-Complex

Melatonin

Antimicrobial Blue Light



Laurie Garrett is a Harvard microbiologist

This book is 750 pages which includes 112 *pages* of references

This is a book on Universal and Innate intelligence

A few select quotes

13

The Revenge of the Germs, or Just Keep Inventing New Drugs

DRUG-RESISTANT BACTERIA, VIRUSES, AND PARASITES

Consider the difference in size between some of the very tiniest and the very largest creatures on Earth. A small bacterium weighs as little as 0.00000000001 gram. A blue whale weighs about 100,000,000 grams. Yet a bacterium can kill a whale. . . . Such is the adaptability and versatility of microorganisms as compared with humans and other so-called "higher" organisms, that they will doubtless continue to colonise and alter the face of the Earth long after we and the rest of our cohabitants have left the stage forever. Microbes, not macrobes, rule the world.

—Bernard Dixon, 1994

1982 Fewer than 10 percent of all clinical staph cases could be cured with penicillin---a dramatic shift from the almost 100 percent penicillin susceptibility of *Staphylococcus* in 1952. [a 30-year period of time]
p. 418

Humans simply accelerated the natural process by exposing billions of microbes at a time to drugs derived from the natural chemicals.
p. 419

Often the genetic changes the microbes underwent in order to overcome the antibiotics offered unexpected additional advantages, enhancing the bacteria's ability to withstand wider temperature variations, outwit more elements of the host immune system, or kill cells with greater certainty.
p. 419

The human gastrointestinal tract was an ideal ecology for such microbial events. More bacteria lived on a single square inch of the human intestine than there were humans living on the entire planet.
p. 424

The shelf life of meat, poultry, eggs, and dairy products was extended through antibiotic treatment of the animals.

Why risk *Salmonella* poisoning due to consumption of undercooked meat if it was possible to sterilize the steer's body before slaughter? Why not extend the unrefrigerated shipping distance of eggs by injecting them, or the hens, with antibiotics?

Of course, the microbes were every bit as likely to share genes and mutate around the antibiotics while inside the gut of a cow as they were in *Homo sapiens* intestinal tract. So, in addition to the five billion humans on the planet that might take antibiotics, there were billions of cows, chickens, pigs, cattle, sheep, ducks, and other livestock undergoing prophylactic or treatment exposure to the chemicals, more than doubling the global selective pressure upon bacterial populations. p. 424

"It's incredible," Lappe said. "You can go into a hospital and you will have a four in a hundred chance of getting an infection you've never had before, while in that hospital. In some hospitals the odds are one in ten. What you will get in that hospital will be much worse that what you would have been contaminated with at home. They are the most tenacious organisms you can imagine. They can survive in the detergent. They can actually live on a bar of soap. These are organisms that are part of our endgame."

Unfortunately, we played a trick on the natural world by seizing control of these [natural] chemicals, making them more perfect in a way that has changed the whole microbial constitution of the developing countries. We have organisms now proliferating that never existed before in nature. We have selected them. We have organisms that probably caused a tenth of a percent of human disease in the past that now cause twenty, thirty percent of the disease that we're seeing. We have changed the whole face of the earth by the use of antibiotics.
p. 437

Is Crohn's Disease Caused By Antibiotics?

Hepato-Gastroenterology
December 1994; Vol. 41; No. 6; pp. 549-551

L. Demling
From the Medical Department at the University of Erlangen-Nurnber, Germany

FROM ABSTRACT:

The increase in Crohn's Disease that has taken place over the last 50 years has paralleled the increasing use of antibiotics in human and veterinary medicine.

Antibiotics can induce a capacity for toxin production in bacteria, or can make them invasive.

Prior antibiotic therapy also promotes the outbreak of Crohn's Disease to a statistically demonstrable extent.

It may clearly be assumed that Crohn's Disease is caused in genetically susceptible persons by intestinal bacteria whose biological properties have been altered by antibiotics.

THIS AUTHOR ALSO NOTES:

"Until the 1950s, Crohn's Disease was a rare condition." Crohn's Disease has increased dramatically since the mid 1950s. "After 1950, Crohn's Disease spread like an epidemic, initially in northern Europe and the USA."

Oral penicillin has been available since 1953. Tetracycline has also been on the market since 1953.

Antibiotics have been added to animal feeds since the early 1950s. "They have thus been able to enter the human organism other than by way of a doctor's prescription, namely via the consumption of chicken, pork, and beef."

Importantly, small doses of antibiotics ("subinhibitory") induce toxin production from intestinal organisms.

Studies involving twins and different ethnic groups show that there is a genetic component in susceptibility to Crohn's Disease.

"The epidemic-like spread of Crohn's Disease over roughly the last 50 years started with the introduction of antibiotics and developed in parallel with the increase in antibiotic consumption." **[Important]**

Crohn's Disease is an infectious disease whose pathogen is controlled by normal intestinal flora. This pathogen becomes toxic and invasive as the result of low level "contact with non-killing (insufficient) amounts of antibiotics."

Whenever antibiotics are used early in life and in large quantities, "the incidence and prevalence of Crohn's Disease is high."

Children treated with antibiotics "develop Crohn's Disease particularly frequently."

KEY POINTS FROM DAN MURPHY

1) "The increase in Crohn's Disease that has taken place over the last 50 years has paralleled the increasing use of antibiotics in human and veterinary medicine."

2) "Antibiotics can induce a capacity for toxin production in bacteria, or can make them invasive."

3) "Prior antibiotic therapy promotes the outbreak of Crohn's Disease to a statistically demonstrable extent."

4) "It may clearly be assumed that Crohn's Disease is caused in genetically susceptible persons by intestinal bacteria whose biological properties have been altered by antibiotics."

5) "Until the 1950s, Crohn's Disease was a rare condition." Crohn's Disease has increased dramatically since the mid 1950s. "After 1950, Crohn's Disease spread like an epidemic."

6) Antibiotics have been available for human and livestock consumption since the early 1950s. "They have thus been able to enter the human organism other than by way of a doctor's prescription, namely via the consumption of chicken, pork, and beef."

7) There is a genetic component in susceptibility to Crohn's Disease.

8) "The epidemic-like spread of Crohn's Disease over roughly the last 50 years started with the introduction of antibiotics and developed in parallel with the increase in antibiotic consumption." **[Important]**

9) Crohn's Disease is an infectious disease whose pathogen is controlled by normal intestinal flora. This pathogen becomes toxic and invasive as the result of low level "contact with non-killing (insufficient) amounts of antibiotics."

10) Whenever antibiotics are used early in life and in large quantities, "the incidence and prevalence of Crohn's Disease is high."

11) Children treated with antibiotics "develop Crohn's Disease particularly frequently."

Antibiotic resistance is at crisis point

The world needs "more science, more attention to outsmarting these bacteria because we're losing the race at this point."

Melanie Lawrence

31
0 89505 03005 7
PLEASE RECYCLE
©COPYRIGHT 2023 USA TODAY, A division of Gannett Co., Inc.

HOME DELIVERY
1-800-872-0001, USATODAYSERVICE.COM

Melanie Lawrence, 43, who has cystic fibrosis, testified before Congress in hopes of rallying more attention and funding behind antibiotic resistance.
PROVIDED BY MELANIE LAWRENCE

Worldwide deaths from infections could rise to tens of millions a year

Karen Weintraub and Adrianna Rodriguez
USA TODAY

8/2/23

In some ways, Melanie Lawrence is living a future that awaits us all.

She's resistant to nearly every antibiotic and allergic or intolerant to the rest.

Now when Lawrence develops an infection, which she does every few months, she has to hope her immune system can fight it without much help from modern medicine.

Despite more than a century of antibiotic research and development, the world is quickly running out of these lifesaving drugs.

Antibiotics, either found in nature or developed intentionally, are designed to kill bacteria. But bacteria have been evolving for more than 3 billion years and have learned to change themselves to survive. The more we use them, the more they adapt.

In 2019, the last year for which data is available, more than 2.8 million Americans had antimicrobial-resistant

See ANTIBIOTICS, Page 6A

Antibiotics

Continued from Page 1A

infections and more than 35,000 died, according to the Centers for Disease Control and Prevention. Worldwide, deaths already have surpassed 5 million a year and are expected to grow into the tens of millions within a few decades.

"We are truly right now in the midst of this crisis," Brenda Wilson, a professor of microbiology at the University of Illinois, said in a discussion recently at the American Society for Microbiology.

The United States was making solid progress against antibiotic resistance before the coronavirus pandemic. Thanks to improved infection prevention and control and better stewardship, deaths from antimicrobial resistance declined by 18% overall and 30% in hospitals from 2012 to 2017.

But COVID-19 pushed hospitals and other health facilities near their breaking point in 2020, leading to an increase in antibiotic use, trouble following infection prevention and a significant increase in resistant infections in hospitals, the CDC found. Resistant hospital-onset infections and deaths increased at least 15% that year, although data outside hospitals is lacking.

Overuse, both among people who would have recovered without the drugs and in livestock that get them to promote growth, not treat illness, helps drive resistance.

Dealing with antibiotic-resistant infections already costs about $5 billion a year, said Brian Ho, who co-wrote a book with Wilson called "Revenge of the Microbes."

And there's a tremendous human cost, in addition to the financial one.

To limit the overuse of antibiotics, doctors are now prescribing the drugs less often and for shorter periods. Where someone 30 years ago might have been prescribed 10 days of antibiotics, and someone 15 years ago would have gotten a five-day prescription, they're now getting the drug for two days. GETTY IMAGES

and fungi, in just one day.

Still, Lawrence says, the world needs "more science, more attention to outsmarting these bacteria because we're losing the race at this point."

Careful use

Resistance develops when a small group of bacteria is different enough from the rest to survive an antibiotic onslaught. These remaining microbes then reproduce, taking over the infection, which is now unaffected by or resistant to the antibiotic.

"We should not be taking antibiotics

the end of this year. It uses essential oils and botanicals like oregano and thyme, as well as probiotics as antibiotic alternatives, and says it is "making significant progress eliminating the use of antibiotics also important to human health from our chicken production."

Though most farms don't use "medically important" antibiotics, using disinfectants or other methods to prevent certain types of bacteria from taking hold can inadvertently favor other dangerous bacteria, Johnson said.

When bacteria develop drug-resistant genes, he said, they can jump from one pathogen to another. This tends to

cause pills aren't working against something as seemingly simple as a urinary tract infection.

Sometimes, she'll try combinations of drugs. In a few cases, she has had to "simply tell the person, 'I've run out of options.' Those are heartbreaking."

A climate change factor

Climate change also is fueling antibiotic resistance, several experts said.

"It's important to understand and acknowledge that as our global temperature rises, the number of microbes that are present in the environment and where they tend to flourish will change," said Tim Johnson, a professor at the University of Minnesota's College of Veterinary Medicine. "If the temperature is increasing in the soils or ambient, that promotes their survival in places where they normally just hang out but don't grow."

A life-threatening turn

In her University of Illinois discussion, Wilson told the story of Aimee Copeland, who was a 24-year-old grad student when she fell off a zip line in 2012 and scraped her knee on rocks in the river below.

Copeland's leg was stitched up and she was sent home with antibiotics, but the wound quickly got infected. Available drugs were no match for the naturally antibiotic-resistant bacteria she had picked up in the water.

Kidney and heart failure followed; then came amputation of all four limbs.

Stories like Copeland's will become more common, Wilson fears, as more bacteria and other microbes become drug-resistant.

Bacteria don't all become resistant at

and in livestock that get them to promote growth, not treat illness, helps drive resistance.

Dealing with antibiotic-resistant infections already costs about $5 billion a year, said Brian Ho, who co-wrote a book with Wilson called "Revenge of the Microbes."

And there's a tremendous human cost, in addition to the financial one.

"A lot of what we do in medicine relies on our ability to handle bacterial infections that occur along the way," said William Hanage, who co-directs the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health.

Minor injuries can become life-threatening without antibiotics. Many surgeries wouldn't be able to happen without knowing there were antibiotics to prevent any later infections. And patients need antibiotics if they're being treated with steroids or for cancer, rheumatoid arthritis, and other conditions that limit their immune response, as do people like Lawrence, who has cystic fibrosis, which makes her vulnerable to every passing bug.

"We want to be able to handle these things," Hanage said.

Urging action

Lawrence, 43, traveled to Washington, D.C., last month from her home in Fairhaven, Massachusetts, an hour south of Boston, to lobby the Senate for more funding and attention for antibacterial resistance.

She and others are encouraging Congress to pass a bill called the Pioneering Antimicrobial Subscriptions To End Up surging Resistance (or PASTEUR) Act, named for Louis Pasteur, the 19th-century Frenchman often considered the father of germ theory and modern microbiology. The bill was first introduced in 2020 and would create new incentives for drug companies to discover and develop antibiotics.

Right now, there's no financial incentive for a company to spend as long as a decade and upward of $1.5 billion developing an antibiotic that someone will

Careful use

Resistance develops when a small group of bacteria is different enough from the rest to survive an antibiotic onslaught. These remaining microbes then reproduce, taking over the infection, which is now unaffected by or resistant to the antibiotic.

"We should not be taking antibiotics unless it's absolutely necessary," said Dr. Adi Shah, an infectious disease specialist at the Mayo Clinic in Minnesota. "Giving an antibiotic for unclear or unnecessary reasons is like sending bacteria or a fungus to a gym to work out and form stronger defenses."

To limit the overuse of antibiotics, doctors are now prescribing them less often and for shorter periods. Where someone 30 years ago might have been prescribed 10 days of antibiotics, and someone 15 years ago would have gotten a five-day prescription, they're now getting the drug for two days.

Hanage said there was never any magic to 10 days. When researchers started testing, they realized there was no real benefit to longer courses over shorter ones.

"Giving an antibiotic for unclear or unnecessary reasons is like sending bacteria or a fungus to a gym to work out and form stronger defenses."

Dr. Adi Shah, an infectious disease specialist at the Mayo Clinic in Minnesota

Antibiotics also have been shown not to be useful for things like childhood ear infections, shaving at most a half-day off the course of an infection.

But habits die hard. When that news arrived in Hanage's native Britain, emergency room doctors didn't stop prescribing antibiotics for ear infections; they just stopped writing the

health from our chicken production."

Though most farms don't use "medically important" antibiotics, using disinfectants or other methods to prevent certain types of bacteria from taking hold can inadvertently favor other dangerous bacteria, Johnson said.

When bacteria develop drug-resistant genes, he said, they can jump from one pathogen to another. This tends to occur in microbiomes, like the gut, which are rich in microorganisms and motivate the drug-resistant gene to spread between bacteria to survive.

Drug-resistant genes also can hop from nonthreatening bacteria found in animals to pathogens that are more harmful to humans.

"Those resistances don't tend to go away easily," Johnson said.

Shattering prognosis

Lawrence has cystic fibrosis, an inherited lung disorder that makes her mucus sticky, which attracts lots of bacteria and other microbes.

When she was diagnosed as a child, her parents were told she probably would not make it past age 16. She's obviously grateful for all the extra time, but anxious too. "In some ways, I'm just getting started. I have so much left in me," Lawrence said.

She has been on antibiotics almost nonstop since her diagnosis. Oral antibiotics worked until puberty. By her teenage years, she had run out of those and had to go to the hospital for IV antibiotics that would take a week or two to work their magic.

In her 30s, the antibiotics would take five weeks to knock out the bugs, and another two months after that for her body to finish healing.

Now she gets the most cutting-edge treatment for cystic fibrosis, a combination of three medications approved by the FDA in 2019. In younger people, that therapy, called Trikafta from Vertex Pharmaceuticals, helps reduce infections and the need for antibiotics.

But Lawrence, like other older cystic fibrosis patients with some lung damage, still has infections roll in every few

able drugs were no match for the naturally antibiotic-resistant bacteria she had picked up in the water.

Kidney and heart failure followed; then came amputation of all four limbs.

Stories like Copeland's will become more common, Wilson fears, as more bacteria and other microbes become drug-resistant.

Bacteria don't all become resistant at the same rate.

Group A streptococcus, for instance, which causes a variety of infections including strep throat, has remained mostly susceptible to penicillin for a century, Hanage said. The bacterium that causes tuberculosis, meanwhile, is increasingly resistant to most available antibiotics.

It's not clear why this difference exists, Hanage said. "We need to understand more about that kind of thing because it will mean whether any of our interventions will be successful."

What's next?

Prevention is a growing focus, today and in the future.

Lawrence does everything she can to boost her immune system and prevent infections, from exercise to power yoga to traditional Chinese medicine known as Qigong. Others put their hopes in probiotics, hoping that boosting "good" microbes will help stave off the "bad."

Vaccines, including some under development, offer the potential to fight infections that would otherwise need to be controlled with antibiotics. A study in The New England Journal of Medicine, for instance, showed an experimental vaccine given during pregnancy, can prevent dangerous group B streptococcus infections in infants.

Nature also has offered a potential solution.

Graham Hatfull, a professor of biotechnology at the University of Pittsburgh, studies bacteriophages, viruses that naturally destroy bacteria. For more than a century, researchers have tried to use phages as a treatment for bacterial infections. "In the next short while, we'll learn whether it's finally

named for Louis Pasteur, the 19th-century Frenchman often considered the father of germ theory and modern microbiology. The bill was first introduced in 2020 and would create new incentives for drug companies to discover and develop antibiotics.

Right now, there's no financial incentive for a company to spend as long as a decade and upward of $1.5 billion developing an antibiotic that someone will use only for a week or two – limiting the amount a company can charge – and which might be obsolete in four or five years as bacteria become resistant.

"The market is broken because it's focused on volume. Antibiotics should not be used in high volume," said Dr. Helen Boucher, dean of the Tufts University School of Medicine, who also testified in favor of the PASTEUR Act. "PASTEUR reimburses for value, regardless of volume."

Other places already have implemented similar financial models.

In the U.K., the government signed contracts last month with drugmakers Pfizer and Shionogi, guaranteeing them a fixed annual fee of up to $13 million for the next decade for two new antibiotics. Rather than paying the companies based on the volume of drugs sold, the new subscription model removes any incentive for overuse.

Also on the horizon are tests that help doctors quickly distinguish between an infection caused by a virus, which won't benefit from an antibiotic, and one caused by bacteria, which might.

Also last month, the Food and Drug Administration cleared a test from Lumos Diagnostics of Australia that can rapidly identify a bacterial infection. And a study July 13 found that the Karius Test, commonly used in hospitals, could distinguish among 700 types of microbes, including bacteria, viruses

at the Mayo Clinic in Minnesota

Antibiotics also have been shown not to be useful for things like childhood ear infections, shaving at most a half-day off the course of an infection.

But habits die hard. When that news arrived in Hanage's native Britain, emergency room doctors didn't stop prescribing antibiotics for ear infections; they just stopped writing the medical term for "ear infection" as their diagnosis.

"Cultural change in medicine is a really difficult thing to achieve," he said. "It's rightly a small-c conservative field."

Antibiotics and the food supply

The commercial raising of animals for food has contributed to the problem. For decades, breeders have fed their livestock antibiotics. At first, they started out trying to help sick animals get well. But they noticed that animals fed antibiotics got big faster. So it became standard practice to include antibiotics in the feed of every animal, from poultry to fish to pigs to cows.

"The nature of raising animals in the backyard or a big barn really motivates the spread of microbes," Johnson said. "Those microbes have the potential to enter humans."

In recent years, under pressure from advocates, some companies have promised to cut back on the routine feeding of antibiotics. But some of those promises ring hollow, advocates say, or have been hard to maintain in a competitive marketplace.

Tyson Foods, the largest chicken producer in the United States, has moved away from the "no antibiotics ever" pledge it made in 2015. Instead, the company is transitioning to "no antibiotics important to human medicine" by

body to finish healing.

Now she gets the most cutting-edge treatment for cystic fibrosis, a combination of three medications approved by the FDA in 2019. In younger people, that therapy, called Trikafta from Vertex Pharmaceuticals, helps reduce infections and the need for antibiotics.

But Lawrence, like other older cystic fibrosis patients with some lung damage, still has infections roll in every few months. Even during the pandemic, when she rarely left the house and wore a mask everywhere, antibiotic-resistant infections still found her. "It's in the soil. It's in the environment. It's everywhere," she said.

Shah, of the Mayo Clinic, said he noticed about six years ago that patients would come in with harder-to-treat infections. They were sicker than he would have expected, and the typical drugs didn't work or took longer to make a difference.

Boucher, of Tufts, said she sometimes has to offer patients the choice of saving their life with an antibiotic, but at the cost of harming their kidneys or hearing or both. Some antibiotics damage the cranial nerves, which are involved in hearing and balance, as well as the kidneys.

Dr. Lilian Abbo, an infectious disease specialist at the University of Miami Miller School of Medicine, said she also has been seeing more patients resistant to first-, second- and third-line antibiotics, as well as antimicrobials – drugs that work against viruses and fungi.

"Even in children who are healthy, we're seeing resistance, which before we would not have seen," she said. "Most people may not be aware until it's their turn to experience it."

It's tough, she said, when she has to tell a patient they need to be hospitalized to get intravenous antibiotics be-

coccus infections in infants.

Nature also has offered a potential solution.

Graham Hatfull, a professor of biotechnology at the University of Pittsburgh, studies bacteriophages, viruses that naturally destroy bacteria. For more than a century, researchers have tried to use phages as a treatment for bacterial infections. "In the next short while, we'll learn whether it's finally going to get traction and take off, or whether it's doomed to another cycle of disappointment," Hatfull said.

Phages are extremely specific. That's good because they're like "targeted missiles to go and take out the bad guys in the body without disturbing the rest of your natural biology," Hatfull said.

"In contrast, antibiotics are like cluster bombing. They get everything in their way."

The downside of such specificity is that a phage might knock out the bacteria in only one sick person.

But solving the problem of antibiotic resistance with phages or anything else will take time – and especially money. "The impediment is ultimately more financial than it is intellectual," Hatfull said.

The threat of antibiotic resistance has felt largely theoretical, but it is becoming more real all the time, experts said.

"The alarm has been sounding. You hear the train far, far, far away. Hey, the train is coming. Now the train is getting closer," Abbo said. "By the year 2050, if we don't do something, it's going to be very, very serious."

Health and patient safety coverage at USA TODAY is made possible in part by a grant from the Masimo Foundation for Ethics, Innovation and Competition in Healthcare. The Masimo Foundation does not provide editorial input.

HEALTH

The 'Silent Pandemic' Putting Kids at Risk

Bacterial infections that commonly affect children are becoming increasingly resistant to antibiotics, causing infant deaths to rise

by **JESS THOMSON**

ANTIBIOTICS USED TO TREAT COMMON childhood ailments are becoming less and less effective, according to a new study.

Many of the antibiotics often used to treat infections like pneumonia, sepsis (bloodstream infections) and meningitis, which children often contract, are now less than 50 percent effective, the study published in the journal *The Lancet Regional Health—Southeast Asia* says.

The regions most affected by this are Southeast Asia and the Pacific, including Indonesia and the Philippines. Antibiotics in the United States are also getting less effective.

"It is already affecting us in the U.S. This has been deemed a silent pandemic," André O. Hudson, a professor of biochemistry at Rochester Institute of Technology, tells *Newsweek*.

The Problem with Antibiotics

Antimicrobial resistance, or AMR, is one of the top 10 public health threats, according to the World Health Organization. Illnesses like sepsis kill over 500,000 newborns worldwide every year, with many of these being attributed to antibiotic resistance.

"The WHO, G7 and World Economic Forum all formally recognize antimicrobial resistance as a global threat to human health. We depend on antibiotics for so much of modern medicine, including all kinds of invasive surgeries (like hip and knee replacements, tumor removal), protecting those who are immunocompromised such as cancer patients or premature babies—the list is long," Lori L. Burrows, a professor of biochemistry and biomedical sciences at the MDG Institute for Infectious Disease Research, McMaster University, says.

"Antimicrobials are unique medicines in that they are intended to kill other living things like viruses, bacteria and fungi," Burrows says. "These organisms, like all living things, are constantly evolving through random mutation, and when exposed to antimicrobials, those that are sensitive will die, while those that remain are resistant. Microbes can then trade DNA, so even those never exposed can become resistant courtesy of those exchanges."

The more we use antibiotics, the more pressure we put on the organisms to evolve resistance. The wide use of antimicrobials in agriculture to protect crops and animals, as well as the uncontrolled access to antibiotics in some parts of the world where no prescriptions are needed, has led to widespread resistance.

"Certain bacteria can circumvent drugs that are designed to kill them using the natural process of evolution via two primary means: genetic mutation and horizontal gene transfer. A genetic mutation occurs when the DNA of the bacteria changes over time, and if these changes are involved in a gene that is involved in resistance, then the bacteria can evade the drug," Hudson says.

"The changes are then passed on

HUMAN COST Many of the antibiotics used to treat diseases children often get are now less than 50 percent effective.

FROM LEFT: ANDREW BROOKES/GETTY; SASIISTOCK/ISTOCK/GETTY

to the next generation of bacteria to perpetuate resistance. In horizontal gene transfer. one bacterium acquires resistance genes from another source, either through their environment (transformation) directly from another bacterium (conjugation) or via bacterial virus (transduction)."

What New Research Shows

The study, which looked into 11 countries across Southeast Asia and the Pacific, reveals that the antibiotic ceftriaxone is now only effective at treating sepsis and meningitis in newborns in one in every three cases. Another antibiotic, gentamicin, was only effective in one in every two cases of newborn sepsis.

While this is a major issue in Southeast Asia and the Pacific due to lack of infrastructure for alternative treatments, it is an increasing problem in the U.S. and other countries, too.

"Approximately 2.8 million people are infected with bacteria deemed resistant to clinically relevant antibiotics, of which 35,000 and 700,000 [die] in the United States and globally, respectively," Hudson says. "In the 2019 report, the World Health Organization states that if no action is taken, drug-resistant diseases could cause 10 million deaths each year by 2050 and that by 2030, antimicrobial resistance could force up to 24 million people into extreme poverty."

"If clinically relevant antibiotics are not effective, this can lead to organ failure, death, etc. Sometimes doctors use last-resort antibiotics," Hudson says. "These drugs are used in very restricted cases as they have severe side effects; for example, the last-resort antibiotic, aminoglycosides, can lead to hearing loss and kidney damage."

If no action is taken, drug-resistant diseases could cause 10 million deaths each year by 2050.

AMR is especially dangerous for children, as new antibiotics are less likely to be tested on and available to children, the authors explain in the paper.

Solutions Hit Roadblocks

One of the best ways to tackle antibiotic resistance in childhood infections is the development of new antibiotic treatments for children and newborns.

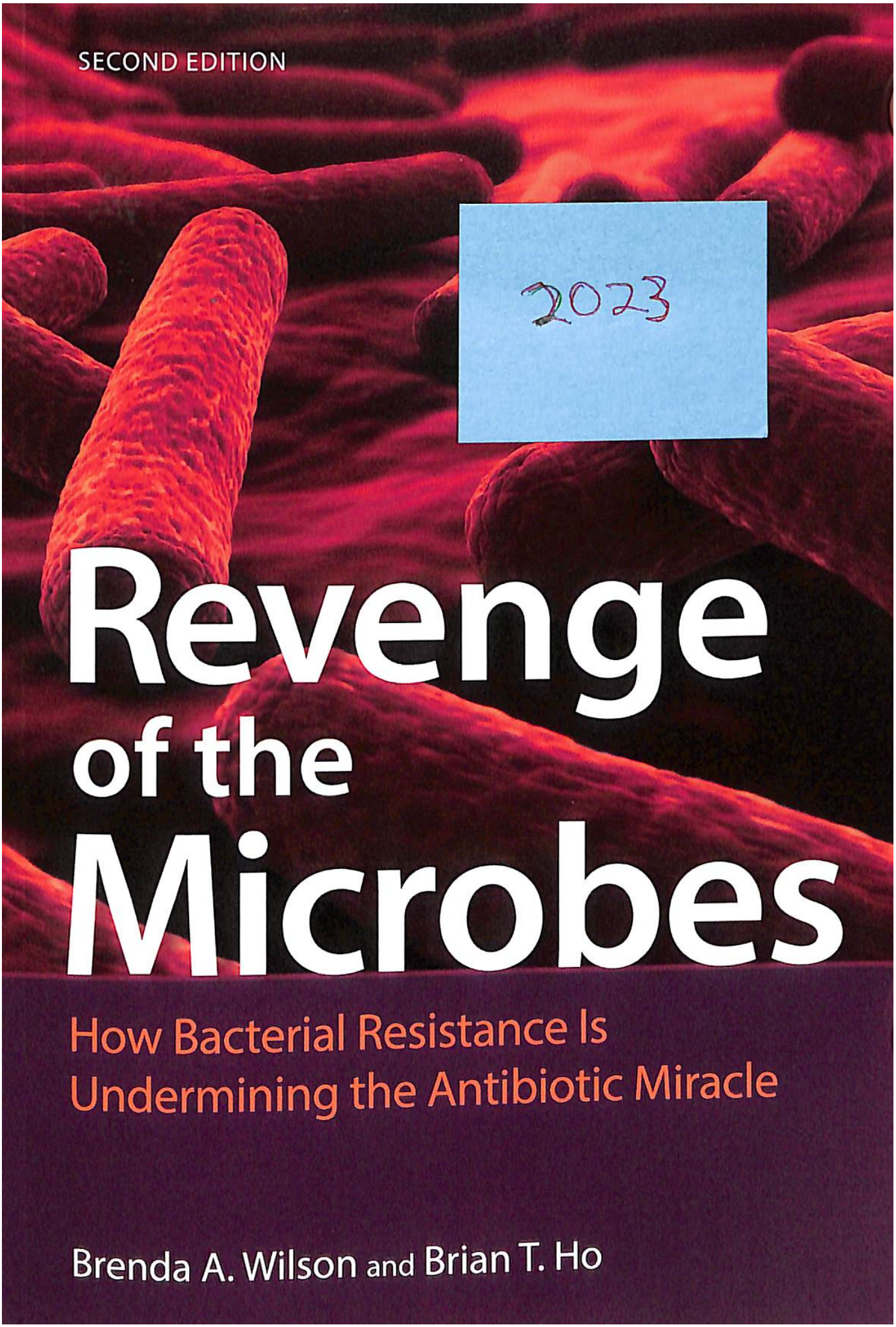
"Antibiotic clinical focus on adults and too often children and newborns are left out. That means we have very limited options and data for new treatments," Phoebe Williams, an infectious disease specialist from the University of Sydney's School of Public Health and co-author of the paper, said in a statement.

This requires making funding available for development of new drugs.

"Because companies can charge more for antibiotics in the U.S. than elsewhere in the world, there are more options, but the newer drugs are very expensive," Burrows says.

"Most large pharma companies are no longer interested in looking for new antibiotics because they make more money from drugs that people have to take for months or years for chronic conditions versus days or weeks for an infection. This is a big problem when combined with the increase in resistance that we're seeing—we're already being forced to use last resort drugs and there's almost nothing left beyond that." N

▸ **Jess Thomson** *is a* NEWSWEEK *reporter based in London who covers science, technology and health care. Follow her on X @thomsonjessic*


SECOND EDITION
2023
Revenge of the Microbes
How Bacterial Resistance Is Undermining the Antibiotic Miracle
Brenda A. Wilson and Brian T. Ho

OUR CANCER MYSTERY

WHY IT'S NOW STRIKING US SO YOUNG | *by* JAMIE DUCHARME

From left:
Giancarlo, diagnosed with lung cancer at 18
Kelly, diagnosed with colorectal cancer at 28
Imtiaz, diagnosed with colon cancer at 26
Carrie, diagnosed with ovarian cancer at 40

DAN MURPHY
PO BOX 7044
AUBURN CA 95604-7044
#5442742
P00094 2508

HEALTH

More young adults are getting cancer. Researchers are racing to understand why

By Jamie Ducharme

emotional toll, force patients to cumulatively fork out billions of dollars in out-of-pocket costs—more than $16 billion in 2019 alone, according to federal data. Today, about 40 out of every 100 U.S. adults can expect to be diagnosed with cancer at some point in their lifetimes. For an estimated 1 in 17 U.S. women and 1 in 29 U.S. men, that news will come before their 50th birthdays.

The rise in early-onset diagnoses partly comes down to advances in our ability to detect and diagnose different kinds of cancers. "With much more sophisticated tools now, inevitably we're doing more tests on younger people [and] we're using more accurate imaging," which leads to more cancers detected, Powles says. Some screening protocols have also been modified in recent years to include younger adults; since 2018, for example, the American Cancer Society has recommended colonoscopies starting at age 45, down from 50.

But this is only one part of what scientists say is a more complex web of factors they are still attempting to understand. The data suggest that some element—or perhaps combination of elements—of modern life is sickening progressively younger adults. And right now, no one knows for sure what that is.

There are plenty of known risk factors for cancer, from the genes someone is born with to the unhealthy lifestyle habits they pick up, such as smoking, drinking lots of alcohol, or spending time in the sun. Such habits can speed up the natural degradation of cells, which over time acquire genetic mutations as they lose their ability to repair damage. As that damage accumulates with age, cells may become cancerous, growing and multiplying too fast for the body's immune system to keep them in check and potentially choking out vital organs. The immune system also loses some of its strength with age, making it easier for cancer cells to colonize the body.

But classic risk factors do not seem to fully explain the recent rise in early-onset cancers, says Dr. Cathy Eng, director of the Young Adult Cancers Program at Vanderbilt University's Ingram Cancer Center in Tennessee. Some of the trends are baffling; young, nonsmoking women, for example, are being diagnosed with lung cancer in strangely high numbers. Many times, Eng's patients were extremely healthy: vegetarians, marathon runners, avid swimmers. "That's why I really believe there's other risk factors to account for this," she says.

There's no shortage of theories about what those may be. Many scientists point to modern diets, which tend to be heavy on potentially carcinogenic products—including ultra-processed foods, red meat, and alcohol—and may also contribute to weight gain, another cancer risk factor. The foods we eat can also affect the gut microbiome, the colony of microbes that lives in the digestive system and appears linked to overall health. Alterations to the gut microbiome via diet, or perhaps exposure to drugs like antibiotics, have also been implicated.

Other researchers blame the microplastics littering our environment and leaching into our food and water supplies, some of which, according to a 2024 study, have even shown up in cancer patients' tumors. Other environmental factors could also be to blame, given that everything from cosmetics to food packaging contains substances that

SOPHIE PARK FOR TIME

many researchers aren't convinced are safe. Even our near constant exposure to artificial light could be messing with normal biological rhythms in ways that have profound health consequences, some research suggests.

For now, these are all just hypotheses. Some may turn out to be wrong, and more theories will emerge in time. It's also likely that different risk factors are linked to different cancers, Frizelle says. Even in a single patient, multiple overlapping triggers may be in play.

Frizelle's research on colorectal cancer, for example, suggests there may be a dysfunctional relationship between microplastics, certain foods, and some types of gut bacteria. Studies suggest that when microplastics get into the body, they can penetrate the mucous lining that protects the bowels and carry bacteria and toxins to the bowel lining. This leaves the bowel more susceptible to damage from pathogens inside the body—including strains of gut bacteria that are known to become more virulent when they interact with

Barreto—who started researching early-onset cancer after not just his patients, but also several of his relatives and friends, were diagnosed at young ages—has theorized that damage may start in the womb. It's well established that the prenatal period can have long-term effects on a baby's health, and Barreto believes that phenomenon may extend to cancer risk if parents are exposed to carcinogens during this critical developmental time. This theory could help explain mysterious cases like those Cercek describes, involving patients

PubMed

Format: Abstract

Full text links

ELSEVIER FULL-TEXT ARTICLE

J Hosp Infect. 2014 Sep;88(1):1-11. doi: 10.1016/j.jhin.2014.06.004. Epub 2014 Jul 3.

405 nm light technology for the inactivation of pathogens and its potential role for environmental disinfection and infection control.

Maclean M[1], **McKenzie K**[2], Anderson JG[2], Gettinby G[3], MacGregor SJ[2].

Author information

1 The Robertson Trust Laboratory for Electronic Sterilisation Technologies, University of Strathclyde, Glasgow, UK. Electronic address: michelle.**maclean**@strath.ac.uk.

2 The Robertson Trust Laboratory for Electronic Sterilisation Technologies, University of Strathclyde, Glasgow, UK.

3 Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK.

Abstract

BACKGROUND: Although the germicidal properties of ultraviolet (UV) light have long been known, it is only comparatively recently that the antimicrobial properties of visible violet-blue 405 nm light have been discovered and used for environmental disinfection and infection control applications.

AIM: To review the antimicrobial properties of 405 nm light and to describe its application as an environmental decontamination technology with particular reference to disinfection of the hospital environment.

METHODS: Extensive literature searches for relevant scientific papers and reports.

FINDINGS: A large body of scientific evidence is now available that provides underpinning knowledge of the 405 nm light-induced photodynamic inactivation process involved in the destruction of a wide range of prokaryotic and eukaryotic microbial species, including resistant forms such as bacterial and fungal spores. For practical application, a high-intensity narrow-spectrum light environmental disinfection system (HINS-light EDS) has been developed and tested in hospital isolation rooms. The trial results have demonstrated that this 405 nm light system can provide continuous disinfection of air and exposed surfaces in occupied areas of the hospital, thereby substantially enhancing standard cleaning and infection control procedures.

CONCLUSION: Violet-blue light, particularly 405 nm light, has significant antimicrobial properties against a wide range of bacterial and fungal pathogens and, although germicidal efficacy is lower than UV light, this limitation is offset by its facility for safe, continuous use in occupied

PubMed

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://w
Get the latest research from NIH: https://www.nih.go

Full text links
SpringerLink FULL-TEXT ARTICLE
PMC FREE Full text

The new PubMed site will become the default in mid-May.
Click here to try it now!
Frequently asked questions

Format: Abstract

Food Environ Virol. 2017 Jun;9(2):159-167. doi: 10.1007/s12560-016-9275-z. Epub 2016 Dec 31.

New Proof-of-Concept in Viral Inactivation: Virucidal Efficacy of 405 nm Light Against Feline Calicivirus as a Model for Norovirus Decontamination.

Tomb RM[1], Maclean M[2,3], Coia JE[4], Graham E[5], McDonald M[5], Atreya CD[6], MacGregor SJ[2], Anderson JG[2].

Author information

Abstract

The requirement for novel decontamination technologies for use in hospitals is ever present. One such system uses 405 nm visible light to inactivate microorganisms via ROS-generated oxidative damage. Although effective for bacterial and fungal inactivation, little is known about the virucidal effects of 405 nm light. Norovirus (NoV) gastroenteritis outbreaks often occur in the clinical setting, and this study was designed to investigate potential inactivation effects of 405 nm light on the NoV surrogate, feline calicivirus (FCV). FCV was exposed to 405 nm light whilst suspended in minimal and organically-rich media to establish the virucidal efficacy and the effect biologically-relevant material may play in viral susceptibility. Antiviral activity was successfully demonstrated with a 4 Log_{10} (99.99%) reduction in infectivity when suspended in minimal media evident after a dose of 2.8 kJ cm^{-2}. FCV exposed in artificial faeces, artificial saliva, blood plasma and other organically rich media exhibited an equivalent level of inactivation using between 50-85% less dose of the light, indicating enhanced inactivation when the virus is present in organically-rich biologically-relevant media. Further research in this area could aid in the development of 405 nm light technology for effective NoV decontamination within the hospital environment.

Light as a Potential Treatment for Pandemic Coronavirus Infections: A Perspective

Journal of Photochemistry & Photobiology, B: Biology
2020 [epub pre-publication]

Chukuka Samuel Enwemeka, Violet Vakunseh Bumah, Daniela Santos Masson-Meyers: From San Diego State University, and Marquette University School of Dentistry. This study cites 99 references.

"This paper cites several studies showing that phototherapy has immense potential to reduce the impact of coronavirus diseases."

KEY POINTS FROM THIS ARTICLE:

1) "The recent outbreak of COVID-19, which continues to ravage communities with high death tolls and untold psychosocial and catastrophic economic consequences, is a vivid reminder of nature's capacity to defy contemporary healthcare."

- "The pandemic calls for rapid mobilization of every potential clinical tool, including phototherapy."

- Phototherapy was "one of the most effective treatments used to reduce the impact of the 1918 'Spanish influenza' pandemic."

2) "The evidence shows that violet/blue (400–470 nm) light is antimicrobial against numerous bacteria, and that it accounts for Niels Ryberg Finsen's Nobel-winning treatment of tuberculosis." **[Key Point]**

- "Evidence shows that blue light inactivates several viruses, including the common flu coronavirus, and that in experimental animals, red and near infrared light reduce respiratory disorders, similar to those complications associated with coronavirus infection." **[Key Point]**

- "In patients, red light has been shown to alleviate chronic obstructive lung disease and bronchial asthma."

- "These findings call for urgent efforts to further explore the clinical value of light, and not wait for another pandemic to serve as a reminder."

3) Violet/blue (400–470 nm) light has the "potential to reduce infections, sanitize equipment, hospital facilities, emergency care vehicles, homes, and the general environment as pilot studies have shown."

treat various diseases and ailments, has evolved scientifically, allowing evidence-based practice." **[Important]**

- "This development now enables clinicians and others to exploit the specific effect of each wavelength or spectrum of light for treatment purposes."

12) "We do not need UV to kill bacteria, viruses and other pathogens, and that safer wavelengths adjacent to UV, such as violet or blue light, are antimicrobial against microorganisms." **[Very Important]**

13) "Evidence shows that red and near infrared light have immense therapeutic value as well, and can be effective in treating a range of ailments, including the respiratory complications of coronavirus disease."

14) "Light in the blue 400–470 nm range is antimicrobial against numerous bacteria and has the potential to mitigate opportunistic bacterial infections associated with COVID-19 and other coronavirus infections." **[Important]**

- "Recent studies demonstrate that various wavelengths in the blue spectrum are antimicrobial against the deadly methicillin-resistant Staphylococcus aureus (MRSA), Escherichia. Coli, Helicobacter pylori, Listeria monocytogenes, Pseudomonas aeruginosa, Salmonella, Acinetobacter baumannii, Aggregatibacter actinomycetemcomitans, Propionibacterium acnes, Neisseria gonorrhoeae, Porphyromonas gingivalis, Fusobacterium nucleatum, and others."

15) "Laboratory experiments show that red and near infrared light, with wavelengths approximately in the range of 600–700 nm and 700–1000 nm respectively, have the potential to reduce lung inflammation and fibrosis, and hence acute respiratory disorder syndrome, a major cause of death in every coronavirus pandemic, including the prevailing COVID-19 pandemic."

- "Acute Respiratory Distress Syndrome (ARDS) a critical complication of COVID-19 infection, often characterized by airway edema, pulmonary inflammation, and lung fibrosis, could be ameliorated with photobiomodulation."

- Red laser irradiation of the skin over the inflamed bronchus with a single dose of 1.3 J cm-2 of continuous wave red 650 nm laser inhibited pulmonary edema and reduced activation and influx of neutrophils, damage to endothelial cytoskeleton, and the amount of TNF-α, and IL-1β in the lung and bronchoalveolar fluid.

- "Early results suggest that red and near infrared light have the potential to reduce some of the critical complications of coronavirus infections, i.e., pulmonary inflammation and lung fibrosis." **[Important]**

16) "In relation to COVID-19, some relatively easy targets are the nasal and oral cavities, and the upper respiratory tract, particularly as the nasal passage is an acclaimed point of entry of the virus into the human body." **[Important]**

17) "Antimicrobial blue light may serve another useful purpose in reducing the COVID-19 pandemic; it could be used effectively to sanitize equipment, tools, hospital facilities, emergency care vehicles, homes, and the general environment."

18) There may be as many as four [two reviewed here] mechanisms underlying the antimicrobial effect of blue light:

- First, "blue light triggers endogenous bacterial chromophores such as porphyrins, flavins, NADH and other photosensitive receptors to produce reactive oxygen species, which in adequate amount results in [bacterial] cell death."

    - Porphyrins have absorption peaks in the 405 to 470 nm range.

    - The dominant chromophores in P. acnes and MRSA emit red light with peak emission between 612 and 660 nm when excited with blue/violet light." [The theory behind the value of the violet-red laser]

- Second, "irradiation with blue light alters bacterial cell membrane integrity with a consequent decrease in membrane polarization and rapid alteration of cellular functions"

19) At a sub-lethal dose level, treatment with pulsed blue light disrupts the structural architecture of MRSA cell membrane and its internal organelles. **[Very Important]**

20) "It would be highly beneficial to patients with coronavirus disease if their loads of opportunistic bacterial infection could be reduced with blue light; such treatment—when fully developed—will give their immune systems a better chance of overcoming the deadly disease."

21) "Light in the red and near infrared light spectra can reduce lung inflammation, lung fibrosis, pneumonia, acute respiratory disorders, and other severe complications of coronavirus infections."

22) Recent clinical results indicate that patients with chronic obstructive lung disease and others with bronchial asthma and allergy improved significantly following treatment with light.

23) Most "striking are reports showing that certain wavelengths of light inactivate viruses, including baculoviruses."

- Exposure to blue light inactivates the leukemia virus.

24) There is "strong reason to suggest that blue light—particularly pulsed blue light, which recent reports have shown to be 40 to 100 times more potent than continuous wave blue light—has great potential to inactivate coronaviruses." **[Very Important]**

- "Recent developments buttress the suggestion that blue light, in particular, pulsed blue light, which recent reports have shown to be 40 to 100 times more potent than the commonly available continuous wave blue light, has great potential to inactivate COVID-19 and other coronaviruses, in addition to suppressing related opportunistic bacterial infections."

25) A recent report (2020) showed that "the common cold virus—a coronavirus—is inactivated by light."

26) "Convincing clinical results prove that blue light is antiviral, in addition to being antibiotic against coronavirus opportunistic bacteria, it would be a revolutionary paradigm shift."

- "This recent finding further elevates the urgency to explore the potential of blue light as an antiviral agent."

27) "It will be a wise investment to urgently investigate these initial results clinically, and not wait for another deadly coronavirus pandemic to remind us of the inherent potential of light as a therapeutic tool."

COMMENTS FROM DAN MURPHY:

For a number of years, in laser class, we have covered a section titled "Antimicrobial Blue Light." The primary wavelength used in these studies is 405 nm.

Traditional models of chronic low back pain is that it results from a combination of inflammation and subsequent tissue fibrosis. As reviewed here, red light is both anti-inflammatory and anti-fibrotic. The Erchonia FX red laser was given FDA 510k clearance for chronic low back pain in 2018, the first laser to achieve this milestone.

Recent evidence is indicating that some chronic low back pain is driven by infectious inflammation (inflammation alters the threshold of the nociceptive afferent system). Recent clinical trials show that the combination of the red laser with the violet laser is superior to red laser alone in managing pain syndromes. As such, the new (2020) Erchonia Fx will include a violet diode along with the traditional three red diodes, a unique first in applications.

We use the Erchonia EVRL (Erchonia Violet Red Laser) device. This technology has already been granted FDA 510k for acne and onchomycosis (toe nail fungus), infections.
This study's theoretical applications for COVID-19 and other microbes is cutting-edge.

FULL TEXT LINKS

Mary Ann Liebert

> Photobiomodul Photomed Laser Surg. 2020 Jul;38(7):395-397. doi: 10.1089/photob.2020.4882. Epub 2020 Jun 9.

Photobiomodulation: Shining Light on COVID-19

Adriana Barrinha Fernandes [1 2], Carlos José de Lima [1 2], Antônio G J Balbin Villaverde [1 2], Pamela Camila Pereira [1], Henrique Cunha Carvalho [2], Renato Amaro Zângaro [1 2]

Affiliations

PMID: 32579049 DOI: 10.1089/photob.2020.4882

Abstract

Objective: To evaluate the hypothesis that light could reduce the lethality of COVID-19. ***Methods:*** Most models for projections of the spread and lethality of COVID-19 take into account the ambient temperature, neglecting light. Recent advances in understanding the mechanism of action of COVID-19 have shown that it causes a systemic infection that significantly affects the hematopoietic system and hemostasis, factors extremely dependent of light, mainly in the region of visible and infrared radiation. ***Results:*** In the COVID-19 patients hemoglobin is decreasing and protoporphyrin is increasing, generating an extremely harmful accumulation of iron ions in the bloodstream, which are able to induce an intense inflammatory process in the body with a consequent increase in C-reactive protein and albumin. Observing the unsaturation characteristics of the cyclic porphyrin ring allows it to absorb and emit radiation mainly in the visible region. This characteristic can represent an important differential to change this process in the event of an imbalance in this system, through the photobiomodulation to increase the production of adenosine triphosphate (ATP) using red and near-infrared radiation (R-NIR) and vitamin D using ultraviolet B (UVB) radiation. These two compounds have the primary role of activating the defense mechanisms of the immune system, enabling greater resistance of the individual against the attack by the virus. According to the theory of electron excitation in photosensitive molecules, similar to hemoglobin heme, after the photon absorption there would be an increase in the stability of the iron ion bond with the center of the pyrrole ring, preventing the losses of heme function oxygen transport (HbO_2). The light is also absorbed by cytochrome c oxidase in the R-NIR region, with a consequent increase in electron transport, regulating enzyme activity and resulting in a significant increase of oxygen rate consumption by mitochondria, increasing ATP production. ***Conclusions:*** The most favorable range of optical radiation to operate in this system is between R-NIR region, in which cytochrome c oxidase and porphyrin present absorption peaks centered at 640 nm and HbO_2 with absorption peak centered at 900 nm. Based on the mechanisms described earlier, our hypothesis is that light could reduce the lethality of COVID-19.

Keywords: COVID-19; light; photobiomodulation.

Related information

MedGen

LinkOut - more resources

Full Text Sources

Atypon

Research Materials

NCI CPTC Antibody Characterization Program

Light-based Technologies for Management of COVID-19 Pandemic Crisis

Journal of Photochemistry & Photobiology, B: Biology
November 2020

Caetano P. Sabino, Anthony R. Ball, Mauricio S. Baptista, Tianhong Dai, Michael R. Hamblin, Martha S. Ribeiro, Ana L. Santos, Fabio P. Sellera, George P. Tegos, Mark Wainwright

"This review examines the potential of light-based technologies to prevent COVID-19 infection and control its dissemination by direct viral inactivation and to treat COVID-19 by modulating the host immune system."

"The global dissemination of the novel coronavirus disease (COVID-19) has accelerated the need for the implementation of effective antimicrobial strategies to target the causative agent SARS-CoV-2."

"Light-based technologies have a demonstrable broad range of activity over standard chemotherapeutic antimicrobials and conventional disinfectants, negligible emergence of resistance, and the capability to modulate the host immune response."

"Photobiomodulation, a light-based anti-inflammatory therapy, may have some palliative effects on patients suffering from severe COVID-19."

"UV-C is directly absorbed by pyrimidine bases causing their dimerization, which leads to viral inactivation via DNA or RNA damage. Thymine is the main chromophore in DNA while uracil is its counterpart in RNA. Upon UV-C exposure, thymine and uracil form cross-links. It must be stressed that UV-C usage must be limited to inanimate objects since it is highly dangerous to human skin."

"Antimicrobial photodynamic therapy (aPDT) is used to treat localized microbial infections caused by viruses, bacteria, fungi, and parasites. Among the many pathogens that can be targeted by aPDT, viruses are perhaps the most vulnerable."

"Visible blue light exhibits microbicidal effects in the wavelength range of 405–470 nm. High-intensity narrow-spectrum light at 405 nm has been used for continuous decontamination of inpatient and outpatient burn units and patient-occupied intensive care isolation rooms, as well as the treatment of surgical site infections in an orthopedic operating room."

"The exact mechanisms underlying the antimicrobial effects of blue light are not yet completely understood but appear to involve the formation of short-lived reactive oxygen species (ROS)."

"aBL might be able to kill SARS-CoV-2 by photoexcitation of its acquired porphyrins."

"Photobiomodulation (PBM) employs low levels of red or near-infrared (NIR) light to treat and heal wounds and injuries, reduce pain and inflammation, regenerate damaged tissue, and protect tissue at risk of dying. Instead of directly targeting viruses, PBM mainly acts on the host cells, which absorb light in the red and near-infrared spectral region. Literature indicates that photons are absorbed by multiple cellular chromophores, including mitochondrial enzymes, to trigger the biological effects of PBM. Cytochrome c oxidase (i.e., unit IV in the mitochondrial respiratory chain) appears to play a main role in this process."

"Nanostructured water (interfacial water) is also likely to act as a chromophore. Upon irradiation, the mitochondrial membrane potential is raised and oxygen consumption and ATP generation are increased. Subsequent activation of signaling pathways and transcription factors leads to fairly long-lasting effects even after relatively brief exposure of the tissue to light."

"Because COVID-19 involves a 'cytokine storm', PBM delivered to the torso (chest and back) might not only allow some light to reach the lungs but might also reduce the systemic inflammation responsible for COVID-19 sepsis-like syndrome and disseminated intravascular coagulation that can be deadly."

"Moreover, PBM is more effective on hypoxic cells, suggesting it could be effective for COVID-19 infection, which seems to be characterized by severe hypoxia."

An official website of the United States government
Here's how you know

FULL TEXT LINKS

ELSEVIER
OPEN ACCESS

J Photochem Photobiol B. 2021 Sep;222:112282. doi: 10.1016/j.jphotobiol.2021.112282.
Epub 2021 Aug 8.

Pulsed blue light inactivates two strains of human coronavirus

Chukuka S Enwemeka [1], Violet V Bumah [2], John L Mokili [3]

Affiliations

PMID: 34404018 PMCID: PMC8349404 DOI: 10.1016/j.jphotobiol.2021.112282

Free PMC article

Abstract

Emerging evidence suggests that blue light has the potential to inactivate viruses. Therefore, we investigated the effect of 405 nm, 410 nm, 425 nm and 450 nm pulsed blue light (PBL) on human alpha coronavirus HCoV-229 E and human beta coronavirus HCoV-OC43, using Qubit fluorometry and RT-LAMP to quantitate the amount of nucleic acid in irradiated and control samples. Like SARS-CoV-2, HCoV-229E and HCoV-OC43 are single stranded RNA viruses transmitted by air and direct contact; they have similar genomic sizes as SARS-CoV-2, and are used as surrogates for SARS-CoV-2. Irradiation was carried out either at 32.4 J cm^{-2} using 3 mW cm^{-2} irradiance or at 130 J cm^{-2} using 12 mW cm^{-2} irradiance. Results: (1) At each wavelength tested, PBL was antiviral against both coronaviruses. (2) 405 nm light gave the best result, yielding 52.3% (2.37 log_{10}) inactivation against HCoV-OC43 ($p < .0001$), and a significant 1.46 log_{10} (44%) inactivation of HCoV-229E ($p < .01$). HCoV-OC43, which like SARS-CoV-2 is a beta coronavirus, was more susceptible to PBL irradiation than alpha coronavirus HCoV-229E. The latter finding suggests that PBL is potentially antiviral against multiple coronavirus strains, and that, while its potency may vary from one virus to another, it seems more antiviral against beta coronaviruses, such as HCoV-OC43. (3) Further, the antiviral effect of PBL was better at a higher irradiance than a lower irradiance, and this indicates that with further refinement, a protocol capable of yielding 100% inactivation of viruses is attainable.

Keywords: Alpha coronavirus HCoV-229E; Beta coronavirus HCoV-OC43; Human coronavirus; Photobiomodulation; Pulsed blue light; SARS-CoV-2; Viral nucleic acid quantification.

Copyright © 2021 The Authors. Published by Elsevier B.V. All rights reserved.

Figures

FULL TEXT LINKS

nature publishing group

> Sci Rep. 2021 Oct 18;11(1):20595. doi: 10.1038/s41598-021-99917-2.

Visible blue light inhibits infection and replication of SARS-CoV-2 at doses that are well-tolerated by human respiratory tissue

Nathan Stasko [1], Jacob F Kocher [1], Abigail Annas [1], Ibrahim Henson [1], Theresa S Seitz [2], Joy M Miller [2], Leslee Arwood [1], Rachel C Roberts [1], Thomas M Womble [1], Emily G Keller [1], Soren Emerson [1], Michael Bergmann [1], Ashley N Y Sheesley [3], Rebecca J Strong [3], Brett L Hurst [3], David Emerson [1], E Bart Tarbet [3], Shelton S Bradrick [2], Adam S Cockrell [4]

Affiliations

Affiliations

1 EmitBio Inc., 4222 Emperor Blvd, Suite 470, Durham, NC, 27703, USA.
2 Division of Infectious Diseases, Surveillance and Diagnostics, MRIGlobal, Kansas City, MO, 64110, USA.
3 Institute for Antiviral Research, Department of Animal, Dairy and Veterinary Sciences, Utah State University, Logan, UT, 84321, USA.
4 EmitBio Inc., 4222 Emperor Blvd, Suite 470, Durham, NC, 27703, USA. acockrell@knowbiollc.com.

PMID: 34663881 PMCID: PMC8523529 DOI: 10.1038/s41598-021-99917-2
Free PMC article

Abstract

The delivery of safe, visible wavelengths of light can be an effective, pathogen-agnostic, countermeasure that would expand the current portfolio of SARS-CoV-2 intervention strategies beyond the conventional approaches of vaccine, antibody, and antiviral therapeutics. Employing custom biological light units, that incorporate optically engineered light-emitting diode (LED) arrays, we harnessed monochromatic wavelengths of light for uniform delivery across biological surfaces. We demonstrated that primary 3D human tracheal/bronchial-derived epithelial tissues tolerated high doses of a narrow spectral band of visible light centered at a peak wavelength of 425 nm. We extended these studies to Vero E6 cells to understand how light may influence the viability of a mammalian cell line conventionally used for assaying SARS-CoV-2. The exposure of single-cell monolayers of Vero E6 cells to similar doses of 425 nm blue light resulted in viabilities that were dependent on dose and cell density. Doses of 425 nm blue light that are well-tolerated by Vero E6 cells also inhibited infection and replication of cell-associated SARS-CoV-2 by > 99% 24 h post-infection after a single five-minute light exposure. Moreover, the 425 nm blue light inactivated cell-free betacoronaviruses including SARS-CoV-1, MERS-CoV, and SARS-CoV-2 up to 99.99% in a dose-dependent manner. Importantly, clinically applicable doses of 425 nm blue light dramatically inhibited SARS-CoV-2 infection and replication in primary human 3D tracheal/bronchial tissue. Safe doses of visible light should be considered part of the strategic portfolio for the development of SARS-CoV-2 therapeutic countermeasures to mitigate coronavirus disease 2019 (COVID-19).

© 2021. The Author(s).

FULL TEXT LINKS

ELSEVIER FULL-TEXT ARTICLE

Review > Photodiagnosis Photodyn Ther. 2021 Dec 12;102682.
doi: 10.1016/j.pdpdt.2021.102682. Online ahead of print.

How Biophotonics Can Help Dentistry to Avoid or Minimize Cross Infection by SARS-CoV-2?

João Felipe Besegato [1], Priscila Borges Gobbo de Melo [2], Patrícia Eriko Tamae [3], Ana Paula Aparecida Raimundo Alves [4], Luis Felipe Rondón [5], Leon G Leanse [6], Carolina Dos Anjos [7], Heitor Hussni Casarin [8], Michelle Alexandra Chinelatti [9], Gisele Faria [10], Tianhong Dai [11], Vanderlei Salvador Bagnato [12], Alessandra Nara de Souza Rastelli [13]

Affiliations

PMID: 34910994 PMCID: PMC8666148 DOI: 10.1016/j.pdpdt.2021.102682
Free PMC article

Abstract

Biophotonics is defined as the combination of biology and photonics (the physical science of the light). It is a general term for all techniques that deal with the interaction between biological tissues/cells and photons (light). Biophotonics offers a great variety of techniques that can facilitate the early detection of diseases and promote innovative theragnostic approaches. As the COVID-19 infection can be transmitted due to the face-to-face communication, droplets and aerosol inhalation and the exposure to saliva, blood, and other body fluids, as well as the handling of sharp instruments, dental practices are at increased risk of infection. In this paper, a literature review was performed to explore the application of Biophotonics approaches in Dentistry focusing on the COVID-19 pandemic and how they can contribute to avoid or minimize the risks of infection in a dental setting. For this, search-related papers were retrieved from PubMED, Scielo, Google Schoolar, and American Dental Association and Centers for Disease Control and Prevention databases. The body of evidence currently available showed that Biophotonics approaches can reduce microorganism load, decontaminate surfaces, air, tissues, and minimize the generation of aerosol and virus spreading by minimally invasive, time-saving, and alternative techniques in general. However, each clinical situation must be individually evaluated regarding the benefits and drawbacks of these approaches, but always pursuing less-invasive and less aerosol-generating procedures, especially during the COVID-19 pandemic.

Keywords: Aerosol; Antimicrobial blue light; Antimicrobial photodynamic therapy; Biofilm; Biophotonics; COVID-19; COVID-19 dentistry biosafety; COVID-19 safety protocols; Cross-infection; Curcumin; Dental caries; Dental practice management; Dentistry; Endodontic treatment; Endodontics; High intensity laser; High-Level Laser; Laser; Laser therapy; Low-level laser; Meta-analysis; Oral decontamination; Oral infections; Oral mucosa; Oral soft tissues; Periodontal disease; Periodontics; Periodontitis; Photobiomodulation; Photochemotherapy; Photodynamic inactivation; Photodynamic therapy; Photosensitizer; SARS-CoV-2; Systematic review; UVC decontamination; transmission.

Copyright © 2021. Published by Elsevier B.V.

Figures

Viral Inactivation by Light

eLight
2022; Vol. 2; No. 18; Epub September 26, 2022

Mohammad Sadraeian, Le Zhang, Farzaneh Aavani, Esmaeil Biazar, Dayong Jin

"Viral infections are one of the greatest challenges for medical sciences and human society."

- Antiviral compounds and chemical inactivation remain inadequate."
- Physical approaches based on irradiation provide new potentials for prevention and treatment of viral infections, without the risk of drug resistance and other unwanted side effects."

"For several hundreds of years, light has been recognized as a potential antimicrobial device to fight against infection diseases."

Non-ionizing radiation
Blue light

Blue light is considered to be the high-energy visible in the 380 to 500 nm range.

"Blue light (> 405 nm) does not have sufficient photon energy to release a bound electron from a single atom or molecule, therefore it is not considered as ionizing radiation."

"The use of blue light for the treatment of viral infectious diseases is a new area that warrants further investigation."

Photo-biomodulation (PBM)

"Photobiomodulation (PBM) employs low-level non- ionizing forms of blue, green, red or near-infrared (NIR) light."

- "PBM, also known as Low Level Laser Light therapy (LLLT), is a photon therapy based on the use of a light source, such as lasers and light-emitting diodes (LEDs)."

"PBM with red light can reduce inflammation and stimulate collagen production, PBM with blue light can destroy acne-causing bacteria and other pathogens."

"PBM laser therapy has various effects on cell proliferation and activation of cell signaling cascades, including the release of ROS and nitric oxide (NO)."

"Viruses are unlikely to increase resistance to light radiation, as is the case with drugs."

"Viral inactivation of tissues and organs could be accomplished by low energy lasers."

"New advances in the characterization of viral genome and proteins during irradiation will be the key to better understanding of mechanism and quantifying each key parameter for efficient viral inactivation without harmful side effects to human and the environment."

"When it goes to antiviral therapy, the implementation ability, repeatability, affordability, and lack of long-term toxicity of the method are the most important factors."

- "Irradiation strategies are preferred because they do not destroy the cells and our bodies, are environmentally friendly, and are cost-effective."

"Using physical waves and irradiations with non- destructive controlled parameters are promising to inactivate viruses, including SARS-CoV-2, without the risk of drug resistance."

"Recent reports from different research groups claim the non-ionizing blue light can inactivate the virus in an unknown mechanism."

An official website of the United States government
Here's how you know

FULL TEXT LINKS

WILEY Full Text Article

J Biophotonics. 2022 Dec 12;e202200203. doi: 10.1002/jbio.202200203. Online ahead of print.

Effect of near-infrared and blue laser light on vero E6 cells SARS-CoV-2 infection model

Luisa Zupin [1], Libera Clemente [2], Francesco Fontana [2], Sergio Crovella [3]

Affiliations

PMID: 36510366 DOI: 10.1002/jbio.202200203

Abstract

Photobiomodulation therapy (PBMT) employing laser light has been emerging as a safe strategy to challenge viruses. In this study the effect of blue and near-infrared (NIR) laser light was assessed in an in vitro model of SARS-CoV-2 infection. PBMT at blue wavelength inhibited viral amplification when the virus was directly irradiated and then transferred to cell culture and when cells already infected were treated. The NIR wavelength resulted less efficacious showing a minor effect on the reduction of the viral load. The cells receiving the irradiated virus or directly irradiated rescued their viability to level comparable to not treated cells. Virion integrity and antigenicity were preserved after blue and NIR irradiation, suggesting that the PBMT antiviral effect was not correlated to viral lipidic envelope disruption. Our results suggested that PBMT can be considered a valid strategy to counteract SARS-CoV-2 infection, at least in vitro.

Keywords: SARS-CoV-2; antiviral; blue and near-infrared laser light; photobiomodulation therapy; vero E6 cells.

© 2022 The Authors. Journal of Biophotonics published by Wiley-VCH GmbH.

LinkOut - more resources

Full Text Sources
Wiley

Miscellaneous
NCI CPTAC Assay Portal

An official website of the United States government
Here's how you know

J Clin Laser Med Surg. 2002 Dec;20(6):325-33. doi: 10.1089/104454702320901116.

Effects of 630-, 660-, 810-, and 905-nm laser irradiation delivering radiant exposure of 1-50 J/cm2 on three species of bacteria in vitro

Ethne L Nussbaum [1], Lothar Lilge, Tony Mazzulli

Affiliations

Affiliation

1 Rehabilitation Services, Mount Sinai Hospital and Department of Physical Therapy, University of Toronto, Toronto, Ontario, Canada. e.nussbaum@utoronto.ca

PMID: 12513919 DOI: 10.1089/104454702320901116

Abstract

Objective: To examine the effects of low-intensity laser therapy (LILT) on bacterial growth in vitro.

Background data: LILT is undergoing investigation as a treatment for accelerating healing of open wounds. The potential of coincident effects on wound bacteria has received little attention. Increased bacterial proliferation could further delay recovery; conversely inhibition could be beneficial.

Materials and methods: Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus were plated on agar and then irradiated with wavelengths of 630, 660, 810, and 905 nm (0.015 W/cm(2)) and radiant exposures of 1-50 J/cm(2). In addition, E. coli was irradiated with 810 nm at an irradiance of 0.03 W/cm(2) (1-50 J/cm(2)). Cells were counted after 20 h of incubation post LILT. Repeated measures ANOVA and Tukey adjusted post hoc tests were used for analysis.

Results: There were interactions between wavelength and species ($p = 0.0001$) and between wavelength and radiant exposure ($p = 0.007$) in the overall effects on bacterial growth; therefore, individual wavelengths were analyzed. Over all types of bacteria, there were overall growth effects using 810- and 630-nm lasers, with species differences at 630 nm. Effects occurred at low radiant exposures (1-20 J/cm(2)). Overall effects were marginal using 660 nm and negative at 905 nm. Inhibition of P. aeruginosa followed irradiation using 810 nm at 5 J/cm(2) (-23%; $p = 0.02$). Irradiation using 630 nm at 1 J/cm(2) inhibited P. aeruginosa and E. coli (-27%). Irradiation using 810 nm (0.015 W/cm(2)) increased E. coli growth, but with increased irradiance (0.03 W/cm(2)) the growth was significant ($p = 0.04$), reaching 30% at 20 J/cm(2) ($p = 0.01$). S. aureus growth increased 27% following 905-nm irradiation at 50 J/cm(2).

Conclusion: LILT applied to wounds, delivering commonly used wavelengths and radiant exposures in the range of 1-20 J/cm(2), could produce changes in bacterial growth of considerable importance for wound healing. A wavelength of 630 nm appeared to be most commonly associated with bacterial inhibition. The findings of this study might be useful as a basis for selecting LILT for infected wounds.

Related information

MedGen

LinkOut - more resources

"A MONUMENTAL WORK."
—DAVID PERLMUTTER, MD,
author of the #1 *New York Times* bestsellers *Grain Brain* and *Brain Maker*

The End *of* Alzheimer's

The First Program to Prevent and Reverse Cognitive Decline

2017

DALE E. BREDESEN, MD

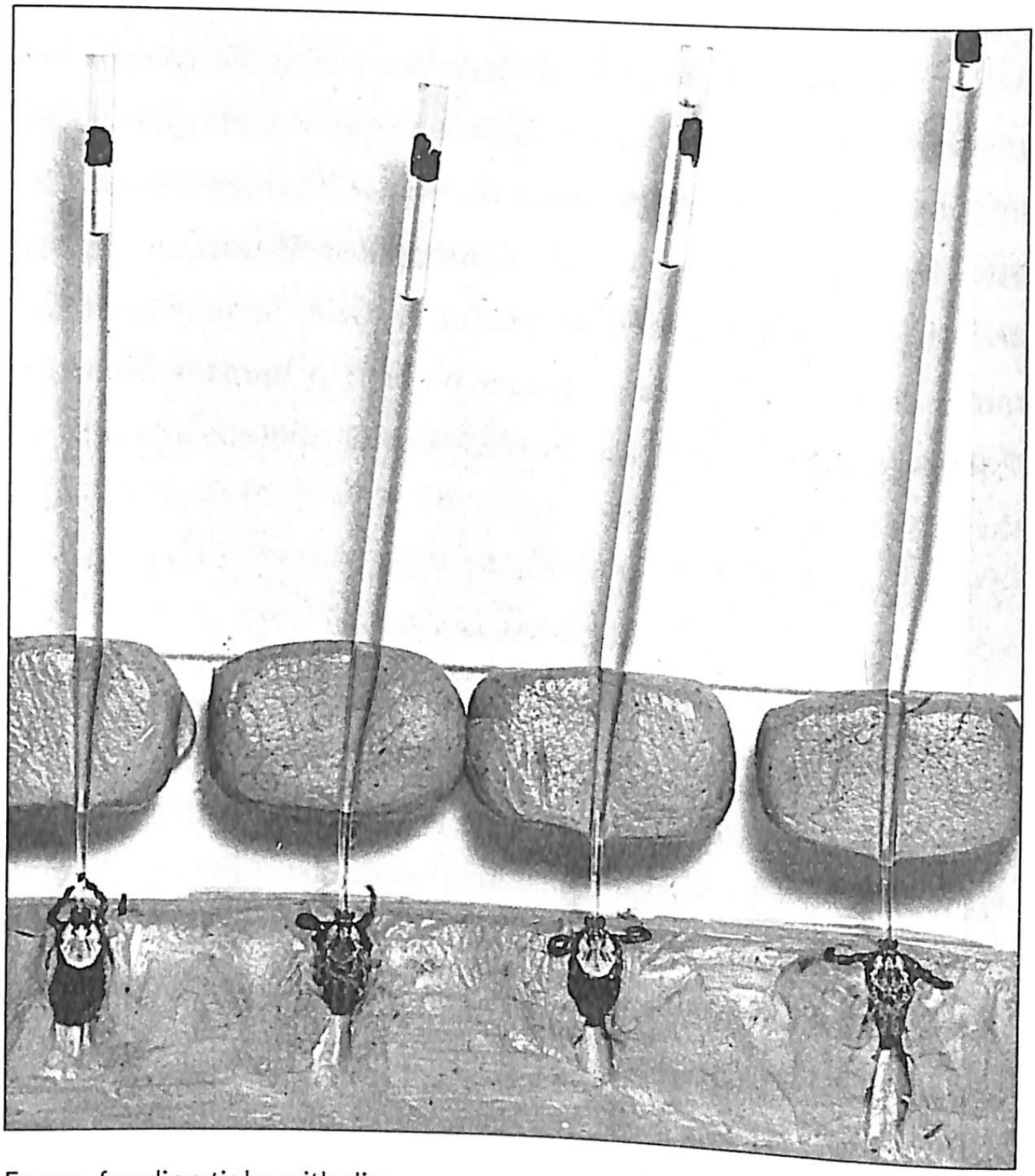
Professor and Founding President, Buck Institute; Professor, UCLA

2019

BITTEN

The Secret History of Lyme Disease and Biological Weapons

KRIS NEWBY



Force-feeding ticks with disease agents

Bitten
The Secret History of Lyme Disease and Biological Weapons

Kris Newby
2019

pp. 241-242

"My mother's mental decline started after the second of two tick bites [1993 and 1998]." Her first bout of Lyme disease was diagnosed at the Bethesda Naval Hospital. Five years later she began a "slide into an ever crazy, ever-changing array of neurological symptoms, my mother tested positive for Lyme disease."

"She was on and off antibiotics fort years, and even went to a special Lyme clinic in Switzerland. But the disease and several other health complications were taking over. Now she is too weak for any kind of heroic medical intervention."

"After breakfast, I helped her up and gently hugged her good-bye. It felt as if she were made of paper-mache, hollow inside."

"My father's parting words to me were 'Don't get yourself killed over this book'."

Low-Level-Lasers for All

Integrating the relationship between mitochondria, free radicals, ATP, cytochrome c oxidase enzyme, Quantum Biology, and laser photon therapy

FULL TEXT LINKS

Mary Ann Liebert

> Photobiomodul Photomed Laser Surg. 2020 Jul 21;38(9):527-530.
doi: 10.1089/photob.2020.4905. Online ahead of print.

What Lies at the Heart of Photobiomodulation: Light, Cytochrome C Oxidase, and Nitric Oxide–Review of the Evidence

Brendan J Quirk [1], Harry T Whelan [1]

Affiliations

Affiliation

1 Department of Neurology, The Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

PMID: 32716711 PMCID: PMC7495914 DOI: 10.1089/photob.2020.4905
Free PMC article

Abstract

Objective: The underlying mechanisms of photobiomodulation (PBM) remain elusive. The most attractive hypotheses revolve around the role of cytochrome c oxidase (CCO) and cellular energetics. ***Background:*** No reliable demonstration of any PBM-related light-induced mechanistic effect on CCO has been reported. Studies on PBM have proven to be either nonreproducible, of questionable relevance, or involve wavelengths unlikely to be operative *in vivo*. The literature reveals very few demonstrable mechanistic light effects of any sort on CCO. Nitric oxide (NO) is involved in a number of the reported light effects on CCO. NO inhibits CCO at high reductive pressures by binding to the heme a_3 moiety. This complex is white light labile. ***Methods:*** The reported photolability of the heme-NO complex seems to be a prime target for PBM studies, as removal of inhibiting NO from the active site of CCO could restore normal activity to inhibited CCO. Another aspect of CCO-NO chemistry has been revealed that shows intriguing possibilities. ***Results:*** A novel nitrite reductase activity of solubilized mitochondria has been demonstrated attributable to CCO. NO production was optimal under hypoxic conditions. It was also found that 590 nm irradiation increased NO production by enhancing NO release. The presence of cellular NO has usually been considered metabolically detrimental, but current thinking has expanded the importance and the physiological roles of NO. Evidence shows that NO production is likely to play a role in cardioprotection and defenses against hypoxic damage. ***Conclusions:*** Studies combining PBM and hypoxia also point to a connection between light irradiation, hypoxia protection, and NO production. This leads the authors to the possibility that the intrinsic nature of PBM involves the production of NO. The combination of CCO and hemoglobin/myoglobin NO production with photorelease of NO may constitute the heart of PBM.

Keywords: cytochrome c oxidase; nitric oxide; photobiomodulation.

LinkOut - more resources

Full Text Sources
Atypon
Europe PubMed Central

Wavelength- and irradiance-dependent changes in intracellular nitric oxide level

Nathaniel J. Pope,[a,†] Samantha M. Powell,[b,‡] Jeffrey C. Wigle,[c] and Michael L. Denton[c,*]

[a]Oak Ridge Institute of Science and Education, Air Force Research Laboratory, Joint Base San Antonio Fort Sam Houston, Texas, United States
[b]National Research Council, Air Force Research Laboratory, Joint Base San Antonio Fort Sam Houston, Texas, United States
[c]Air Force Research Laboratory, Joint Base San Antonio Fort Sam Houston, Texas, United States

Abstract

Significance: Photobiomodulation (PBM) refers to the beneficial effects of low-energy light absorption. Although there is a large body of literature describing downstream physiological benefits of PBM, there is a limited understanding of the molecular mechanisms underlying these effects. At present, the most popular hypothesis is that light absorption induces release of nitric oxide (NO) from the active site of cytochrome *c* oxidase (COX), allowing it to bind O_2 instead. This is believed to increase mitochondrial respiration, and result in greater overall health of the cell due to increased adenosine triphosphate production.

Aim: Although NO itself is a powerful signaling molecule involved in a host of biological responses, less attention has been devoted to NO mechanisms in the context of PBM. The purpose of our work is to investigate wavelength-specific effects on intracellular NO release in living cells.

Approach: We have conducted in-depth dosimetry analyses of NO production and function in an *in vitro* retinal model in response to low-energy exposure to one or more wavelengths of laser light.

Results: We found statistically significant wavelength-dependent elevations (10% to 30%) in intracellular NO levels following laser exposures at 447, 532, 635, or 808 nm. Sequential or simultaneous exposures to light at two different wavelengths enhanced the NO modulation up to 50% of unexposed controls. Additionally, the immediate increases in cellular NO levels were independent of the function of NO synthase, depended greatly on the substrate source of electrons entering the electron transport chain, and did not result in increased levels of cyclic guanosine monophosphate.

Conclusions: Our study concludes the simple model of light-mediated release of NO from COX is unlikely to explain the wide variety of PBM effects reported in the literature. Our multi-wavelength method provides a novel tool for studying immediate and early mechanisms of PBM as well as exploring intracellular NO signaling networks.

© The Authors. Published by SPIE under a Creative Commons Attribution 4.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: 10.1117/1.JBO.25.8.085001]

Keywords: photobiomodulation; nitric oxide; low-level light; low-level laser; retinal pigment epithelium; fluorescence.

Paper 200106R received Apr. 16, 2020; accepted for publication Jul. 23, 2020; published online Aug. 12, 2020.

*Address all correspondence to Michael L. Denton, E-mail: michael.denton.10@us.af.mil

†Present address: Science Applications International Corp., Inc., Air Force Research Laboratory, Joint Base San Antonio Fort Sam Houston, Texas, United States

‡Present address: Biological Sciences Division, Pacific Northwest National Laboratory, Richland, Washington, United States

Conclusions

"PBM is a rapidly growing field that is becoming increasingly utilized as a therapeutic treatment and has recently been approved as a first-line medical intervention."

"For over 20 years, cytochrome c oxidase has been theorized to be the primary chromophore for PBM effects, whereby subsequent NO eviction is the cited mechanism by which light induces changes in mitochondrial function."

- However, a variety of other potential mechanisms and chromophores have been suggested to also be involved.

"Our finding that multiple wavelengths of light caused release of intracellularly stored NO provides further support that other mechanisms are in play."

"This is particularly true since 447- and 532-nm wavelengths are rarely used for PBM."

"Our surprising finding that light-mediated (635 nm) NO release required pyruvate suggests that the metabolic state of the mitochondria may play a key role in how our cells respond to photostimulation." **[Important]**

"Considering the ongoing debate regarding the molecular mechanisms underlying PBM, continued study of NO and its downstream effects are warranted."

"Having combinations of wavelengths that induce similar or altered levels of NO release, we can begin to uncouple whether or not these downstream indicators of PBM are due to NO, the light, or both."

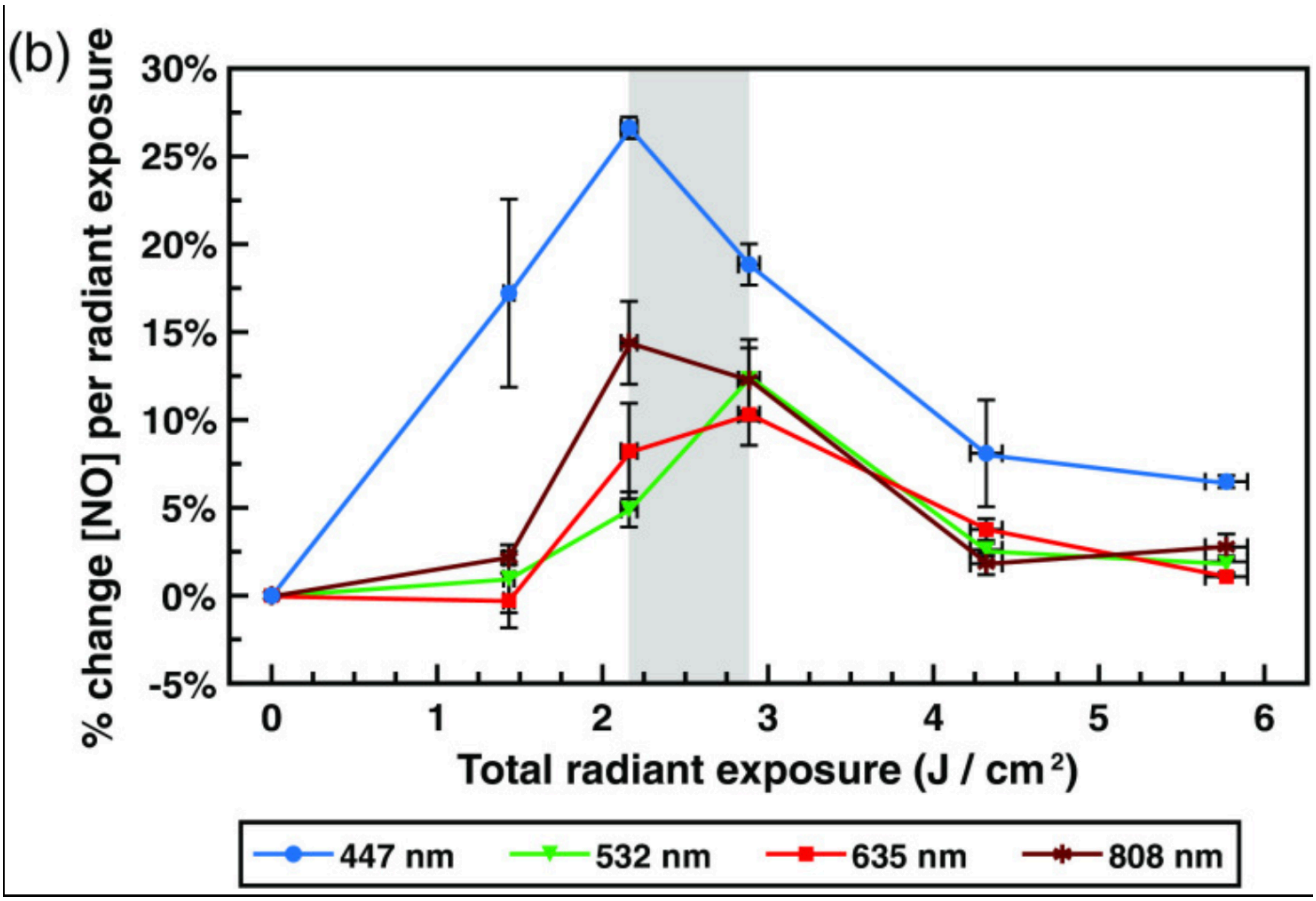
"Finally, we are currently pursuing spectroscopic methods to identify whether or not low levels of red/NIR light dislodges NO bound to cytochrome c oxidase."

Wavelength- and Irradiance-Dependent Changes in Intracellular Nitric Oxide Level

Journal of Biomedical Optics

August 2020; Vol. 25; No. 8; pp. 1020

Nathaniel Pope, Samantha Powell, Jeffery Wigle, Michael Denton
From the United States Air Force Research Laboratory



"Light exposure increases NO levels in a wavelength-dependent manner, with a biphasic dose–response pattern."

Green
520 nm

An official website of the United States government
Here's how you know

FULL TEXT LINKS

ELSEVIER FULL-TEXT ARTICLE

Randomized Controlled Trial > Am J Ophthalmol. 2010 Nov;150(5):726-730.e1.
doi: 10.1016/j.ajo.2010.05.027. Epub 2010 Aug 5.

Pain perception at laser treatment of peripheral retinal degenerations with green and infrared wavelengths

Rodrigo Pessoa Cavalcanti Lira [1], Mauricio Abujamra Nascimento, Carlos Eduardo Leite Arieta, Keila Miriam Monteiro de Carvalho, Valdir Balarin Silva

Affiliations
PMID: 20691418 DOI: 10.1016/j.ajo.2010.05.027

Abstract

Purpose: To compare the pain perception at laser treatment of peripheral retinal degenerations with green (532-nm) and infrared (810-nm) wavelengths.

Design: Prospective randomized clinical trial.

Methods: Sequential patients with indications for photocoagulation of bilateral peripheral retinal degenerations were invited to participate in the study. Thirty patients (60 eyes) were enrolled in the study. Each patient had 1 eye treated with infrared laser (diode, 810-nm wavelength) and the other eye treated with green laser (frequency-doubled solid-state laser, diode-pumped, with 532-nm wavelength). The eyes were randomized to infrared or green wavelengths. The right eye was the first treated in all cases regardless of the wavelength arrangement. Immediately after photocoagulation of each eye, the patient was asked to grade pain perception according to an 11-point (ie, 0-10) numerical rating scale (NRS), with 0 meaning "No pain" and 10 meaning "Pain as bad as you can imagine." The primary outcome was the assessment of pain.

Results: The mean grading of pain perception was 2.80 (SD 1.27; mode and median = 2) to green wavelengths and 5.07 (SD 1.36; mode = 4 and median = 5) to infrared wavelengths ($P < .001$).

Conclusions: The results showed a statistically and clinically significant difference of pain perception between the 2 groups, with advantage to the green laser group.

Trial registration: ClinicalTrials.gov NCT01033968.

Copyright © 2010 Elsevier Inc. All rights reserved.

Related information

MedGen
PubChem Compound
PubChem Substance

LinkOut - more resources

Full Text Sources
ClinicalKey
Elsevier Science

An official website of the United States government
Here's how you know

FULL TEXT LINKS

Mary Ann Liebert

Comparative Study > Photomed Laser Surg. 2016 Nov;34(11):556-563.
doi: 10.1089/pho.2015.4025. Epub 2016 May 31.

Mesenchymal Stem Cells Synergize with 635, 532, and 405 nm Laser Wavelengths in Renal Fibrosis: A Pilot Study

Megan O'Connor [1], Rachana Patil [1], Jiangzhou Yu [1], Richard Hickey [1], Kavitha Premanand [1], Andre Kajdacsy-Balla [2], Enrico Benedetti [1 3], Amelia Bartholomew [1]

Affiliations
PMID: 27244220 DOI: 10.1089/pho.2015.4025

Abstract

Objective: To address whether a single treatment of one of three visible light wavelengths, 635, 532, and 405 nm (constant wave, energy density 2.9 J/m^2), could affect the hallmarks of established renal fibrosis and whether these wavelengths could facilitate mesenchymal stem cell (MSC) beneficence.

Background data: Chronic kidney disease is a global health problem with only 20% receiving care worldwide. Kidneys with compromised function have ongoing inflammation, including increased oxidative stress and apoptosis, peritubular capillary loss, tubular atrophy, and tubulointerstitial fibrosis. Promising studies have highlighted the significant potential of MSC-based strategies to mitigate fibrosis; however, reversal of established fibrosis has been problematic, suggesting that methods to potentiate MSC effects require further development. Laser treatments at visible wavelengths have been reported to enhance mitochondrial potential and available cellular ATP, facilitate proliferation, and inhibit apoptosis. We hypothesized that laser-delivered energy might provide wavelength-specific effects in the fibrotic kidney and enhance MSC responses.

Materials and methods: Renal fibrosis, established in C57BL6 mice following 21 days of unilateral ureter obstruction (UUO), was treated with one of three wavelengths alone or with autologous MSC. Mitochondrial activity, cell proliferation, apoptosis, and cytokines were measured 24 h later.

Results: Wavelengths 405, 532, and 635 nm all significantly synergized with MSC to enhance mitochondrial activity and reduce apoptosis. Proliferative activity was observed in the renal cortices following combined treatment with the 532 nm laser and MSC; endothelial proliferation increased in response to the 635 nm laser alone and to the combined effects of MSC and the 405 nm wavelength. Reductions of transforming growth factor-β were observed with 532 nm alone and when combined with MSC.

Conclusions: Specific wavelengths of laser energy appear to induce different responses in renal fibrotic tissue. These findings support further study in the development of a customized laser therapy program of combined wavelengths to optimize MSC effects in the treatment of renal fibrosis.

Keywords: kidney fibrosis; laser wavelength; mesenchymal stem cell; tissue regeneration.

Related information

MedGen

An official website of the United States government
Here's how you know

FULL TEXT LINKS

WILEY Full Text Article

J Biophotonics. 2022 Jan;15(1):e202100213. doi: 10.1002/jbio.202100213. Epub 2021 Oct 26.

Comparative analysis of two laser wavelengths in the stimulation of acupuncture points for analgesic effects in an animal model

Marcos Aurélio Teixeira [1], Juliana Zampoli Boava Papini [1], Aguinaldo Garcez [1], Giovana Radomille Tofoli [1]

Affiliations

PMID: 34658149 DOI: 10.1002/jbio.202100213

Abstract

This study compares the effectiveness of two laser wavelengths for stimulating acupoints in an experimental model of acute postoperative pain. Forty-five Wistar rats were randomly assigned to receive treatment on their left hind paw, contralateral to a surgical procedure. Laser treatments were performed with Green Laser-GL (532 nm, 70 mW and 7 J/cm^2 of energy), Red Laser-RL (660 nm, 100 mW and 7 J/cm^2 of energy), or with Laser Off-LO. After each application, the animals were evaluated with a Von Frey analgesiometer to check for painful sensitivity on their right (with surgery) and left (without surgery) hind paws. Neuropeptides and cytokine levels in the incision site tissue of the right paw were measured by ELISA after 1, 6 and 24 hours. It was possible to observe that, in this pain model, both lasers promoted analgesia and that the GL altered the levels of TNF-α and IL-1β.

Keywords: acupoints; laser acupuncture; laser puncture; laser therapy; low-power laser acupuncture; postoperative pain.

© 2021 Wiley-VCH GmbH.

Related information

MedGen

LinkOut - more resources

Full Text Sources

Wiley

An official website of the United States government
Here's how you know

FULL TEXT LINKS

Mary Ann Liebert

Randomized Controlled Trial

Photobiomodul Photomed Laser Surg. 2021 Nov;39(11):705-710.
doi: 10.1089/photob.2021.0046.

Clinical Evaluation of 532-nm Green Laser on Dentin Hypersensitivity: A Randomized Double-Blind Clinical Trial

Su-Ning Hu [1 2], Lin-Tian Yuan [1 3], Meng-Qi Wang [3 4], Yu-Guang Wang [1 3], Yong-Sheng Zhou [1]

Affiliations

PMID: 34762532 DOI: 10.1089/photob.2021.0046

Abstract

Objective: The aim of this study was to evaluate the therapies of low-level green laser and chemical desensitizer in the treatment of dentin hypersensitivity (DH). ***Methods:*** Forty-eight patients with 96 sensitive teeth were invited to participate in this clinical trial and were randomly divided into three groups. One group was treated with low-level green laser, the second group was treated with desensitizer [sodium fluoride (NaF)], and the third group acted as the placebo group and was treated with distilled water and placebo laser. The wavelength of green laser was 532 nm and the irradiance was 15 J/cm^2 per treatment site. Hypersensitivity was assessed by visual analogue scale (VAS) according to cold test and probing at baseline. Immediately, 2 weeks, and 3 months after the application of green laser, NaF, and placebo, the participants' sensitivity level was accessed by new VAS analysis. ***Results:*** Forty-five patients with 90 teeth (n = 15 patients/group; 30 teeth/group) were followed up for 2 weeks and 3 months after treatment. There were significant differences in VAS scores between the placebo group and intervention group (green laser group and NaF group; analysis of variance, $p < 0.05$) at all three time points. The mean pain scores in DH reduced significantly immediately after treatment in the green laser group and NaF group when stimulated by cold and probing, whereas no significant difference was observed with these two therapies after 2 weeks ($p > 0.05$). After 3 months, mean VAS scores of the NaF group were higher than those of the green laser group ($p < 0.01$). ***Conclusions:*** Therefore, the green laser displayed similar effectiveness as NaF in treatment of DH and could be a promising new therapy to reduce DH.

Keywords: 532 nm green laser; dentin hypersensitivity; sodium fluoride.

Related information

MedGen
PubChem Compound (MeSH Keyword)

LinkOut - more resources

Full Text Sources
Atypon

An official website of the United States government
Here's how you know

FULL TEXT LINKS

ELSEVIER
OPEN ACCESS

Biochimie. 2022 May;196:225-233. doi: 10.1016/j.biochi.2021.07.009. Epub 2021 Jul 27.

Single and consecutive application of near-infrared and green irradiation modulates adipose derived stem cell proliferation and affect differentiation factors

Anine Crous [1], Madeleen Jansen van Rensburg [2], Heidi Abrahamse [3]

Affiliations

PMID: 34324922 DOI: 10.1016/j.biochi.2021.07.009

Free article

Abstract

Regenerative medicine uses undifferentiated adipose-derived mesenchymal stem cells (ADMSCs) to differentiate into multiple cell types. Photobiomodulation (PBM) is a rapidly growing treatment for pain and inflammation reduction, as well as tissue healing. PBM's efficacy is dependent on wavelength and energy dosage. Red (600-700 nm) and near-infrared (780-1100 nm) wavelengths have been shown to promote cell proliferation. Light wavelengths such as green (495 nm-570 nm) have been found to influence ADMSC differentiation. The initiation of ADMSC proliferation and differentiation requires physiologically relevant levels of reactive oxygen species (ROS), while increased levels inhibit self-renewal. Stem cell differentiation is guided by mitochondrial metabolism, where an increased mitochondrial membrane potential (MMP) is associated with higher in vitro differentiation capacity. ADMSCs must home to and accumulate at the sites of injury in regenerative medicine, so cell homing is critical. The aim of this in vitro study was to compare consecutive NIR (825 nm) and green (525 nm) applications on ADMSC morphology and physiology with the possibility that multiple wavelengths could lead to a combination of the two effects. The results showed that concurrent use of NIR-green irradiation significantly stimulated ADMSC proliferation, increasing population density and cellular ATP. Furthermore, NIR-green showed a time dependent increase in ROS production and was significantly higher at 7 days. Consecutive NIR-green irradiation significantly increased MMP and was most effective at facilitating ADMSC migration over time. Findings suggest that with consecutive NIR and green irradiation, the ADMSCs can rapidly proliferate, but can also be modulated for regenerative purposes.

Keywords: Adipose-derived mesenchymal stem cells; Green light; Near-infrared irradiation; Photobiomodulation; Regenerative medicine.

Copyright © 2021 The Authors. Published by Elsevier B.V. All rights reserved.

Related information

MedGen

LinkOut - more resources

Full Text Sources

Elsevier Science

An official website of the United States government
Here's how you know

FULL TEXT LINKS

WILEY Full Text Article

J Cosmet Dermatol. 2022 Nov;21(11):5696-5703. doi: 10.1111/jocd.15298. Epub 2022 Sep 19.

Low-level green laser promotes wound healing after carbon dioxide fractional laser therapy

Chengchen Gong [1], Yongzhou Lu [1], Chuanlong Jia [1], Nan Xu [1]

Affiliations

PMID: 35947511 DOI: 10.1111/jocd.15298

Abstract

Background: The carbon dioxide (CO_2) fractional laser resurfacing has become one of the hottest therapies for dermatoses. However, complications such as skin swelling, prolonged erythema, post-inflammatory hyperpigmentation, and scar formation remain. Low-level laser (LLL) therapy is accepted to promote skin wound healing and regeneration, decrease inflammation and pain, and modulate immunoreaction with low-dose laser of different wavelength. 532 nm laser therapy is commonly used to remove pigmented spots and to tender skin, but not utilized in wound care.

Objective: We aimed to determine the efficacy of the low-level 532 nm green laser in wound healing after CO_2 fractional laser.

Methods: Six adult male mice (C57BL/6, 8 weeks old) were prepared for animal experiments. The dorsum of each mouse was divided into four parts that, respectively, received designed treatments, as controlled (group Ctrl), 532 nm LLL-treated (group GL), CO_2 fractional laser-treated (group FL), and CO_2 fractional laser followed by three times 532 nm LLL-treated (group FG). Hematoxylin-eosin staining (H&E), Masson-trichrome staining, CD31 immunohistochemical staining were performed to evaluate the efficacy of wound healing after treated by different irradiations. Western blotting was used to detect the expression of related proteins. Mouse skin fibroblasts (MSFs) were treated with LLL using a wavelength of 532 nm once. Cellular responses were observed and analyzed after 48 hours. Cell viability and migration of different groups were assessed by scratch and the Cell Counting Kit-8 (CCK8) assays, respectively.

Results: Collagen remodeling and epidermis thickness were significantly enhanced in group FG than that in group FL in morphology. Besides, CD31 immunohistochemical staining indicated prominently increased angiogenesis in both groups FL and FG than non-irradiation group. The expression of extracellular matrix (ECM)-related protein (Col1, Col3 and MMP1) showed a remarkable improvement in wound healing in group FG than that in group FL. Irradiated MSFs showed a better migration ability compared with non-irradiated controls. LLL enhanced the secretion function of MSFs on Collagen I and III.

Conclusions: Low-level green laser promotes wound healing after CO_2 fractional laser by improving the integrity of skin barrier and allowing for scarless healing. Therefore, low-level green laser therapy might serve as a sequential therapy of invasive laser surgery to ensure a better wound care.

Keywords: collagen regeneration and remodeling; fractional carbon dioxide laser; low-level green laser; scar formation; wound healing.

© 2022 Wiley Periodicals LLC.

AMERICA IN PAIN 12/26/22

Soon, science of treatment could turn a corner

ABOUT THIS SERIES

This is the fifth of a five-part series exploring chronic pain, the challenges of treatment and the scientific advances offering hope for the future.

Monday: The biology of pain

Tuesday: Pediatric pain

Wednesday: Complementary therapies for pain

Thursday: Cannabis for pain control

Today: The future of pain control

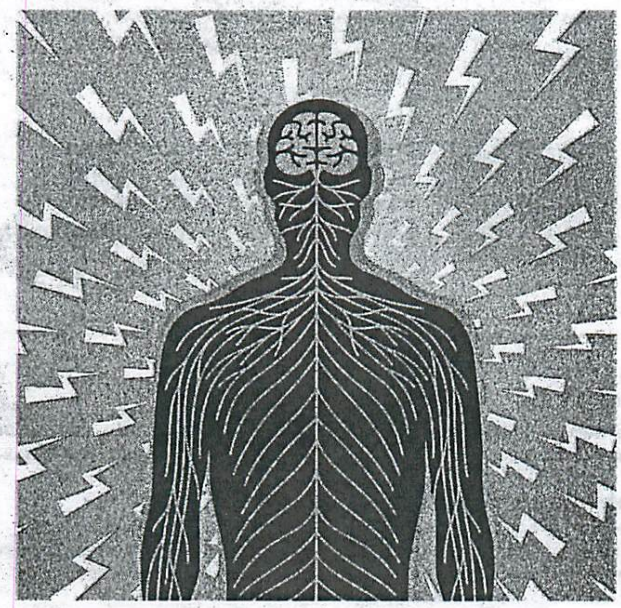


ILLUSTRATION: ANDREA BRUNTY/USA TODAY; GETTY IMAGES

Lighting the way

USAT 12-23-22

One day Dr. Mohab Ibrahim had a headache.

A pain expert at the University of Arizona College of Medicine, Ibrahim didn't have any ibuprofen or acetaminophen at home. He could go to the drugstore and buy some, or listen to his brother's pet theory that being around trees relieved his pain.

Ibrahim

Ibrahim decided to go for a walk in the park.

"It worked for me." His headache went away and he began investigating why the park might have had a pain-killing benefit.

He thought it could have been chemicals in the air, but that would "take several lifetimes worth of investigations to find out." So Ibrahim decided to study the color green instead.

He exposed rats to different wavelengths of light. Blue and green light seemed to increase their tolerance for high temperatures and mechanical stimulation. Blue light is known to interfere with sleep, so he decided to pursue green light as a pain therapy.

So far, he has done two small clinical trials with strings of green LED lights, exposing people with migraine or the pain condition fibromyalgia who hadn't been helped by conventional treatment.

At the end of the study period, the trial volunteers were supposed to return their green lights, but they refused. Periodically, they reach out to Ibrahim to ask for replacement bulbs, said Ibrahim, who has started a company to commercialize green light technology and phototherapy.

An official website of the United States government
Here's how you know

FULL TEXT LINKS

Wolters Kluwer

Pain. 2017 Feb;158(2):347-360. doi: 10.1097/j.pain.0000000000000767.

Long-lasting antinociceptive effects of green light in acute and chronic pain in rats

Mohab M Ibrahim [1 2], Amol Patwardhan [1 2], Kerry B Gilbraith [1], Aubin Moutal [2], Xiaofang Yang [2], Lindsey A Chew [2], Tally Largent-Milnes [2], T Philip Malan [1 2], Todd W Vanderah [1 2], Frank Porreca [1 2], Rajesh Khanna [2]

Affiliations

Affiliations

1 Departments of Anesthesiology and.
2 Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, USA.

PMID: 28092651 PMCID: PMC5242385 DOI: 10.1097/j.pain.0000000000000767
Free PMC article

Abstract

Treatments for chronic pain are inadequate, and new options are needed. Nonpharmaceutical approaches are especially attractive with many potential advantages including safety. Light therapy has been suggested to be beneficial in certain medical conditions such as depression, but this approach remains to be explored for modulation of pain. We investigated the effects of light-emitting diodes (LEDs), in the visible spectrum, on acute sensory thresholds in naive rats as well as in experimental neuropathic pain. Rats receiving green LED light (wavelength 525 nm, 8 h/d) showed significantly increased paw withdrawal latency to a noxious thermal stimulus; this antinociceptive effect persisted for 4 days after termination of last exposure without development of tolerance. No apparent side effects were noted and motor performance was not impaired. Despite LED exposure, opaque contact lenses prevented antinociception. Rats fitted with green contact lenses exposed to room light exhibited antinociception arguing for a role of the visual system. Antinociception was not due to stress/anxiety but likely due to increased enkephalins expression in the spinal cord. Naloxone reversed the antinociception, suggesting involvement of central opioid circuits. Rostral ventromedial medulla inactivation prevented expression of light-induced antinociception suggesting engagement of descending inhibition. Green LED exposure also reversed thermal and mechanical hyperalgesia in rats with spinal nerve ligation. Pharmacological and proteomic profiling of dorsal root ganglion neurons from green LED-exposed rats identified changes in calcium channel activity, including a decrease in the N-type (CaV2.2) channel, a primary analgesic target. Thus, green LED therapy may represent a novel, nonpharmacological approach for managing pain.

Figures

An official website of the United States government
Here's how you know

FULL TEXT LINKS

SAGE journals

Clinical Trial > Cephalalgia. 2021 Feb;41(2):135-147. doi: 10.1177/0333102420956711. Epub 2020 Sep 9.

Evaluation of green light exposure on headache frequency and quality of life in migraine patients: A preliminary one-way cross-over clinical trial

Laurent F Martin [1 2], Amol M Patwardhan [1 2 3 4], Sejal V Jain [5], Michelle M Salloum [1], Julia Freeman [1], Rajesh Khanna [1 2 4], Pooja Gannala [1], Vasudha Goel [6], Felesia N Jones-MacFarland [5], William Ds Killgore [7], Frank Porreca [1 2], Mohab M Ibrahim [1 2 3 4]

Affiliations

Affiliations

1 Department of Anesthesiology, College of Medicine, University of Arizona, Tucson, AZ, USA.
2 Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, USA.
3 Department of Neurosurgery, College of Medicine, University of Arizona, Tucson, AZ, USA.
4 Comprehensive Pain and Addiction Center, University of Arizona, Tucson, AZ, USA.
5 Department of Neurology, College of Medicine, University of Arizona, Tucson, AZ, USA.
6 Department of Anesthesiology, University of Minnesota, Minneapolis, MN, USA.
7 Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, USA.

PMID: 32903062 PMCID: PMC8034831 DOI: 10.1177/0333102420956711
Free PMC article

Abstract

Background: Pharmacological management of migraine can be ineffective for some patients. We previously demonstrated that exposure to green light resulted in antinociception and reversal of thermal and mechanical hypersensitivity in rodent pain models. Given the safety of green light emitting diodes, we evaluated green light as a potential therapy in patients with episodic or chronic migraine.

Material and methods: We recruited (29 total) patients, of whom seven had episodic migraine and 22 had chronic migraine. We used a one-way cross-over design consisting of exposure for 1-2 hours daily to white light emitting diodes for 10 weeks, followed by a 2-week washout period followed by exposure for 1-2 hours daily to green light emitting diodes for 10 weeks. Patients were allowed to continue current therapies and to initiate new treatments as directed by their physicians. Outcomes consisted of patient-reported surveys. The primary outcome measure was the number of headache days per month. Secondary outcome measures included patient-reported changes in the intensity and frequency of the headaches over a two-week period and other quality of life measures including ability to fall and stay asleep, and ability to perform work. Changes in pain medications were obtained to assess potential reduction.

Results: When seven episodic migraine and 22 chronic migraine patients were analyzed as separate cohorts, white light emitting diodes produced no significant change in headache days in

either episodic migraine or chronic migraine patients. Combining data from the episodic migraine and chronic migraine groups showed that white light emitting diodes produced a small, but statistically significant reduction in headache days from (days ± SEM) 18.2 ± 1.8 to 16.5 ± 2.01 days. Green light emitting diodes resulted in a significant decrease in headache days from 7.9 ± 1.6 to 2.4 ± 1.1 and from 22.3 ± 1.2 to 9.4 ± 1.6 in episodic migraine and chronic migraine patients, respectively. While some improvement in secondary outcomes was observed with white light emitting diodes, more secondary outcomes with significantly greater magnitude including assessments of quality of life, Short-Form McGill Pain Questionnaire, Headache Impact Test-6, and Five-level version of the EuroQol five-dimensional survey without reported side effects were observed with green light emitting diodes. Conclusions regarding pain medications reduction with green light emitting diode exposure were not possible. No side effects of light therapy were reported. None of the patients in the study reported initiation of new therapies.

Discussion: Green light emitting diodes significantly reduced the number of headache days in people with episodic migraine or chronic migraine. Additionally, green light emitting diodes significantly improved multiple secondary outcome measures including quality of life and intensity and duration of the headache attacks. As no adverse events were reported, green light emitting diodes may provide a treatment option for those patients who prefer non-pharmacological therapies or may be considered in complementing other treatment strategies. Limitations of this study are the small number of patients evaluated. The positive data obtained support implementation of larger clinical trials to determine possible effects of green light emitting diode therapy.This study is registered with clinicaltrials.gov under NCT03677206.

Keywords: Green light; light therapy; migraine; non-pharmacological therapy.

Figures

Figure 1. Study design. One-way cross-over clinical...

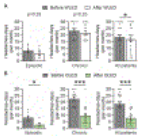


Figure 2. GLED exposure decreased headache days/month....

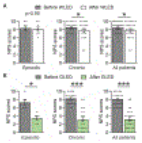


Figure 3. GLED exposure decreased the numeric...

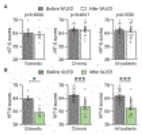


Figure 4. GLED exposure improved the Headache...

Figure 5. GLED exposure improved all quality...

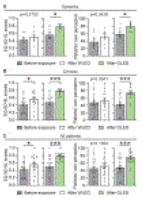


Figure 6. Five-level version of the EuroQol...

Related information

MedGen

An official website of the United States government
Here's how you know

FULL TEXT LINKS
OXFORD ACADEMIC

Clinical Trial > Pain Med. 2021 Feb 4;22(1):118-130. doi: 10.1093/pm/pnaa329.

Green Light Exposure Improves Pain and Quality of Life in Fibromyalgia Patients: A Preliminary One-Way Crossover Clinical Trial

Laurent Martin [1], Frank Porreca [1 2], Elizabeth I Mata [3], Michelle Salloum [3], Vasudha Goel [4], Pooja Gunnala [1], Wiliam D S Killgore [5], Sejal Jain [6], Felesia N Jones-MacFarland [6], Rajesh Khanna [1 2 7], Amol Patwardhan [1 2], Mohab M Ibrahim [1 2]

Affiliations

Affiliations

1 Departments of Pharmacology, University of Arizona, Tucson, Arizona, USA.
2 Anesthesiology, University of Arizona, Tucson, Arizona, USA.
3 College of Medicine, University of Arizona, Tucson, Arizona, USA.
4 Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota, USA.
5 Psychiatry, University of Arizona, Tucson, Arizona, USA.
6 Neurology, University of Arizona, Tucson, Arizona, USA.
7 Graduate Interdisciplinary Program in Neuroscience, University of Arizona, Tucson, Arizona, USA.

PMID: 33155057 PMCID: PMC7861466 DOI: 10.1093/pm/pnaa329
Free PMC article

Abstract

Objective: Fibromyalgia is a functional pain disorder in which patients suffer from widespread pain and poor quality of life. Fibromyalgia pain and its impact on quality of life are not effectively managed with current therapeutics. Previously, in a preclinical rat study, we demonstrated that exposure to green light-emitting diodes (GLED) for 8 hours/day for 5 days resulted in antinociception and reversal of thermal and mechanical hypersensitivity associated with models of injury-related pain. Given the safety of GLED and the ease of its use, our objective is to administer GLED as a potential therapy to patients with fibromyalgia.

Design: One-way crossover clinical trial.

Setting: United States.

Method: We enrolled 21 adult patients with fibromyalgia recruited from the University of Arizona chronic pain clinic who were initially exposed to white light-emitting diodes and then were crossed over to GLED for 1 to 2 hours daily for 10 weeks. Data were collected by using paper surveys.

Results: When patients were exposed to GLED, but not white light-emitting diodes, they reported a significant reduction in average pain intensity on the 10-point numeric pain scale. Secondary outcomes were assessed by using the EQ-5D-5L survey, Short-Form McGill Pain Questionnaire, and Fibromyalgia Impact Questionnaire and were also significantly improved in patients exposed to GLED. GLED therapy was not associated with any measured side effects in these patients.

Conclusion: Although the mechanism by which GLED elicits pain reduction is currently being studied, these results supporting its efficacy and safety merit a larger clinical trial.

Trial registration: ClinicalTrials.gov NCT03677206.

Keywords: Complementary Therapy; EQ-5D-5L; Fibromyalgia; Green Light.

© The Author(s) 2020. Published by Oxford University Press on behalf of the American Academy of Pain Medicine. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Figures

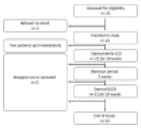


Figure 1. Study design: one-way crossover clinical...

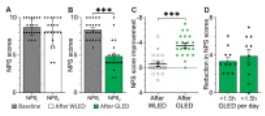


Figure 2. Pain score evaluation before and...

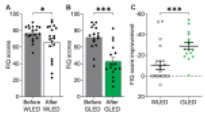


Figure 3. FIQ scores before and after...

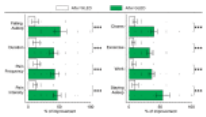


Figure 4. Patients' subjective improvement of several...

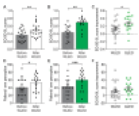


Figure 5. Quality of life and patients'...

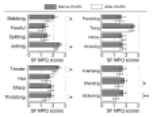


Figure 6. SF MPQ scores before and...

All figures (7)

Related information

MedGen

LinkOut - more resources

Full Text Sources

Europe PubMed Central
Ovid Technologies, Inc.
PubMed Central
Silverchair Information Systems
Wiley

Medical

ClinicalTrials.gov
Genetic Alliance
MedlinePlus Health Information

Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review

Journal of Pain
July 2021; Vol. 22; No. 7; pp. 763-777

HHS Public Access

Kevin Cheng, Laurent F Martin, Marvin J Slepian, Amol M Patwardhan, Mohab M Ibrahim: From the University of Arizona, Tucson. This study cites 105 references.

A growing body of evidence supports the modulation of pain by light exposure. The exposure to light has many important implications on human biology and behavior.

As such, phototherapy is being increasingly utilized for the management of a variety of pain conditions.

Cutaneous application of red light (660nm) has been shown to reduce pain in neuropathies and complex regional pain syndrome-I.

Visual exposure to green light can result in reduction in pain in variety of pain conditions such as migraine and fibromyalgia. Cutaneous application typically requires exposure on the order of minutes, whereas visual application requires exposure on the order of hours.

Both routes of exposure elicit changes centrally in the brainstem and spinal cord, and peripherally in the dorsal root ganglia and nociceptors.

Light of various colors and wavelengths has since been used to treat a wide variety of conditions, including neonatal jaundice, seasonal affective disorder, acne, circadian rhythm disruptions, and psoriasis.

Investigations into the use of light as a treatment for symptomatic pain and pain syndromes have become particularly attractive as they are considered a low-cost, nonpharmacologic alternative with few side effects.

Green light via the visual system resulted in lesser pain in an acute migraine episode compared to the exposure of other wavelengths such as white, blue, amber, and red.

The fact that light can modulate pain is increasingly being acknowledged with more experimental and clinical evidence forthcoming.

Light travels through the cornea/lens and reaches the retina, where it acts on cone and rod photoreceptors in the outer segment of the retina.

The second route of photoreception and phototransduction occurs through the

integumentary system. The skin in humans is the largest organ in the body, and light that is perceived by the eyes is sensed by the skin as well.

Endogenous noxious signals such as glutamate, prostaglandin E2, and bradkinin are reduced with red light (660 nm).

Green light causing anti-nociception likely act through a cone-driven mechanism in the eye which ultimately elicits downstream analgesic effects.

It is also interesting to note that the duration of light exposure required for green light to be therapeutic is on the order of hours, which is in contrast to that of red and near-infrared light treatments (seconds to minutes). This further supports the difference in mechanisms engaged by different colors of light and routes of administration, as described above.

Green light therapy has also recently been used in the treatment of migraines, significantly reducing the number of the number of headache days as well as the intensity and duration of headache attacks in episodic or chronic migraineurs.

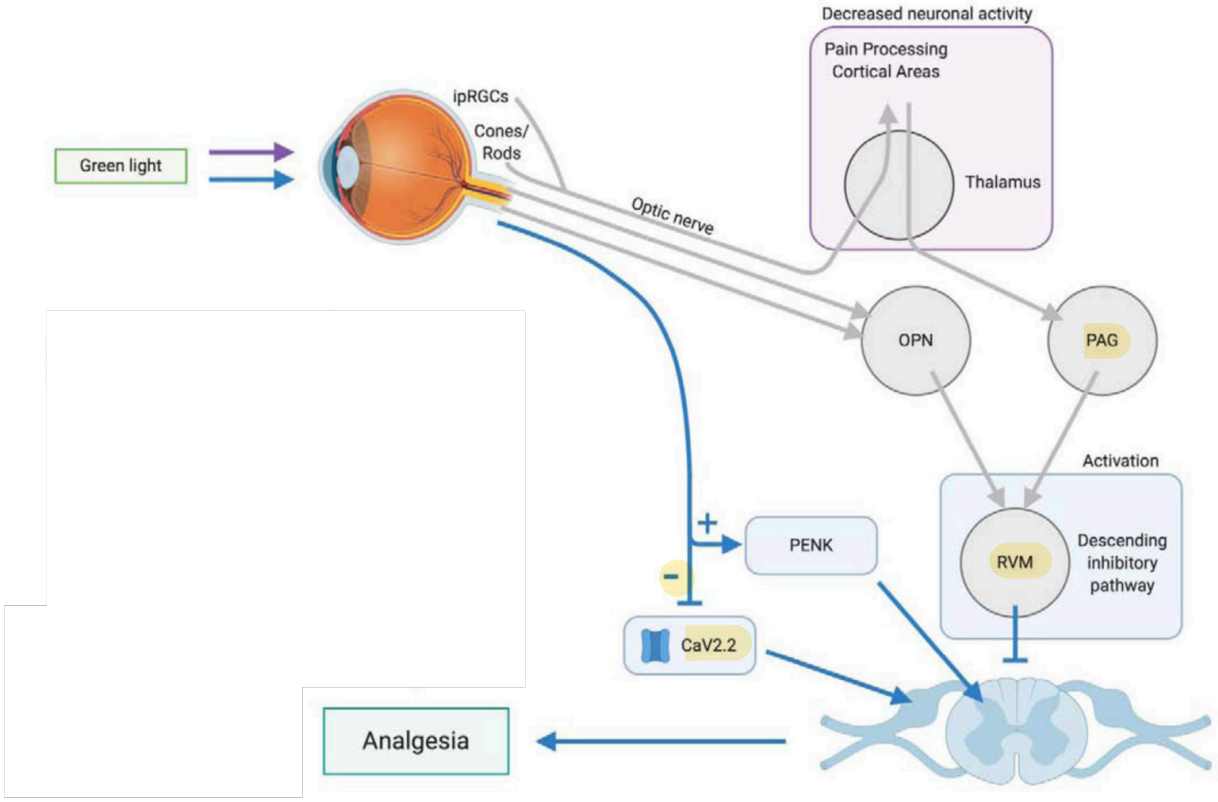
Numerous reports in the past decade have now documented the mechanisms of pain modulation by light.

The color of light is important: “green light decreases pain.”

Cutaneous application acts primarily via peripheral mechanisms, whereas visual application acts via central mechanisms.

For the treatment of pain, red and near-infrared light are administered cutaneously with a short duration of exposure. (i.e. seconds to minutes), whereas green and bright white light are administered visually with long duration of exposure (i.e. hours).

Current evidence shows the efficacy of light treatment for pain in a variety of pain syndromes, including fibromyalgia, complex regional pain syndrome I and chronic low back pain.


Decreased neuronal activity
Pain Processing Cortical Areas
Thalamus
ipRGCs
Cones/ Rods
Green light
Optic nerve
OPN
PAG
Activation
RVM
Descending inhibitory pathway
PENK
+
-
CaV2.2
Analgesia

An official website of the United States government
Here's how you know

FULL TEXT LINKS

ELSEVIER FULL-TEXT ARTICLE

J Pain. 2021 Dec;22(12):1646-1656. doi: 10.1016/j.jpain.2021.05.006. Epub 2021 Jun 19.

Green Light Antinociceptive and Reversal of Thermal and Mechanical Hypersensitivity Effects Rely on Endogenous Opioid System Stimulation

Laurent F Martin [1], Aubin Moutal [2], Kevin Cheng [2], Stephanie M Washington [3], Hugo Calligaro [4], Vasudha Goel [5], Tracy Kranz [3], Tally M Largent-Milnes [2], Rajesh Khanna [6], Amol Patwardhan [7], Mohab M Ibrahim [8]

Affiliations

PMID: 34157406 PMCID: PMC8664962 DOI: 10.1016/j.jpain.2021.05.006

Free PMC article

Abstract

Benefits of phototherapy were characterized in multiple diseases including depression, circadian rhythm disruptions, and neurodegeneration. Studies on migraine and fibromyalgia patients revealed that green light-emitting diodes (GLED) exposure provides a pragmatic and safe therapy to manage chronic pain. In rodents, GLED reversed hypersensitivity related to neuropathic pain. However, little is known about the underlying mechanisms of GLED efficacy. Here, we sought to understand how green light modulates the endogenous opioid system. We first characterized how exposure to GLED stimulates release of β-endorphin and proenkephalin in the central nervous system of male rats. Moreover, by individually editing each of the receptors, we found that μ- and δ-opioid receptors are required for green light's antinociceptive effect in naïve rats and a model of HIV-induced peripheral neuropathy. We investigated how GLED could increase pain thresholds, and explored its potential in reversing hypersensitivity in a model of HIV-related neuropathy. Through behavioral and gene editing approaches, we identified that green light provides antinociception via modulation of the endogenous opioid system in the spinal cord. This work identifies a previously unknown mechanism by which GLED can improve pain management. Clinical translation of these results will advance the development of an innovative therapy devoid of adverse effects. PERSPECTIVE: Development of new pain management therapies, especially for HIV patients, is crucial as long-term opioid prescription is not recommended due to adverse side effects. Green light addresses this necessity. Characterizing the underlying mechanisms of this potentially groundbreaking and safe antinociceptive therapy will advance its clinical translation.

Keywords: GP120; Phototherapy; endogenous opioids; green light; neuropathic pain.

Copyright © 2021 United States Association for the Study of Pain, Inc. Published by Elsevier Inc. All rights reserved.

Figures

An official website of the United States government
Here's how you know

FULL TEXT LINKS

SAGE journals
Open access full text

Case Reports > Clin Med Insights Case Rep. 2022 Sep 20;15:11795476221125164.
doi: 10.1177/11795476221125164. eCollection 2022.

Case Report: Green Light Exposure Relieves Chronic Headache Pain in a Colorblind Patient

Kevin Cheng [1 2], Laurent F Martin [1 2], Hugo Calligaro [3], Amol Patwardhan [1 2 4 5], Mohab M Ibrahim [1 2 4 5]

Affiliations

PMID: 36159182 PMCID: PMC9493681 DOI: 10.1177/11795476221125164

Free PMC article

Abstract

Patients with chronic headaches sometimes prefer non-pharmacological methods for pain management. We have shown previously that green light exposure (GLED, Green Light Emitting Diode) reversed thermal hyperalgesia and mechanical allodynia in a rat model of neuropathic pain. This effect is mediated through the visual system. Moreover, we recently showed that GLED was effective in decreasing the severity of headache pain and the number of headache-days per month in migraine patients. The visual system is comprised of image-forming and non-image-forming pathways; however, the contribution of different photosensitive cells to the effect of GLED is not yet known. Here, we report a 66-year-old man with headaches attributed to other disorders of homeostasis and color blindness who was recruited in the GLED study. The subject, diagnosed with protanomaly, cannot differentiate green, yellow, orange, and red colors. After completing the GLED exposure protocol, the subject noted significant decreases in headache pain intensity without reduction in the number of headache-days per month. The subject also reported improvement in the quality of his sleep. These findings suggest that green light therapy mediates the decrease of the headache pain intensity through non-image-forming intrinsically photosensitive retinal ganglion cells. However, the subject did not report a change in the frequency of his headaches, suggesting the involvement of cones in reduction of headache frequency by GLED. This is the first case reported of a colorblind man with chronic headache using GLED to manage his headache pain and may increase our understanding of the contribution of different photosensitive cells in mediating the pain-relieving effects of GLED.

Keywords: Phototherapy; analgesia; colorblind; green light; headaches attributed to other disorders of homeostasis.

© The Author(s) 2022.

Figures

An official website of the United States government
Here's how you know

FULL TEXT LINKS

ELSEVIER FULL-TEXT ARTICLE

J Pain. 2022 Oct 23;S1526-5900(22)00437-0. doi: 10.1016/j.jpain.2022.10.011.
Online ahead of print.

Green Light Exposure Elicits Anti-inflammation, Endogenous Opioid Release and Dampens Synaptic Potentiation to Relieve Post-surgical Pain

Laurent F Martin [1], Kevin Cheng [2], Stephanie M Washington [3], Millie Denton [3], Vasudha Goel [4], Maithili Khandekar [3], Tally M Largent-Milnes [2], Amol Patwardhan [5], Mohab M Ibrahim [6]

Affiliations
PMID: 36283655 DOI: 10.1016/j.jpain.2022.10.011

Abstract

Light therapy improves multiple conditions such as seasonal affective disorders, circadian rhythm dysregulations, and neurodegenerative diseases. However, little is known about its potential benefits in pain management. While current pharmacologic methods are effective in many cases, the associated side effects can limit their use. Non-pharmacological methods would minimize drug dependence, facilitating a reduction of the opioid burden. Green light therapy has been shown to be effective in reducing chronic pain in humans and rodents. However, its underlying mechanisms remain incompletely defined. In this study, we demonstrate that green light exposure reduced postsurgical hypersensitivity in rats. Moreover, this therapy potentiated the antinociceptive effects of morphine and ibuprofen on mechanical allodynia in male rats. Importantly, in female rats, GLED potentiated the antinociceptive effects of morphine but did not affect that of ibuprofen. We showed that green light increases endogenous opioid levels while lessening synaptic plasticity and neuroinflammation. Importantly, this study reveals new insights into how light exposure can affect neuroinflammation and plasticity in both genders. Clinical translation of these results could provide patients with improved pain control and decrease opioid consumption. Given the noninvasive nature of green light, this innovative therapy would be readily implementable in hospitals. Perspective: This study provides a potential additional therapy to decrease postsurgical pain. Given the safety, availability, and the efficacy of green light therapy, there is a significant potential for advancing the green light therapy to clinical trials and eventual translation to clinical settings.

Keywords: Endogenous opioid; GLED phototherapy; Neuroinflammation; Plasticity; Postsurgical pain.

Copyright © 2022 United States Association for the Study of Pain, Inc. Published by Elsevier Inc. All rights reserved.

LinkOut - more resources

Full Text Sources
Elsevier Science

© Robert Daly | Getty Images

Bottom Line

Green Glasses May Ease Chronic Pain

In a small study, people with fibromyalgia who wore green-tinted glasses for four hours per day for two weeks used fewer opioids than people who wore blue or clear glasses. The research suggests that some wavelengths of green light stimulate the brain pathways that help manage pain. The glasses also reduced fear-based anxiety. Another study linked green LED exposure with fewer episodic and chronic migraine headaches. Jan 2023

American Society of Anesthesiologists

Pain

Inflammatory Chemicals
Brief Summary

Eicosanoids	**Cytokines**
Prostaglandin E2 PGE2 Hormone-Like Molecules Derived from Omega-6 Fatty Acid *Arachidonic Acid* Linoleic Acid (Corn/ Soy) Insulin-D5D → Arachidonic Acid COX → PGE2 High Omega-6/Omega-3 ratio >3/1 <u>Ratio Improved By</u> •Limiting omega-6 and grained meat/egg consumption •Increasing omega-3 and wild fish consumption **COX Enzymes are Inhibited by Red LLLT** **Red LLLT Reduces PGE2 Accumulation** Motion Disperses Accumulation Chiropractic, etc. Inflammatory Eicosanoids Increase Inflammatory Cytokines	Interleukin-6 IL-6 Proteins Derived from Immune Cell Activation Infection Excessive Immunological Responses Autoimmune Diseases Leaky Gut Low Vitamin D Altered Vitamin D Receptor Low Levels of IL-10 <u>Improved/Reduced By</u> Immune Enhancing Supplements •Vitamin D •Vitamin C •Magnesium •Zinc •Omega-3s Heal the Leaky Gut Avoid Harmful Wavelengths >850 nm **Violet LLLT Are Antimicrobial** **Violet LLLT Reduce/Inhibit IL-6** **Red LLLT Reduce/Inhibit IL-6** **Red LLLT Increases IL-10** Vigorous Exercise Increases IL-10 Chiropractic Increased IL-10 Chiropractic May Be Immunoenhancing Motion Disperses Accumulation Chiropractic, etc. Inflammatory Eicosanoids Increase Inflammatory Cytokines

Three Major Drivers of Inflammation Related to Pain Perception

Omega-6/Omega-3	**Inflammatory Cytokines**	**Systemic Inflammation**
Excessive Inflammatory Prostaglandins and Leukotrienes	TNF-alpha Interleukin-6	<u>Leaky Gut</u> Lectins <u>Chronic Infection</u> Lyme Herpes Molds Etc.

PubMed

Display Settings: Abstract

Int J Clin Pharmacol Ther. 1995 Apr;33(4):208-11.

Successful management of female office workers with "repetitive stress injury" or "carpal tunnel syndrome" by a new treatment modality--application of low level laser.

Wong E, **Lee G**, Zucherman J, Mason DT.

Author information

Abstract

Female office workers with desk jobs who are incapacitated by pain and tingling in the hands and fingers are often diagnosed by physicians as "repetitive stress injury" (RSI) or "carpal tunnel syndrome" (CTS). These patients usually have poor posture with their head and neck stooped forward and shoulders rounded; upon palpation, they have pain and tenderness at the spinous processes C5-T1 and the medial angle of the scapula. In 35 such patients we focused the treatment primarily at the posterior neck area and not the wrists and hands. A low level laser (100 mW) was used and directed at the tips of the spinous processes C5-T1. The laser rapidly alleviated the pain and tingling in the arms, hands and fingers, and diminished tenderness at the involved spinous processes. Thereby, it has become apparent that many patients labelled as having RSI or CTS have predominantly cervical radicular dysfunction resulting in pain to the upper extremities which can be managed by low level laser. Successful long-term management involves treating the soft tissue lesions in the neck combined with correcting the abnormal head, neck and shoulder posture by taping, cervical collars, and clavicle harnesses as well as improved work ergonomics.

PMID: 7620690 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

"All laser treatment [should be] proceeded by a stimulating irradiating of the vertebra that innervates the damaged area." Page 146

The biostimulatory action of laser therapy is countered by the presence of NSAIDs and steroids that are non-acceptors of laser therapy, as the latter block the membrane channels and antennae pigment receptors that laser therapy relies upon." Page 91

Laser Therapy

Clinical Practice and Scientific Background

A guide for research scientists, doctors, dentists, veterinarians and other interested parties within the medical field.

By
Jan Tunér and Lars Hode

Prima Books AB
2002

570 pages

1281 references

Laser Phototherapy Clinical Practice and Scientific Background

Lars Hode (physicist) and Jan Tuner (dentist)
Prima Books 2014
936 Pages; 2534 References

Systemic or indirect irradiation include the irradiation of (p. 117):

- Acupuncture Points
- Trigger Points
- Spinous Processes
- The Dermatome
- The Blood
- Lymph Nodes

"In these instances we irradiate areas outside or far from the area where the patient would otherwise locate the problem."

"Direct and indirect treatment can be combined. In fact, even direct irradiation is a mode of indirect irradiation."

"The beam will always find blood, lymph and nerves, influencing the circulating metabolites."

"So every local treatment is also a systemic treatment."

Spinal Processes (p. 131)

"Irradiation of the spinal processes corresponding to the area where the pain is located will reduce the pain."

It may be a nerve entrapment in the nerve passage leading into the spinal cord and laser treatment may reduce edema around the nerve and hence pain relief.

PubMed

Format: Abstract

Full text links

Science

Science. 1973 Mar 9;179(4077):1011-4.

Opiate receptor: demonstration in nervous tissue.

Pert CB, **Snyder** SH.

Abstract

Tritiated naloxone, a powerful opiate antagonist, specifically binds to an opiate receptor of mammalian brain and guinea pig intestine. Competition for the opiate receptor by various opiates and their antagonists closely parallels their pharmacological potency. The opiate receptor is confined to nervous tissue.

PMID: 4687585

[Indexed for MEDLINE]

MeSH terms, Substances

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

How to join PubMed Commons

Candace B. Pert, Ph.D.

Foreword by Deepak Chopra, M.D.

1997

Molecules of Emotion

THE SCIENCE BEHIND MIND-BODY MEDICINE

"Candace B. Pert . . . has managed to take the study of the emotional connection to the body . . . and present this information in not only an understandable manner, but an enjoyable one."

—Caroline Myss, Ph.D., author of *Why People Don't Heal and How They Can*

"An important book."

DAVID S. LUDWIG, MD, PHD, PROFESSOR, HARVARD MEDICAL SCHOOL;
NEW YORK TIMES BESTSELLING AUTHOR

2017

MEMORY

MEMORY RESCUE

SUPERCHARGE YOUR BRAIN, REVERSE MEMORY LOSS, AND REMEMBER WHAT MATTERS MOST

THE OFFICIAL PROGRAM OF THE AMEN CLINICS

DANIEL G. AMEN, MD

“The prefrontal cortex (which is involved with focus, forethought, judgment, and impulse control) is the area of the brain most densely populated with mitochondria.”

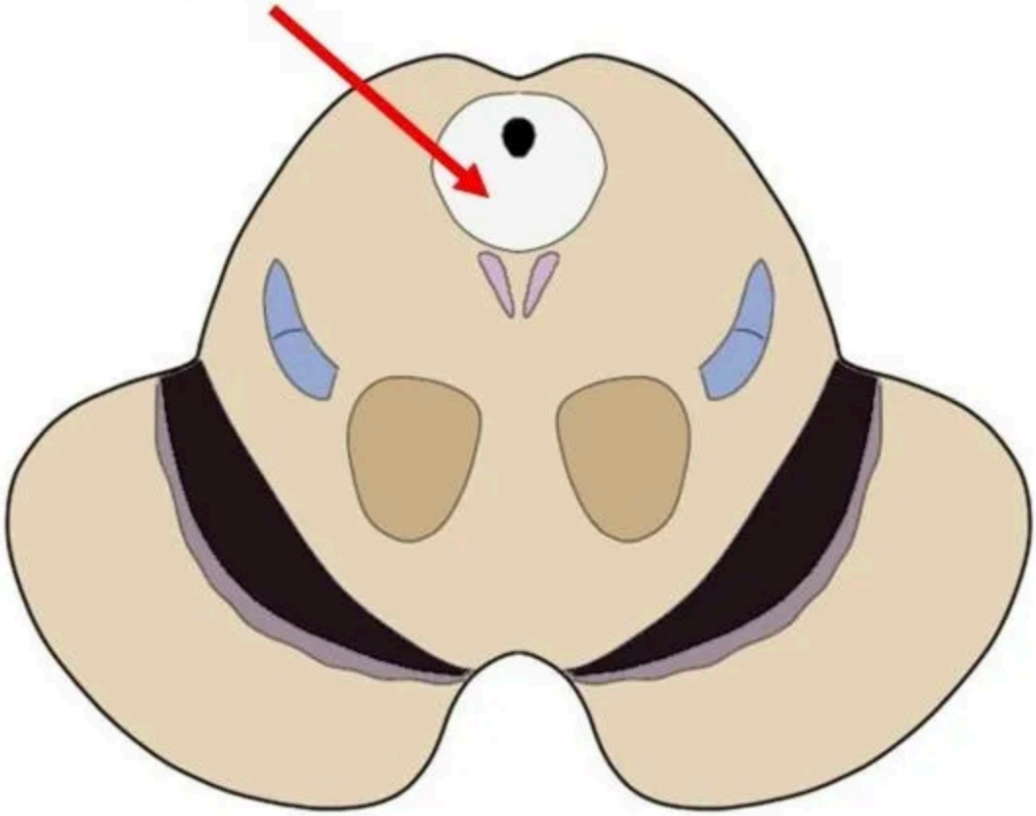
THE BRAIN AND PAIN

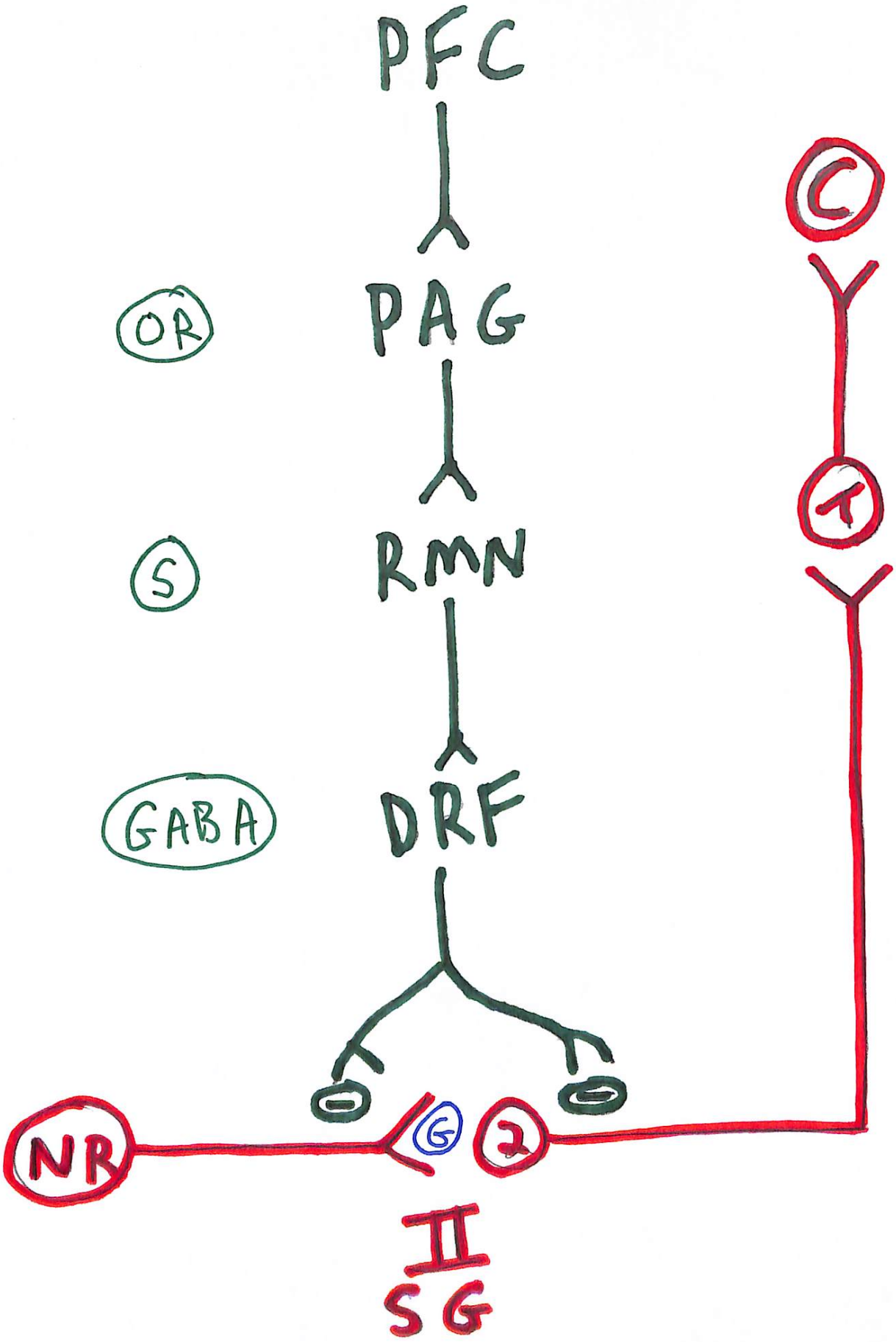
Breakthroughs in Neuroscience

RICHARD AMBRON

Illustrated by Ahmet Sinav

PERIAQUEDUCTAL GRAY




PFC
PAG
OR
RMN
S
DRF
GABA
C
T
NR
G
2
II
SG

Richard Ambron
emeritus professor of pathology, anatomy, and cell biology at Columbia University

PAG = periaqueductal gray

"Studies show that electrical stimulation of the PAG could diminish pain without interfering with touch, pressure, or temperature sensations."

The PAG is "placed" "as an essential center for the perception of pain."

The PAG blocks "synaptic transmission between the first and second-order neurons."

"Activation of neurons in the PAG results in the release of the endogenous opiates in the spinal cord that shuts down the nociceptive pathway to the thalamus."

"The suppression of injury-induced pain is most likely due to the activation of the opioidergic neurons in the PAG."

PFC = prefrontal cortex

"The prefrontal cortex (PFC) comprises the cortical neurons found in the frontal region of the frontal lobe. Its functions are probably the most important for what separates us from other primates."

An increase in the activity of circuits in the PFC reduce responses to noxious stimulus.

Activation if circuits within the "PFC will have a significant impact on the experience of pain."

"The modulation of painfulness is associated with increased activity in the PFC."

"We know that there are connections between the PFC and the PAG."

"The activation of the PAG is controlled by circuits in the PFC."

"Inputs from the PFC to the PAG result in the activation of the opioidergic neurons whose axions descend to the spinal cord, where the release of opioids prevents synaptic transmission at the synapse between the first- and second-order neurons in the nociceptive pathway."

••••••

PubMed jessen na

Format: Abstract

Full text links

SpringerLink FULL-TEXT ARTICLE PMC FREE Full text

Neurochem Res. 2015 Dec;40(12):2583-99. doi: 10.1007/s11064-015-1581-6. Epub 2015 May 7.

The Glymphatic System: A Beginner's Guide.

Jessen NA[1], Munk AS[2], Lundgaard I[2], Nedergaard M[2].

Author information

1 School of Medicine and Dentistry, University of Rochester Medical Center, 601 Elmwood Ave, Box 645, Rochester, NY, 14642, USA. Nadia_Aalling@urmc.rochester.edu.

2 School of Medicine and Dentistry, University of Rochester Medical Center, 601 Elmwood Ave, Box 645, Rochester, NY, 14642, USA.

Abstract

The glymphatic system is a recently discovered macroscopic waste clearance system that utilizes a unique system of perivascular tunnels, formed by astroglial cells, to promote efficient elimination of soluble proteins and metabolites from the central nervous system. Besides waste elimination, the glymphatic system also facilitates brain-wide distribution of several compounds, including glucose, lipids, amino acids, growth factors, and neuromodulators. Intriguingly, the glymphatic system function mainly during sleep and is largely disengaged during wakefulness. The biological need for sleep across all species may therefore reflect that the brain must enter a state of activity that enables elimination of potentially neurotoxic waste products, including β-amyloid. Since the concept of the glymphatic system is relatively new, we will here review its basic structural elements, organization, regulation, and functions. We will also discuss recent studies indicating that glymphatic function is suppressed in various diseases and that failure of glymphatic function in turn might contribute to pathology in neurodegenerative disorders, traumatic brain injury and stroke.

KEYWORDS: Aging; Astrocytes; Cerebrospinal fluid secretion; Neurodegenerative diseases; Perivascular spaces; Sleep; The glymphatic system; Traumatic brain injury; Virchow–Robin spaces

PMID: 25947369 PMCID: PMC4636982 DOI: 10.1007/s11064-015-1581-6

[Indexed for MEDLINE] **Free PMC Article**

Images from this publication. See all images (6) Free text

An official website of the United States government
Here's how you know

1,267 results

1 Exploring Radial Asymmetry in MR Diffusion Tensor Imaging and Its Impact on the Interpretation of **Glymphatic** Mechanisms.
Wright AM, Wu YC, Chen NK, Wen Q.
J Magn Reson Imaging. 2023 Dec 29. doi: 10.1002/jmri.29203. Online ahead of print.
PMID: 38156600

2 **Glymphatic system** dysfunction in recovered patients with mild COVID-19: A DTI-ALPS study.
Wu L, Zhang Z, Liang X, Wang Y, Cao Y, Li M, Zhou F.
iScience. 2023 Dec 7;27(1):108647. doi: 10.1016/j.isci.2023.108647. eCollection 2024 Jan 19.
PMID: 38155770 Free PMC article.

3 Imaging of brain clearance pathways via MRI assessment of the **glymphatic system**.
He Y, Guan J, Lai L, Zhang X, Chen B, Wang X, Wu R.
Aging (Albany NY). 2023 Dec 26;15. doi: 10.18632/aging.205322. Online ahead of print.
PMID: 38149988 Free article.

4 **Glymphatic** dysfunction coincides with lower GABA levels and sleep disturbances in succinic semialdehyde dehydrogenase deficiency.
Tokatly Latzer I, Yang E, Afacan O, Arning E, Rotenberg A, Lee HHC, Roullet JB, Pearl PL.
J Sleep Res. 2023 Dec 26:e14105. doi: 10.1111/jsr.14105. Online ahead of print.
PMID: 38148273

5 Dysfunction of the **glymphatic system** in childhood absence epilepsy.
Pu W, Wei S, Qiu M, Chen X, Zou W, Ge Y, Qiu W.
Front Neurosci. 2023 Dec 8;17:1312676. doi: 10.3389/fnins.2023.1312676. eCollection 2023.
PMID: 38144207 Free PMC article.

6 Interplay between the **Glymphatic System** and the Endocannabinoid **System**: Implications for Brain Health and Disease.
Osuna-Ramos JF, Camberos-Barraza J, Torres-Mondragón LE, Rábago-Monzón ÁR, Camacho-Zamora A, Valdez-Flores MA, Angulo-Rojo CE, Guadrón-Llanos AM, Picos-Cárdenas VJ, Calderón-Zamora L, Magaña-Gómez JA, Norzagaray-Valenzuela CD, Cárdenas-Torres FI, De la Herrán-Arita AK.
Int J Mol Sci. 2023 Dec 14;24(24):17458. doi: 10.3390/ijms242417458.
PMID: 38139290 Free PMC article. Review.

7 Imaging the neurovascular unit in health and neurodegeneration: a scoping review of interdependencies between MRI measures.
Rowsthorn E, Pham W, Nazem-Zadeh MR, Law M, Pase MP, Harding IH.
Fluids Barriers CNS. 2023 Dec 21;20(1):97. doi: 10.1186/s12987-023-00499-0.
PMID: 38129925 Free PMC article. Review.

8 Impaired **glymphatic system** revealed by DTI-ALPS in cerebral palsy due to periventricular leukomalacia: relation with brain lesion burden and hand dysfunction.
Yin Y, Peng Y, Nie L, Li X, Xiao Y, Jiang H, Gao L, Liu H.
Neuroradiology. 2023 Dec 22. doi: 10.1007/s00234-023-03269-9. Online ahead of print.
PMID: 38129651

9 **Glymphatic System** Dysfunction in Myelin Oligodendrocyte Glycoprotein Immunoglobulin G Antibody-Associated Disorders: Association with Clinical Disability.
Hagiwara A, Tomizawa Y, Hoshino Y, Yokoyama K, Kamagata K, Sekine T, Takabayashi K, Nakaya M, Maekawa T, Akashi T, Wada A, Taoka T, Naganawa S, Hattori N, Aoki S.
AJNR Am J Neuroradiol. 2023 Dec 14. doi: 10.3174/ajnr.A8066. Online ahead of print.

The Longevity Paradox
How to Die Young at a Ripe Old Age

Steven Gundry, MD
2019

Sleep and the Glymphatic System

"The glymphatic system is most active during the specific stage of deep sleep that happens very early in the sleep cycle."

"The glymphatic system, just like your digestive system, requires a great deal of blood flow. This means that if you eat too soon before going to bed, your blood will all flow to your gut to aid in digestion and will not be able to reach your brain to complete the all-important brain wash."

"If your glymphatic system cannot wash out your brain effectively, you end up with a building up of amyloid and other toxins, including lectins and LPSs, in the brain."

"This wash cycle is probably the single most overlooked and misunderstood aspect of neurodegenerative diseases."

The "simple solution: leaving as big a gap as possible between your last meal of the day and your bedtime."

"The minimum amount of time between finishing your last meal and going to sleep should be four hours."

The Brain's Waste-Disposal System May Be Enlisted to Treat Alzheimer's and Other Brain Illnesses

An Internal Plumbing System Rids the Brain of Toxic Wastes

Sleep is When this Cleanup Ritual Occurs

Scientific American
March 1, 2016
[modified]

Maiken Nedegaard and Steven Goldman: from the University of Rochester Medical Center and the University of Copenhagen

The human brain weighs about 3 pounds, or roughly 2% of the average adult body mass. Yet its cells consume 20-25% of the body's total energy. In the process, inordinate amounts of potentially toxic protein wastes and biological debris are generated.

Each day, the adult brain eliminates 7 grams of worn-out proteins that must be replaced with newly made ones, a figure that translates into the replacement of about half a pound of detritus a month and nearly 6 pounds, twice the brain's own weight, over the course of a year.

To survive, the brain must have some way of flushing out debris. It is inconceivable that an organ so finely tuned to producing thoughts and actions would lack an efficient waste disposal system.

Disturbances in waste clearance could contribute to cognitive problems encountered in neurodegenerative disease because the disruption would be would lead to the accumulation of protein debris in and around brain cells. The aggregates could impede the transmission of electrical and chemical signals in the brain and cause irreparable harm.

These authors found an undiscovered system for clearing proteins and other wastes from the brain—and this system is *most active during sleep*. The need to remove potentially toxic wastes from the brain may help explain the mystery of why we sleep.

The Glymphatic System

In most regions of the body, a network of intricate fluid-carrying vessels, known as the *lymphatic system*, eliminates protein waste from tissues. Waste-carrying fluid moves throughout this network between cells. The fluid collects into small ducts that then lead to larger ones and eventually into blood vessels. This duct structure also provides a path for immune defense, because lymph nodes, a repository of infection-fighting white blood cells, populate ducts at key points throughout the network. Yet,

neuroscientists had believed that the lymphatic system did not exist in the brain or spinal cord.

Astrocytes are support cells that perform a multitude of functions for the interconnected network of neurons that relay signals throughout the brain. The astrocytes' extensions—*astrocytic end feet*—completely surround the arteries, capillaries and veins in the brain and spinal cord. The hollow, tube-like cavity that forms between the feet and the vessels remains largely free of obstructions, creating a *spillway* that allows for the rapid transport of fluid through the brain.

Arterial pulsations might drive the CSF through the perivascular space. From there, some of it could enter astrocytes through their end feet. Using astrocytes as conduits, the CSF then moved through the brain tissue, where it left the astrocytes and picked up discarded proteins.

The fluids exited the brain through the perivascular space that surrounded small veins draining the brain, and these veins in turn merged into larger ones that continued into the neck. The waste liquids went on to enter the lymph system, from which they flowed back into the general blood circulation.

The astrocytes play a critical role in the brain's counterpart of a lymphatic system.

The authors named this discovery the *glymphatic system*. They combined the words "glia"—a type of brain cell of which the astrocyte is one example—and "lymphatic," thus referencing this newly discovered function of the brain's glial cells.

In a healthy brain, Alzheimer's beta-amyloid is cleared by the glymphatic system. Other proteins implicated in neurodegenerative diseases, such as the synuclein proteins that turn up in Parkinson's, Lewy body disease and multisystem atrophy, might also be carried away and could build up abnormally if the glymphatic system were to malfunction.

Many patients with Alzheimer's experience sleep disturbances long before their dementia becomes apparent. In older individuals, sleep becomes more fragmented and shallow and lasts a shorter time. Epidemiological studies have shown that patients who reported poor sleep in middle age were at greater risk for cognitive decline than control subjects when tested 25 years later.

Healthy individuals who are forced to stay awake exhibit symptoms more typical of neurological disease and mental illness—poor concentration, memory lapses, fatigue, irritability, and emotional ups and downs. The *sleep difficulties* of dementia might not just be a side effect of the disorder but *might contribute* to the disease process itself. If the glymphatic system cleared beta-amyloid during sleep at a higher rate than when awake, perhaps the poor sleeping patterns of patients with neurodegenerative disorders might contribute to a worsening of the disease.

CSF in the glymphatic system falls dramatically while awake. Within *minutes after the onset of sleep influxes of the fluid increased significantly*. The brain's interstitial space—the area between cells through which glymphatic fluid flows on its way to perivascular spaces around veins—rose by more than 60% with sleep. The flow of glymphatic fluid increases during sleep because the space between the cells expands, which helps to push fluid through the brain tissue.

Norepinephrine appears to regulate the volume of the interstitial area and consequently the pace of glymphatic flow. Levels of norepinephrine rise when awake and are scarce during sleep, implying that sleep-related dips in norepinephrine led to enhanced glymphatic flow.

The Power of Sleep

The expansion and contraction of the interstitial space during sleep is important to both brain function and protein-waste clearance. The *waste clearance rate more than doubled with sleep*. The sleeping brain exports protein waste, including beta-amyloid, through the glymphatic transport system.

Normal-pressure hydrocephalus, an illness typically seen in the elderly, is a form of dementia in which excessive CSF accumulates in the hollow central brain cavities, the cerebral ventricles. When a procedure called lumbar puncture removes the fluid by draining it out, patients often exhibit remarkable improvements in their cognitive abilities.

Fluids moving through the glymphatic system may do more than remove wastes; they may deliver various nutrients and other cargo to brain tissue, including delivery of glucose to neurons to provide energy. The glymphatic system may deliver both nutrients and materials needed for maintaining the cells' structural integrity.

MORE TO EXPLORE

The Glymphatic System: A Beginner's Guide. Nadia Aalling Jessen et al.;
Neurochemical Research; December 2015; Vol. 40; No. 12; pp. 2583–2599.

International Journal of
Molecular Sciences

MDPI

Review

The Glymphatic System (En)during Inflammation

Frida Lind-Holm Mogensen [1,†], Christine Delle [1,†] and Maiken Nedergaard [1,2,*]

[1] Center for Translational Neuromedicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark; Frida.lind-holm@lih.lu (F.L.-H.M.); christine.delle@sund.ku.dk (C.D.)
[2] Center for Translational Neuromedicine, University of Rochester Medical Center, Rochester, NY 14642, USA
* Correspondence: Nedergaard@sund.ku.dk
† Contributed equally.

Abstract: The glymphatic system is a fluid-transport system that accesses all regions of the brain. It facilitates the exchange of cerebrospinal fluid and interstitial fluid and clears waste from the metabolically active brain. Astrocytic endfeet and their dense expression of the aquaporin-4 water channels promote fluid exchange between the perivascular spaces and the neuropil. Cerebrospinal and interstitial fluids are together transported back to the vascular compartment by meningeal and cervical lymphatic vessels. Multiple lines of work show that neurological diseases in general impair glymphatic fluid transport. Insofar as the glymphatic system plays a pseudo-lymphatic role in the central nervous system, it is poised to play a role in neuroinflammation. In this review, we discuss how the association of the glymphatic system with the meningeal lymphatic vessel calls for a renewal of established concepts on the CNS as an immune-privileged site. We also discuss potential approaches to target the glymphatic system to combat neuroinflammation.

Keywords: glymphatic system; astrocytes; glia limitans; AQP4; ocular glymphatic system; inflammation; immune privilege; CSF; ISF; immune surveillance

check for updates

Citation: Mogensen, F.L.-H.; Delle, C.; Nedergaard, M. The Glymphatic System (En)during Inflammation. *Int. J. Mol. Sci.* **2021**, *22*, 7491. https://doi.org/10.3390/ijms22147491

Academic Editors: Graça Baltazar and Cláudio Roque

Received: 9 June 2021
Accepted: 8 July 2021
Published: 13 July 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The blood–brain barrier (BBB) is a critical component of the central nervous system (CNS) that dampens environmental perturbations in interstitial ionic and chemical concentrations, and thereby supports the stability of synaptic transmission. Long-distance neural networks require a protected environment with limited fluctuations of the concentrations of interstitial ions, neurotransmitters, essential metabolic intermediates, and toxic xenobiotics. The BBB also restricts the entry to the brain of peripheral inflammatory mediators and pathogens that might negatively impact neuronal activity. In the eye, the blood–retina barrier (BRB) similarly protects the environment of the neuroretina. The CNS lacks a parenchymal lymphatic vessel system that supports fluid homeostasis and provides a path for immune surveillance in the peripheral organs. The lack of lymphatic vessels in the retina and brain presented a conceptual challenge in understanding how fluid homeostasis and the export of waste products are obtained within the confines of the CNS [1]. With the discovery of the glymphatic system initially in brains of rodents [2–5], and later in human brain by magnetic resonance imaging (MRI) studies [6–10], a glial-associated functional homologue of the lymphatic system was established. More recently, the existence of an ocular glymphatic clearance system was demonstrated [11]. Astrocytes play a key role in the glymphatic system. Astrocytes create with their vascular endfeet the perivascular spaces that surround the cerebral vasculature. The perivascular spaces are utilized as "highways" for fast transport of cerebrospinal fluid (CSF) into deep brain regions.

The heterogenic nature and function of astrocytes in neurological diseases has been studied excessively at molecular and cellular levels. Many excellent reviews exist on this topic [12–14]. The existence of the glymphatic system provides, however, a novel perspective on the role of astrocytes in pathological processes: Astrocytes are not only

note that fluid transport in the posterior segment of the optic nerve close to the brain is supported by CSF influx along the central retinal artery [11,60]. However, the periarterial influx of CSF does not reach the eye, but is drained along the dural lymphatic vessels, similarly to aqueous humor efflux from the eye [11]. Thus, CSF tracers do not enter the eye, even in glaucoma models, and (like the aqueous humor) leave the optic nerve via dural lymphatic vessels. In anatomic terms, the brain and optic nerves are ensheathed in the same meningeal–dural membrane, and thus share the same CSF pool. The main difference between the brain and the ocular glymphatic system is the source of fluid entering the neuropil; i.e., CSF in the brain and aqueous humor fluid in the retina. In other respects, the polarized fluid transport is organized in a similar manner.

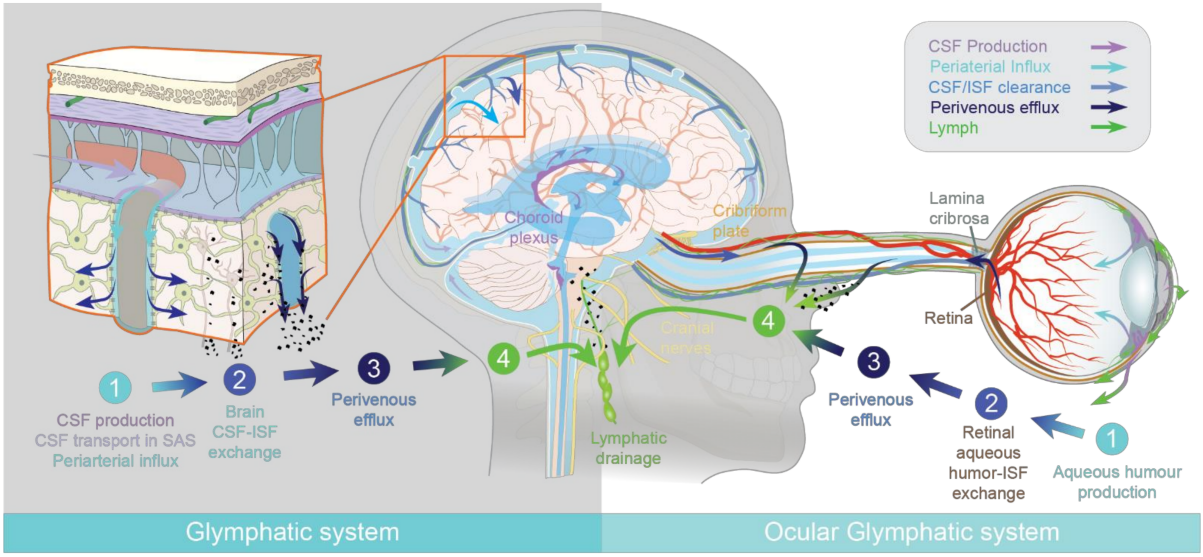


Figure 1. The glymphatic systems in the brain and the eye export fluid and solutes from metabolically active neural tissue. The organization of brain and ocular fluid flow can be divided into four distinct segments that share similarities, but differ in specific respects. (1) The first segment of the brain glymphatic system includes CSF production (purple arrows) and circulation in the subarachnoid space (SAS, light purple arrow), followed by periarterial influx of CSF into the brain tissue (light blue arrows). Two influx paths exist in the eye: the first path is the ciliary body, which produces the aqueous humor fluid. Most of the aqueous humor fluid leaves the eye via the anterior chamber. However, aqueous humor also moves posteriorly, passing the vitreal body before entering the neuroretina to support removal of waste products from that metabolically active tissue. The second inflow path is limited to periarterial influx of CSF along the posterior segment of the optic nerve. CSF does not pass into the eye, but drains into lymphatic vessels located in the dural sheet surrounding the optic nerve prior to the lamina cribrosa barrier [11,60]. (2) The second segment of the brain glymphatics is CSF–ISF exchange supported by AQP4 channels in the vascular endfeet plastered along the arterioles (blue arrows). In the eye, the aqueous humor mixes with interstitial fluid and is transported along axons across the lamina cribrosa barrier. From here the fluid leaves the axons and moves towards the perivenous space in a path supported by astrocytes. Astrocytic AQP4 water channels facilitate this segment as deletion of AQP4 suppresses ocular glymphatic activity [11]. (3) The third segment of the glymphatic system, which is common to the brain and eye, consists of perivenous efflux of interstitial fluid (ISF, dark blue arrows), which drains to the dural lymphatic vessels surrounding the brain and the optic nerve (green). (4) Ultimately, the drainage of perivenous waste from the eye ends up in the cervical lymph nodes (green), which constitute the fourth segment of the fluid-transport system. Fluids from both the brain and the eye thus drain via the cervical lymphatic vessels, which empty into the venous system at the level of the subclavian veins.

2. How Does Neuroinflammation Affect the Glymphatic System?

Among the various pathological events that can lead to neuroinflammation are traumatic brain injury (TBI) [61], meningitis triggered by either viral or bacterial invasion [62], autoimmune diseases such as multiple sclerosis [63], and neurodegeneration [64–69]. An

BODY & BRAIN

Sound, light may fight Alzheimer's

Plaques shrank in mice's brains after clicks and flashes

BY LAURA SANDERS

Fast clicking sounds can boost brainpower in mice with signs of Alzheimer's disease. Like flickering lights, these external sounds spur a type of brain wave that seemed to sweep disease-related plaques from mice's brains, researchers report in the March 14 *Cell*.

It's too early to say whether flickers and clicks could help people with Alzheimer's. If so, the treatment would represent a fundamentally new way to target the neurodegenerative disease.

An earlier study by MIT neuroscientist Li-Huei Tsai and colleagues focused on the eyes. Lights that flickered exactly 40 times a second kicked off gamma waves, a brain wave thought to happen during concentration. In mice, the brain waves seemed to somehow reduce amyloid-beta, a protein that piles up in the brains of Alzheimer's patients (*SN: 1/21/17, p. 13*). But A-beta was reduced only in the part of the brain that handles vision — an area not thought to be key to Alzheimer's progression.

Sounds that hum at a rate of 40 clicks per second, or 40 hertz, also spur gamma waves that appeared to clear mice's A-beta, Tsai and colleagues now find. But that happens in a more relevant brain area: the hippocampus, which is involved in memory and affected by Alzheimer's.

A daily hour of fast clicks for a week also improved the memories of mice genetically engineered to have signs of Alzheimer's. Compared with mice that heard randomly spaced clicks, mice that listened to 40-hertz clicks found a hidden platform in a water maze faster and better recognized a previously seen object.

"That's a very exciting finding, that it can actually affect cognition," says neuroscientist Tara Tracy of the Buck Institute for Research on Aging in Novato, Calif.

Sound-triggered gamma waves appear to kick off other beneficial changes, too. Brain levels of a harmful form of tau, another protein implicated in Alzheimer's, dropped, and blood vessels in the brain expanded, perhaps easing A-beta's disposal. Immune cells called microglia also grew more active, attacking A-beta.

When mice were treated with both flickering lights and clicks, the effect was even stronger, Tsai says. There were fewer A-beta plaques across a big stretch of the brain, including the hippocampus and the prefrontal cortex, an area important for complex thinking. And microglia swarmed into a feeding frenzy. "Microglia pile up on each other, all congregated around the amyloid plaques," Tsai says.

It's not yet clear how increasing gamma waves led to these effects. "How is this particular stimulation affecting all of these properties?" Tracy asks.

Also unknown is whether results from mice that mimic a rare and aggressive form of Alzheimer's apply to people. Tsai has cofounded a company, Cognito Therapeutics, that is testing the light-and-sound approach in older people with mild to moderate cognitive impairment. So far, Tsai says, "we haven't seen any undesirable effects."

C. WANG ET AL/FRONTIERS IN NEUROANATOMY 2013

"THE RAREST OF BOOKS: A COMBINATION OF PAGE-TURNING DISCOVERY AND REMARKABLY READABLE SCIENCE JOURNALISM." —MARK HYMAN, M.D.

THE ANGEL AND THE ASSASSIN

THE TINY BRAIN CELL THAT CHANGED THE COURSE OF MEDICINE

DONNA JACKSON NAKAZAWA

2020

An official website of the United States government
Here's how you know

7 results

Page 1 of 1

1 Treating insomnia with **40 Hz** light flicker.
Bozzelli PL, **Tsai LH.**
Cell Res. 2024 Mar 8. doi: 10.1038/s41422-024-00948-x. Online ahead of print.
PMID: 38459185 No abstract available.

2 Multisensory gamma stimulation promotes glymphatic clearance of amyloid.
Murdock MH, Yang CY, Sun N, Pao PC, Blanco-Duque C, Kahn MC, Kim T, Lavoie NS, Victor MB, Islam MR, Galiana F, Leary N, Wang S, Bubnys A, Ma E, Akay LA, Sneve M, Qian Y, Lai C, McCarthy MM, Kopell N, Kellis M, Piatkevich KD, Boyden ES, **Tsai LH.**
Nature. 2024 Mar;627(8002):149-156. doi: 10.1038/s41586-024-07132-6. Epub 2024 Feb 28.
PMID: 38418876 Free PMC article.

3 Audiovisual gamma stimulation for the treatment of neurodegeneration.
Blanco-Duque C, Chan D, Kahn MC, Murdock MH, **Tsai LH.**
J Intern Med. 2024 Feb;295(2):146-170. doi: 10.1111/joim.13755. Epub 2023 Dec 19.
PMID: 38115692 Review.

4 Vibrotactile stimulation at gamma frequency mitigates pathology related to neurodegeneration and improves motor function.
Suk HJ, Buie N, Xu G, Banerjee A, Boyden ES, **Tsai LH.**
Front Aging Neurosci. 2023 May 18;15:1129510. doi: 10.3389/fnagi.2023.1129510. eCollection 2023.
PMID: 37273653 Free PMC article.

5 Induction of specific brain oscillations may restore neural circuits and be used for the treatment of Alzheimer's disease.
Chan D, Suk HJ, Jackson B, Milman NP, Stark D, Beach SD, **Tsai LH.**
J Intern Med. 2021 Nov;290(5):993-1009. doi: 10.1111/joim.13329. Epub 2021 Jun 22.
PMID: 34156133 Free article. Review.

6 Noninvasive **40**-**Hz** light flicker to recruit microglia and reduce amyloid beta load.
Singer AC, Martorell AJ, Douglas JM, Abdurrob F, Attokaren MK, Tipton J, Mathys H, Adaikkan C, **Tsai LH.**
Nat Protoc. 2018 Aug;13(8):1850-1868. doi: 10.1038/s41596-018-0021-x.
PMID: 30072722

7 Gamma frequency entrainment attenuates amyloid load and modifies microglia.
Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, Adaikkan C, Canter RG, Rueda R, Brown EN, Boyden ES, **Tsai LH.**
Nature. 2016 Dec 7;540(7632):230-235. doi: 10.1038/nature20587.
PMID: 27929004 Free PMC article.

FOLLOW NCBI

Connect with NLM

Article

Multisensory gamma stimulation promotes glymphatic clearance of amyloid

https://doi.org/10.1038/s41586-024-07132-6

Received: 21 February 2022

Accepted: 25 January 2024

Published online: 28 February 2024

Open access

Check for updates

Mitchell H. Murdock[1], Cheng-Yi Yang[1], Na Sun[2,3], Ping-Chieh Pao[1], Cristina Blanco-Duque[1], Martin C. Kahn[1], TaeHyun Kim[1], Nicolas S. Lavoie[1], Matheus B. Victor[1], Md Rezaul Islam[1], Fabiola Galiana[1], Noelle Leary[1], Sidney Wang[1], Adele Bubnys[1], Emily Ma[1], Leyla A. Akay[1], Madison Sneve[4,5,6], Yong Qian[4,5,6], Cuixin Lai[7], Michelle M. McCarthy[8], Nancy Kopell[8], Manolis Kellis[2,3], Kiryl D. Piatkevich[4,5,6,7], Edward S. Boyden[4,5,6] & Li-Huei Tsai[1,3]✉

The glymphatic movement of fluid through the brain removes metabolic waste[1–4]. Noninvasive 40 Hz stimulation promotes 40 Hz neural activity in multiple brain regions and attenuates pathology in mouse models of Alzheimer's disease[5–8]. Here we show that multisensory gamma stimulation promotes the influx of cerebrospinal fluid and the efflux of interstitial fluid in the cortex of the 5XFAD mouse model of Alzheimer's disease. Influx of cerebrospinal fluid was associated with increased aquaporin-4 polarization along astrocytic endfeet and dilated meningeal lymphatic vessels. Inhibiting glymphatic clearance abolished the removal of amyloid by multisensory 40 Hz stimulation. Using chemogenetic manipulation and a genetically encoded sensor for neuropeptide signalling, we found that vasoactive intestinal peptide interneurons facilitate glymphatic clearance by regulating arterial pulsatility. Our findings establish novel mechanisms that recruit the glymphatic system to remove brain amyloid.

The glymphatic system is thought to have a critical role in clearing metabolic waste from the brain[1]. According to the glymphatic model, arterial pulsation drives cerebrospinal fluid (CSF) along an interconnected network of perivascular spaces surrounding blood vessels in the brain[2,9], and the water channel aquaporin-4 (AQP4) localized on astrocytic endfeet facilitates exchange between CSF and interstitial fluid (ISF)[2,10]. Glymphatic transport has been shown to clear parenchymal metabolites, including pathogenic proteins such as amyloid[3,11]. Ageing and Alzheimer's disease impair the fitness of glymphatic clearance by attenuating arterial pulsation[12], reducing CSF–ISF exchange[11,13], and diminishing lymphatic drainage, leading to the pathogenic accumulation of amyloid and tau. Therapeutic interventions to promote glymphatic clearance have been hypothesized to alleviate Alzheimer's disease pathology[14].

In previous studies, we found that 1 h of optogenetic-driven 40 Hz stimulation attenuated pathogenic amyloid burden in a mouse model of Alzheimer's disease compared with non-gamma control stimulations[5]. To extend the clinical translatability of this intervention, we explored noninvasive approaches to induce 40 Hz neural activity. In humans and mice, sensory stimuli at specific frequencies can be used to promote neural activity corresponding to the sensory stimulation[15]. Noninvasive 40 Hz stimulation promotes 40 Hz neural activity in multiple brain regions, including the prefrontal cortex[6,7,16], and we and others found that noninvasive 40 Hz sensory stimulation attenuates amyloid burden in Alzheimer's disease model mice[8]. In particular, multisensory 40 Hz stimulation (that is, combined light and sound stimulation) attenuates amyloid burden throughout the cortex, including the prefrontal cortex[6].

Brain metabolites are removed via glial-mediated phagocytosis and vascular-mediated clearance[17]. It has been unclear whether 40 Hz stimulation attenuates amyloid burden through glymphatic routes. Previous reports suggest that CSF influx to the brain is increased during anaesthesia and sleeping[1,18], indicating that distinct brain rhythms influence glymphatic transport. Arteriolar vasomotion, which drives CSF influx[2,9] and paravascular clearance[19], is coupled to gamma oscillations[20]. We hypothesized that noninvasive gamma stimulation may clear amyloid in part via glymphatic transport.

Gamma stimulation promotes glymphatic clearance

We found that 40 Hz multisensory audio-visual stimulation increased 40 Hz local field potential power in frontal cortex areas of 6-month-old 5XFAD mice (Extended Data Fig. 1a–c), as expected on the basis of prior reports in mice[6] and humans[8,16]. In separate cohorts of 6-month-old 5XFAD mice, 40 Hz stimulation attenuated amyloid burden compared with no stimulation, 8 Hz stimulation and 80 Hz stimulation controls (Fig. 1a,b). Reductions in amyloid by 40 Hz multisensory stimulation were not associated with alterations in plasma corticosterone (Extended Data Fig. 1d), time spent moving (Extended Data Fig. 1e–f) or sleep architecture (Extended Data Fig. 1g,h), including neither rapid eye movement (REM) nor non-REM (NREM) sleep states (Extended Data Fig. 1i–k).

[1]Department of Brain and Cognitive Sciences and the Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA. [2]MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, MA, USA. [3]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [4]Departments of Biological Engineering and Brain and Cognitive Sciences, McGovern Institute, Cambridge, MA, USA. [5]Koch Institute, Massachusetts Institute of Technology, Cambridge, MA, USA. [6]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA, USA. [7]School of Life Sciences, Westlake University, Westlake Laboratory of Life Sciences and Biomedicine, and Westlake Institute for Advanced Study, Hangzhou, China. [8]Department of Mathematics and Statistics, Boston University, Boston, MA, USA. ✉e-mail: lhtsai@mit.edu

New Scientist 3/9/24 pg. 16

Health

Light flashes may slow Alzheimer's by making the brain remove toxins

Clare Wilson

A NEW explanation has emerged for why an experimental treatment for Alzheimer's disease involving sounds and flickering lights may help slow cognitive decline. The frequencies involved seem to ramp up the brain's waste disposal networks, which boosts the clearance of beta-amyloid and other toxic proteins that contribute to memory and concentration problems.

"Once we understand the mechanism, we can probably figure out how to further optimise this whole concept and improve the efficacy," says Li-Huei Tsai at the Massachusetts Institute of Technology.

The treatment involves exposing people to lights flickering at a frequency of 40 times a second, or 40 hertz, and a low-pitched sound, also at 40 Hz. Typically, the stimulation is given for an hour a day.

Key to the novel approach is that large networks of brain cells naturally fire in sync with each other at different frequencies – known as brainwaves. Brainwaves of around 40 Hz are often seen when people are concentrating and when they are forming or accessing memories.

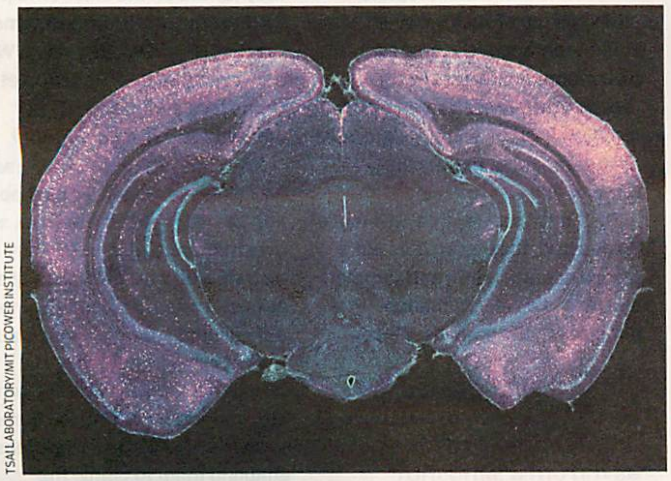
As it was known that visual or auditory stimulation at a certain frequency can boost brainwaves at that same frequency, in 2016, Tsai's team investigated if stimulation at 40 Hz might boost cognitive abilities in people with Alzheimer's.

40 Hz

Frequency of bursts of light and sound used to treat Alzheimer's

Their group and others showed that this lowered amyloid build-up in mice with a version of Alzheimer's and had cognitive benefits in small trials in people with the condition. But it wasn't clear how the treatment works, with one idea being that it boosts the function of the brain's immune cells.

Now, it seems the lights and sound work by enhancing the function of the brain's drainage network, also known as the glymphatic system.



TSAI LABORATORY/MIT PICOWER INSTITUTE

Highlighted neurons in a mouse brain that seem to boost toxin clearance

In the latest work, Tsai's team did experiments to study the treatment's mechanism in mice that had been genetically altered so that they usually develop a build-up of amyloid as they get older and have worse memories than typical mice.

As expected, when the animals were exposed to the light and sounds, they had less amyloid. The new finding was that during the treatment, they had a greater amount of cerebrospinal fluid entering the brain and more waste fluid leaving it through the glymphatic vessels (*Nature*, doi.org/mjjs).

This seemed to be happening because nearby blood vessels were pulsating more, which could help push the glymphatic fluid through its vessels, and because of more water flowing into the glymphatic system.

The team also found that the activity of brain cells known as interneurons seemed to be triggering the increased glymphatic flow by releasing a molecule called vasoactive intestinal peptide. When the team chemically blocked this molecule's production, the treatment no longer boosted amyloid clearance.

Maiken Nedergaard at the University of Rochester in New York, who helped discover the glymphatic system, says the finding fits with what we know about the system. "The brain, blood and cerebrospinal fluid are all contained within the skull. If the blood volume expands, the volume of the cerebrospinal fluid has to move since brain tissue is not compressible." A better understanding of toxin clearance in the brain could help us unlock its therapeutic potential, she says. ▮

Cancer

Light and sound therapy may prevent 'chemo brain'

Clare Wilson

AN EXPERIMENTAL treatment for Alzheimer's disease that involves flickering lights and low-pitched sound might also help prevent cognitive problems after cancer treatment, a study in mice suggests.

For Alzheimer's disease, the method has been shown to ease people's memory and concentration problems in small trials, but it is still being investigated in larger studies.

The lights flicker 40 times a second, or 40 hertz, with the sound also having a frequency of 40 Hz. This frequency was selected because people with Alzheimer's have a lower intensity of 40 Hz brainwaves, which are linked with memory processing. Recent research suggests such waves bring brain benefits, including increasing the activity of immune cells and boosting its drainage system.

Curious about whether the approach might also help people who get memory and concentration problems after chemotherapy, sometimes called chemo brain, Li-Huei Tsai at the Massachusetts Institute of Technology and her colleagues turned to mice.

They found that cancer-free mice exposed to the lights and sounds for 1 hour a day while being dosed with the chemotherapy drug cisplatin showed less of a decline in mental sharpness – assessed by seeing how much interest they showed in novel or familiar objects – than those that just had chemotherapy.

The therapy also lowered brain inflammation, reduced DNA damage and lessened the loss of myelin, the insulation around nerve cell fibres (*Science Translational Medicine*, doi.org/mkkw).

Nazanin Derakhshan at the University of Reading, UK, says the method needs to be tested in people. If the treatment reduces cell death in the brain, it could promote the survival of cancer cells there, she says.

New Scientist

WHAT HAPPENS WHEN THE AI BUBBLE BURSTS?

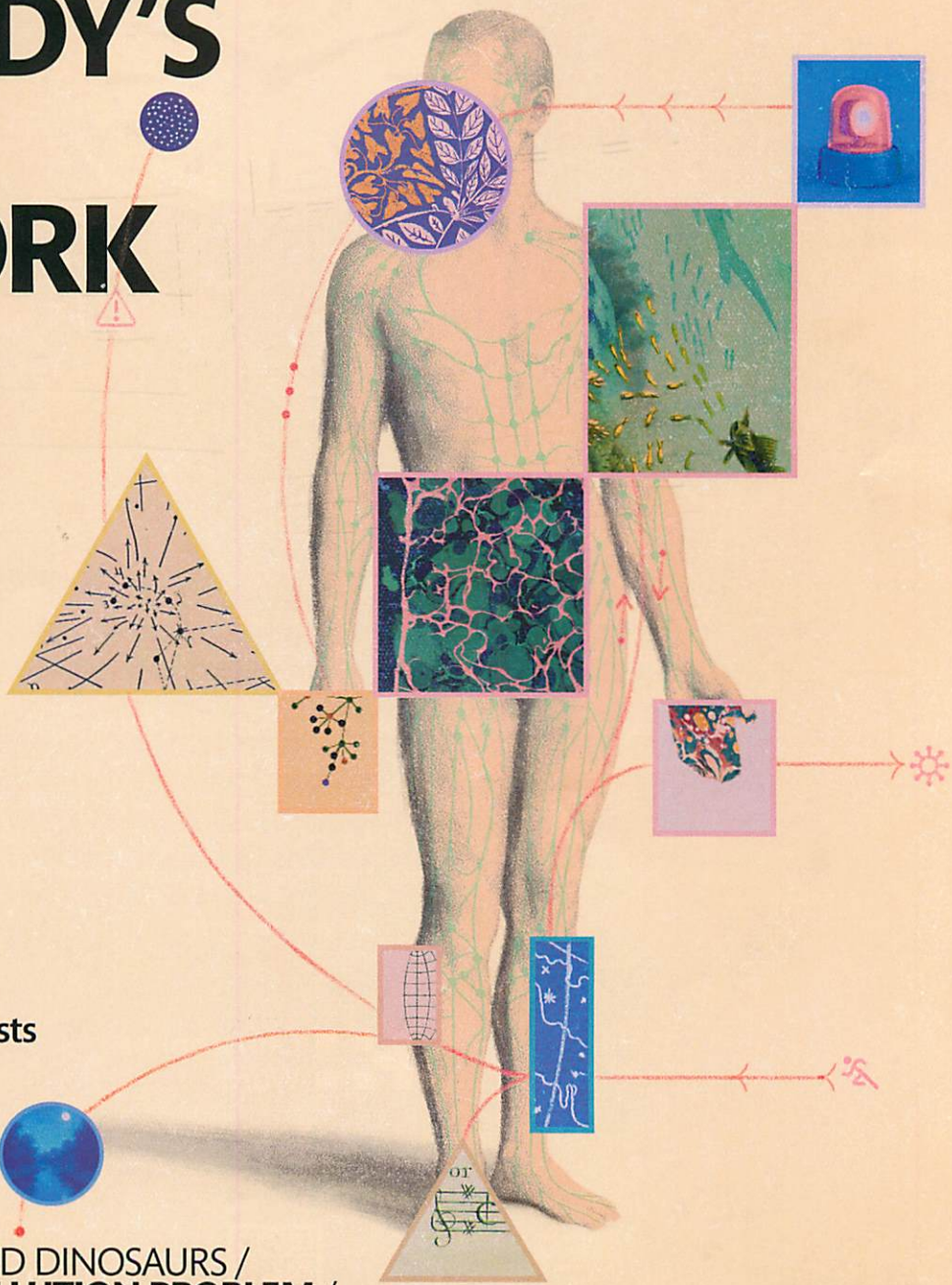
BRAIN IMPLANT GIVES TELEPATHIC CONTROL OF ANOTHER PERSON'S BODY

HOW A GENETIC MISMATCH CURSED NEANDERTHAL-HUMAN HYBRIDS

WEEKLY October 25 - 31, 2025 No3566 US $7.99 Canada CAN$9.99

THE BODY'S SECRET NETWORK

We're finally revealing the lymphatic system's extraordinary powers



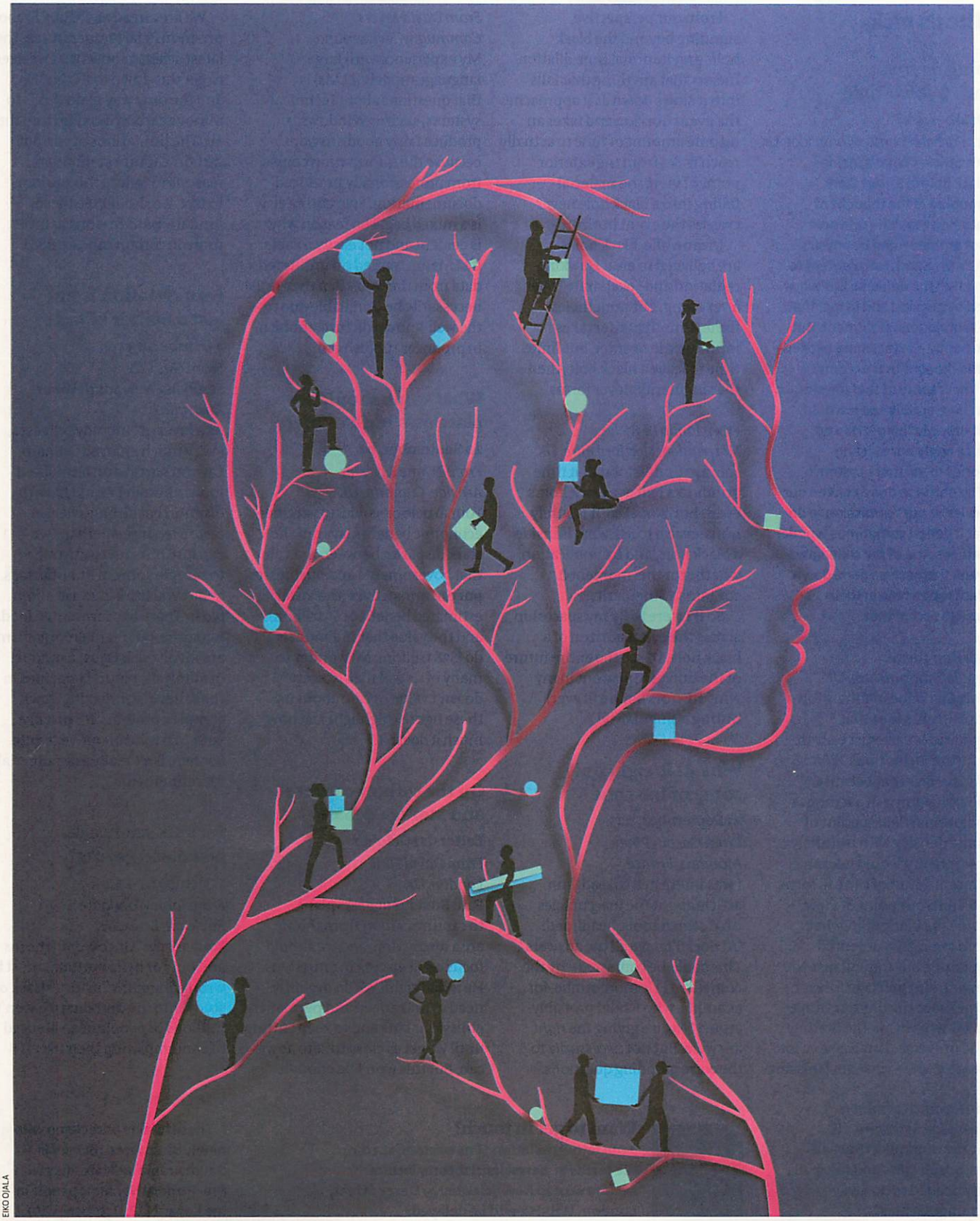
EXCLUSIVE SPECIAL REPORT

Majority of climate scientists expect geoengineering this century

PLUS

ORIGINS OF LONG-NECKED DINOSAURS /
THE DEAD SATELLITE POLLUTION PROBLEM /
WHAT 350 THEORIES OF CONSCIOUSNESS REVEAL ABOUT REALITY

Science and technology news **www.newscientist.com**



EIKO OJALA

Your hidden helper

Our lymphatic system has long been overlooked, but it may hold the key to treating everything from dementia to cancer, finds **Carissa Wong**

I PLACED the cold, jade rolling pin under my cheekbone and gently glided it to the edge of my face. To be honest, I felt a bit like a piece of pastry. But my grandma assured me that I was engaging in a serious traditional Chinese practice that would make my skin glow and my face less puffy. It would be more than a decade before face rolling became the next big beauty fad on social media – and several years more before I realised its supposed benefits may hinge on the lymphatic system, a network spanning the entire body, consisting largely of thread-like vessels and bean-shaped nodes.

Despite having been described in the first known medical scientific paper, the lymphatic system remained a mystery for millennia afterwards. Being extremely elusive and incredibly delicate, it is hard to study – the ruby-red blood system, in contrast, got far more attention. "Lymphatic vessels permeate nearly every organ of our body and yet they sit in our tissues practically invisible," says Kathleen Caron at the University of North Carolina at Chapel Hill. Only in recent decades have researchers begun to appreciate the profound role the system plays in health and illness, thanks to advances in imaging techniques and molecular beacons that shine a light on its inner workings.

This growing interest has fuelled discoveries that suggest our lymphatic network could be a secret ingredient in treating some major health conditions, including Alzheimer's disease and cancer. "In the past 20 years, we have experienced a renaissance in lymphatic biology," says Caron. "It would be transformative to harness the powerful roles of lymphatics in keeping us healthy."

The earliest surviving mention of this ghostly web comes from Egyptian hieroglyphs in a treatise from around 1600 BC that refers to swollen masses in the neck and armpits – structures we now recognise as lymph nodes. A millennium later, the Greek physician and philosopher Hippocrates described the vessels running between these structures, noting that the nodes often swell during infections.

It wasn't until the 1700s, however, that we started to understand the lymphatic network as a sort of waste-disposal system. Blood vessels supply your tissues with a clear, yellowy fluid containing oxygen, nutrients and immune cells. As well as nourishing cells, it sweeps up their metabolic waste products along with fragments of damaged cells and pathogens, before draining back into the vascular system. However, about 10 per cent of the fluid remains in the tissues, and this is where lymphatic vessels come in; they collect the leftovers.

Once inside lymphatic tubes, the fluid is known as lymph – derived from the ancient Roman deity of fresh water, Lympha, and ancient Greece's nymphs, creatures associated with clear streams. Lymph travels to a nearby node, of which there are about 500 to 600 distributed throughout our bodies. There, immune cells called phagocytes gobble up much of the detritus and, in turn, activate nearby T-cells to recognise any pathogens or cancer cells that are present. Lymph, along with these activated T-cells, then travels through the lymphatic system, re-entering the blood via major ducts near the heart. Any remaining waste products are eventually filtered out by the kidneys and excreted. The T-cells, however, continue to circulate until they reach sites where they fight off intruders or mutant cells.

"CAN WE CURE DEMENTIA BY IMPROVING THE LYMPHATIC DRAINAGE FROM THE BRAIN?"

Given the lymphatic system's roles in immunity and waste disposal, it seems surprising that scientists long thought it was disconnected from our most vital organ, the brain. But there's a reason. A healthy immune response includes inflammation, which, as well as fighting pathogens, can damage our cells. The brain was thought to have evolved to avoid this collateral damage. It has a structure called the blood-brain barrier to keep pathogens and toxins out, and was seen as "immune privileged", meaning it lacks immune cells. So, it was assumed not to require the immune services of the lymphatic system – and circulating brain fluid was thought to drain out via non-lymphatic routes, including spaces along nerves that run to lymphatic vessels in the nose.

Such thinking meant that, in the late 1700s, when anatomist Paolo Mascagni injected corpses with mercury and discovered silvery branches, which he claimed were lymphatic vessels bordering the brain, he wasn't taken seriously. It would be more than two centuries before two groundbreaking studies upended the scientific consensus. In 2015, Kari Alitalo at the University of Helsinki in Finland and his team made a surprising discovery while exploring how T-cells move around the brain, which we now know has many immune cells. They noticed that the cells, which they *had* labelled with a fluorescent green marker, lined up in a vessel-shaped arrangement in the dura mater, the outermost of three membranes – collectively known as the meninges – that are wedged between the brain's surface and the skull.

Taking a closer look, the team found that the structures had all the features of lymphatic vessels, and drained fluid into so-called cervical lymph nodes in the neck. Just two weeks later, Jonathan Kipnis at Washington University in St. Louis, Missouri, and his ›

colleagues reported finding the same network, this time using mice genetically engineered to have fluorescent lymphatic vessels. "It was this eureka moment for the entire field," says Sandro Da Mesquita at the Mayo Clinic in Jacksonville, Florida, who wasn't involved in either study.

In 2017, Kipnis's team confirmed that humans also have this meningeal lymphatic network. Soon, a wave of rodent studies showed that the vessels become thinner, shorter and less numerous with age. Such degeneration slows the rate of fluid drainage from the brain and worsens cognitive decline. "Ageing leads to regression of these vessels," says Da Mesquita. "In a very old mouse, the lymphatic system that drains the brain is very impaired, which is even more interesting because in most peripheral tissues you don't see that [so much]."

Crucially, reversing such decline brings cognitive benefits. For instance, Da Mesquita and Kipnis injected the brains of old mice with the genetic code for a protein called VEGFC, which can dilate lymphatic vessels. This boosted the drainage of brain fluid through

"RESEARCHERS ARE HARNESSING LYMPH NODES TO GROW ORGAN TRANSPLANTS"

the meningeal lymphatic vessels and enhanced the animals' performance in memory and learning tests. The same approach partly reversed cognitive decline in mice with features of Alzheimer's disease, the most common form of dementia. It seemed to work by boosting clearance of a toxic form of beta-amyloid, a protein implicated in the condition.

Boosting drainage

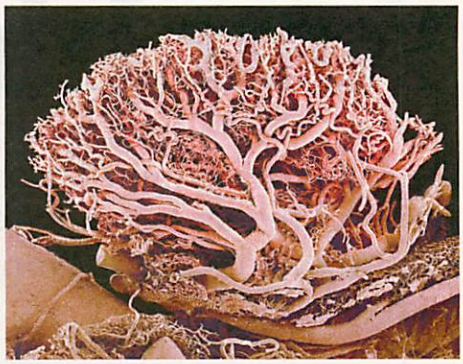
Such findings have prompted scientists to wonder whether lymphatic ageing also impairs cognition in people. There are very early hints that it does. In a study out earlier this year, Sarosh Irani at the Mayo Clinic, Da Mesquita and their colleagues analysed lymph extracted from the cervical lymph nodes of 25 people aged between 22 and 84 who didn't have neurodegenerative disease. They discovered that levels of tau, a protein linked to Alzheimer's, seem to decrease in lymph nodes with age. Irani says this suggests that age-related deterioration of the meningeal lymphatic vessels may reduce their ability to drain and filter out problematic proteins, so they accumulate in the brain, where they could contribute to neurodegenerative conditions like dementia.

"Some of these diseases, at least in some cases, might even be starting or being partly triggered by degeneration of the lymphatics," says Irani. Da Mesquita cautions that much larger studies involving thousands of people are needed to verify such potential links. Nevertheless, these early findings hint at a tantalising possibility. "There's this big therapeutic angle," says Irani. "Can we cure dementia by trying to think of how you might improve the lymphatic drainage from the brain?"

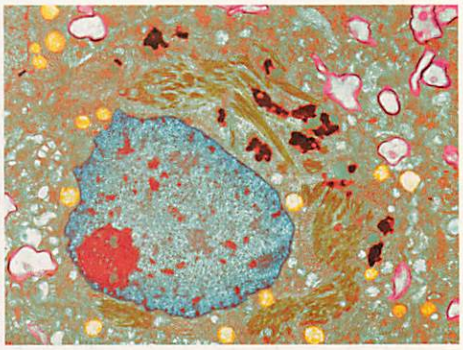
Indeed, some researchers are already pursuing this idea. In a study in May, Rong Hu at the Army Medical University in China and colleagues recruited 26 people with Alzheimer's disease to undergo surgery to their cervical lymphatic vessels that boosted the drainage of fluid from the brain. One month later, the participants performed slightly better in memory, attention and language tests, with about 60 per cent of their caregivers noticing such improvements. But the study was small and lacked a control group of participants with Alzheimer's disease who didn't undergo the procedure, plus the surgery is highly invasive.

In search of a simpler method, Gou Young Koh at the Korea Advanced Institute of Science and Technology in South Korea and his colleagues recently found that gently massaging lymphatic vessels around the face and neck in a very specific pattern could boost brain fluid drainage in old mice to the levels seen in young mice. The researchers didn't assess how this affected the animals' cognitive abilities, but they plan to explore whether the technique can improve such abilities in mice with features of Alzheimer's disease.

Cancer is another key area where tapping into our meningeal lymphatic system could help. After learning about the 2015 discoveries, Eric Song at Yale University and his colleagues wondered whether the VEGFC approach might boost immune responses to glioblastoma, the deadliest form of brain cancer. To put this idea to the test, they injected the genetic code for VEGFC into the brains of mice with this tumour, along with an immunotherapy called anti-PD-1. A control group got just the anti-PD-1 injection and the genetic code for a fluorescent protein that



SUSUMU NISHINAGA/SCIENCE PHOTO LIBRARY



THOMAS DEERINCK, NCMIR/SCIENCE PHOTO LIBRARY

Above: Lymph nodes remove tau proteins from the brain, which can clump together in neurons in Alzheimer's disease

Below: People with Alzheimer's disease could benefit from improved lympahtic drainage

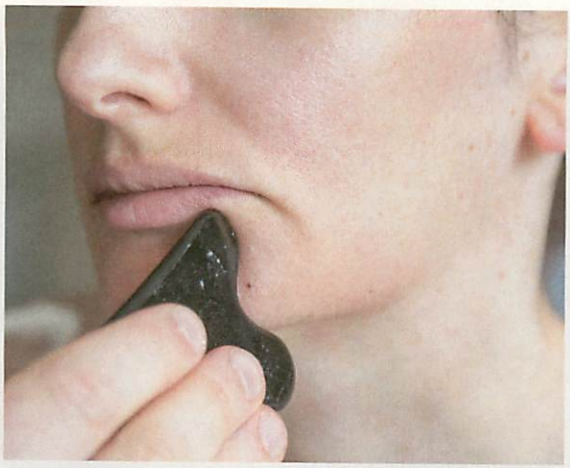
ELISABETH SCHNEIDER CHARPENTIER/SCIENCE PHOTO LIBRARY

doesn't affect the lymphatic system. Three months later, about 20 per cent of mice from the latter group had survived. In the former, the figure was 80 per cent – in some cases, their tumours had completely disappeared. "We were over the moon," says Song.

Further analysis revealed that the treatment probably worked by enhancing the drainage of cancer proteins through the meningeal lymphatic vessels into the cervical lymph nodes, enhancing the activation of cancer-killing T-cells that then migrated into the brain, says Song. That's not all. Mice that survived their initial tumours were also able to resist a subsequent injection of brain cancer cells, suggesting the treatment generated lasting immunity.

But there is one problem with the VEGFC approach. It can also enhance the growth of blood vessels, which is known to help tumours spread to distant sites. To address this, Song and his colleagues at the biotechnology start-up Rho Bio have developed an altered version of VEGFC that only acts on lymphatic vessels. They are now testing its safety in non-human primates and hope to trial it for a range of conditions, including brain cancer and dementia in humans.

Lymphatic therapies could treat cancers beyond the brain, too. Natalie Livingston at Massachusetts General Hospital and her colleagues have developed injectable artificial lymph nodes that boost immune responses against tumours in mice. The approach involves extracting T-cells from a mouse and mixing them with a gel containing a cocktail of proteins that activate T-cells to destroy the cancer. This mixture is then injected back into the mouse to create a factory of cancer-killing T-cells – the artificial lymph node. "It's about half a centimetre in diameter, and forms just like a little mosquito bite under the skin," says Livingston. This procedure nearly halved the size of colon tumours in mice, and improved survival rates compared with a placebo implant. And it worked just as well against melanoma, the deadliest form of skin cancer.



ANA ALVES/ALAMY

The traditional Chinese technique of gua sha supposedly stimulates the lymphatic system

Internal bioreactor

Lymphatic therapy doesn't stop there, though. Other researchers are harnessing lymph nodes to grow organ transplants. The approach involves implanting cells from a donor organ into a lymph node near the failing organ. Nourished by the lymphatic system's rich supply of blood, the cells grow into a mini organ that eventually replaces the lymph node and supplements the damaged tissue. "It turns out that the lymphatic system and lymph nodes are just incredibly effective bioreactors for a variety of tissue types," says Michael Hufford, CEO at Lygenesis.

In experiments with mice, his team has shown that such mini organs can reduce symptoms of liver disease and kidney disease, as well as type 1 diabetes where there is damage to the pancreas. The body can afford to lose one lymph node and the rest of the lymphatic system is unaffected, so the technique doesn't seem to cause any side effects, says Hufford. His team is now trialling the approach in 12 people with end-stage liver disease, four of whom have now received their implants. The results should be available within the next two years.

It is already clear that lymphatic biology has huge and exciting potential in treating disease. But there is still much we don't understand. One key question is the degree to which lymphatic vessels differ across the body. In an ongoing study that has yet to be published, Caron is exploring how gene activity varies between lymphatic vessels associated with eight organs, including the lungs, liver and heart. It is the first comparative study. "Prior studies looked at gene expression profiles in just one organ," says Caron. "We found a lot of very fascinating differences that really underscore just how different lymphatic vessels are throughout the body."

In another ongoing study, Caron is generating a list of protein receptors on lymphatic vessels that are potential targets for drugs. This could reveal new ways of manipulating our lymphatic system – it may even uncover previously unknown ways that existing treatments work. "Lots of drugs might be acting on lymphatics and we just didn't know it," says Caron. Supporting this idea, her team has recently shown that many migraine drugs boost the drainage of brain fluid through meningeal lymphatic vessels. "It's awe-inspiring when you consider just how much we need to learn about this understudied vascular system that is so critical for keeping us healthy," she says.

All this may leave you wondering whether popular "lymphatic drainage" practices might actually work. Here the news is less rosy. Admittedly, face rolling can temporarily sharpen your jawline by increasing fluid drainage, but there is little good-quality evidence to back up health claims for things like reduced inflammation or cellulite removal. So, although I have come to marvel at my lymphatic system, I won't be including a jade rolling pin in my morning routine. Sorry, Grandma! ▮

Carissa Wong is a health reporter at *New Scientist*

Brain Basics

PubMed

Display Settings: Abstract

NEJM FULL TEXT

N Engl J Med. **1994** Mar 3;330(9):613-22.

Excitatory amino acids as a final common pathway for neurologic disorders.

Lipton SA, Rosenberg PA.

Harvard-Longwood Neurology Program, Boston, MA 02115.

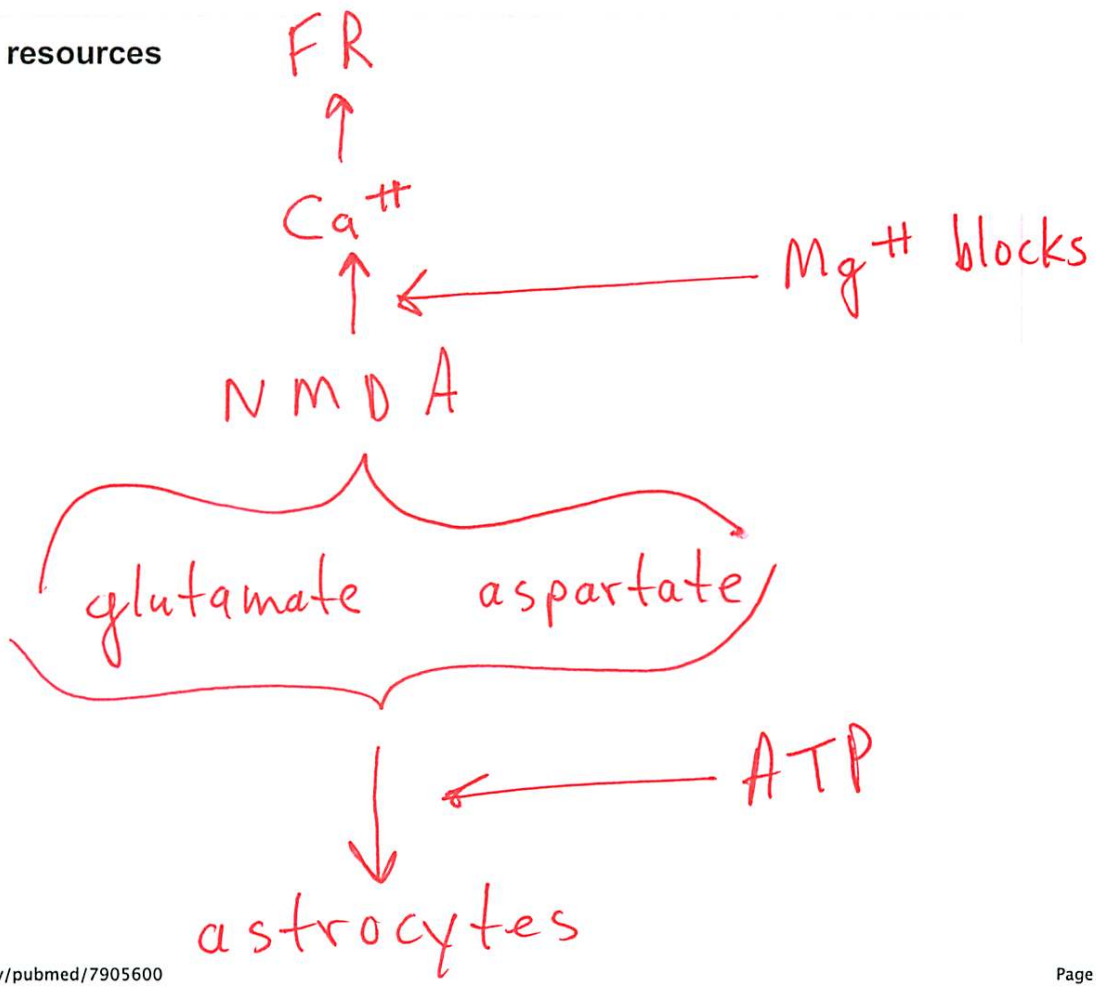
Comment in

Excitatory amino acids in neurologic disorders. [N Engl J Med. 1994]
Excitatory amino acids in neurologic disorders. [N Engl J Med. 1994]

PMID: 7905600 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources



Over the past several decades, an overwhelming body of research has greatly expanded our understanding of the mechanisms underlying excitotoxicity in brain ischemia as well as in many chronic neurodegenerative diseases.

"The purpose of this work is to provide a general overview of neuronal excitotoxicity and the inevitable downstream consequences of Ca++ overload. We also discuss the contribution of Ca++ transporters in excitotoxicity. This article is part of a Special Issue entitled 'Calcium Pumps and Exchangers in Neuronal Injury and Neurodegeneration'."

••••••••••••••••••

In 2001, professor of neuroscience Mark Bear, PhD, and colleagues from Brown University, wrote a book titled:

Neuroscience
Exploring the Brain

Their book has a section titled:

"The Brain's Exciting Poisons"

They note:

"Neurons of the brain rarely regenerate, so each dead neuron is one less we have for thinking."

"One of the fascinating ironies of neuronal life and death is that glutamate, the most essential neurotransmitter in the brain, is also one of the biggest killers of neurons."

The brain stores a large quantity of glutamate. **"An ominous observation is that when you apply** [a small excess] **amount of glutamate to the outside of isolated neurons, they die within minutes."**

"The voracious metabolic rate of the brain demands a constant supply of oxygen and glucose" to generate enough ATP to keep the neuron's glutamate and ion pumps working hard."

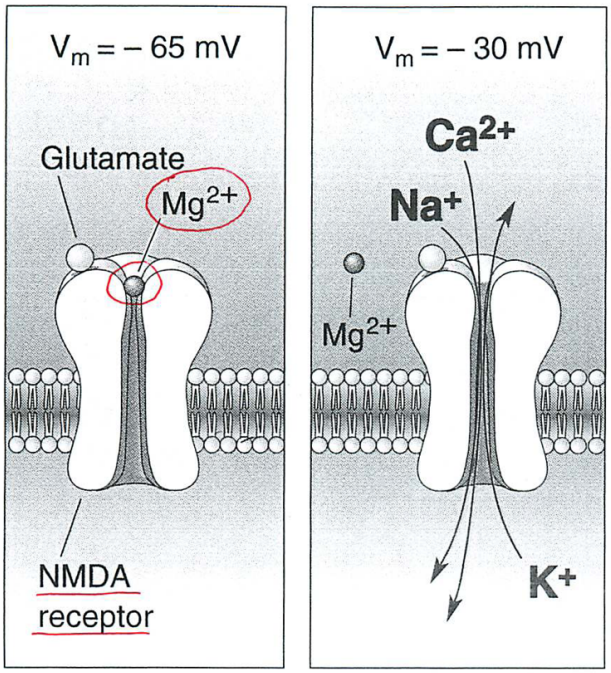
"Excess glutamate depolarizes neurons, which raises intracellular Ca++ which causes still more glutamate to be released." [feedback loop]

"When glutamate reaches high concentrations, it kills neurons by overexciting them, a process called *excitotoxicity*."

"The NMDA type of glutamate channel is a critical player in excitotoxicity because it is the main route for Ca++ entry."

"Neuron damage or death occurs because of stimulation by Ca++ of intracellular enzymes that degrade proteins, lipids, and nucleic acids. Neurons literally digest themselves."

"Excitotoxicity has recently been implicated in several progressive neurodegenerative diseases, such as *amyotrophic lateral sclerosis* (ALS), also known as Lou Gehrig's disease, *Alzheimer's* disease, and *Parkinson's* disease."



(a) Glutamate **(b)** Glutamate and depolarization

Figure 6.20
The flow of inward ionic current through the NMDA-gated channel. (a) Glutamate alone causes the channel to open, but at the resting membrane potential, the pore becomes blocked by Mg^{2+} ions. **(b)** Depolarization of the membrane

"Too much Ca++ can be a bad thing. If neurons become overloaded with Ca++, they die (excitotoxicity)."

••••••••••••••••••

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Mol Neurobiol. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Mol Neurobiol. 2018 August ; 55(8): 6601–6636. doi:10.1007/s12035-017-0852-4.

Brain Photobiomodulation Therapy: A Narrative Review

Farzad Salehpour[a,b], **Javad Mahmoudi**[a], **Farzin Kamari**[a], **Saeed Sadigh-Eteghad**[a], **Seyed Hossein Rasta**[b,c,d], and **Michael R Hamblin**[e,f,g]

[a]Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran

[b]Department of Medical Physics, Tabriz University of Medical Sciences, Tabriz, Iran

[c]Department of Medical Bioengineering, Tabriz University of Medical Sciences, Tabriz, Iran

[d]School of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom

[e]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, Massachusetts 02114, United States

[f]Department of Dermatology, Harvard Medical School, Boston, Massachusetts 02115, United States

[g]Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts 02139, United States

Abstract

Brain photobiomodulation (PBM) therapy using red to near-infrared (NIR) light is an innovative treatment for a wide range of neurological and psychological conditions. Red/NIR light is able to stimulate complex IV of the mitochondrial respiratory chain (cytochrome c oxidase) and increase ATP synthesis. Moreover, light absorption by ion channels results in release of Ca^{2+} and leads to activation of transcription factors and gene expression. Brain PBM therapy enhances the metabolic capacity of neurons and stimulates anti-inflammatory, anti-apoptotic, and antioxidant responses, as well as neurogenesis and synaptogenesis. Its therapeutic role in disorders such as dementia and Parkinson's disease, as well as to treat stroke, brain trauma, and depression has gained increasing interest. In the transcranial PBM approach, delivering a sufficient dose to achieve optimal stimulation is challenging due to exponential attenuation of light penetration in tissue. Alternative approaches such as intracranial and intranasal light delivery methods have been suggested to overcome this limitation. This article reviews the state-of-the-art preclinical and clinical evidence regarding the efficacy of brain PBM therapy.

Keywords

photobiomodulation therapy; low-level laser therapy; brain function; cortical neurons; traumatic brain injury; stroke; dementia; depression

Conflict of Interest: The authors declare no conflict of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

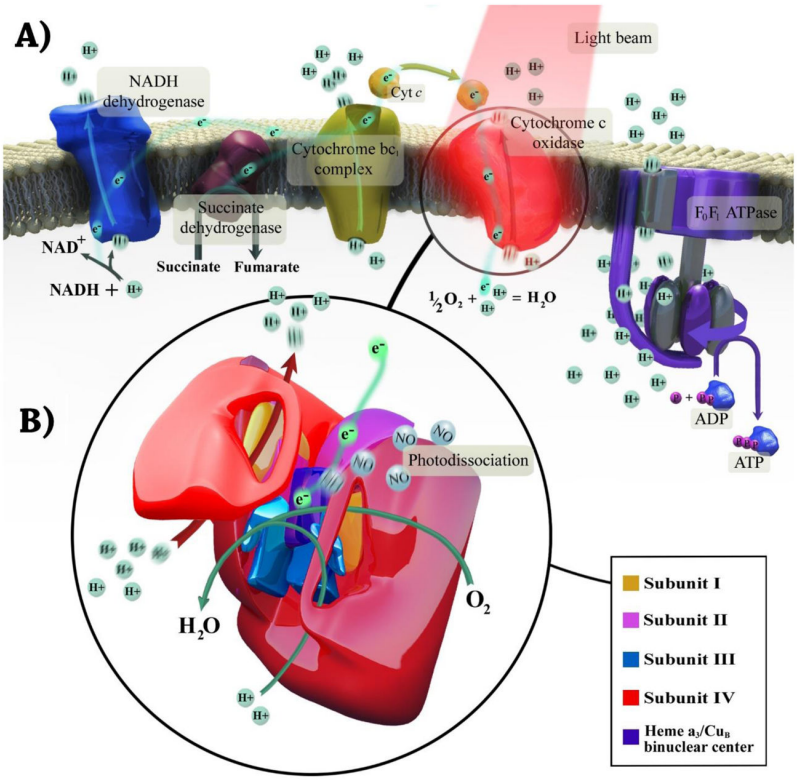


Fig. 1. Mechanism of photobiomodulation therapy in mitochondria

(A) The flow of electrons and protons through the mitochondrial respiratory chain. Photobiomodulation stimulates cytochrome c oxidase, improves its catalytic activity, and elevates ATP synthesis. All these results in enhancement of neuronal respiration and metabolic capacity. (B) The structure of cytochrome c oxidase and electrons path through its subunits. The complex contains two copper centers as well as two heme prosthetic groups. Photobiomodulation may dissociate nitric oxide from binuclear center (a_3/Cu_B), allowing oxygen to return, and facilitates electron transfer and increases proton gradient.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

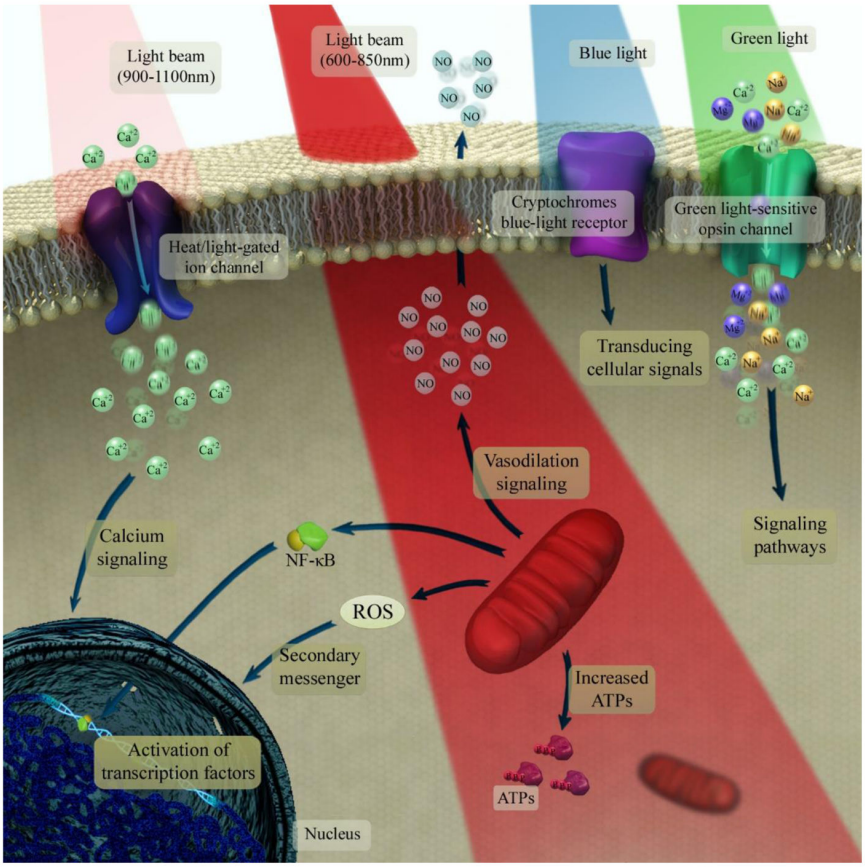


Fig. 2. Photobiomodulation underlying mechanisms at the cellular and molecular levels

Light at 600–850 nm is absorbed by the mitochondrial electron transfer chain and leads to upregulation of the neuronal respiratory capacity. The near-infrared light at range of 900–1100 nm is absorbed by structured water clusters formed in or on a heat/light-gated ion channels. An increase in vibrational energy of water cluster leads to perturb the protein structure and opening the channel which ultimately allows modulation of intracellular Ca^{2+} levels. The absorption of green light by neuronal opsin photoreceptors (OPN2–5) activates transient receptor potential channels which causes non-selective permeabilization to Ca^{2+}, Na^{+} and Mg^{2+}. The cryptochromes (a class of flavoprotein blue-light signaling receptors) absorb blue light and seems to activate the transducing cellular signals via part of the optic nerve to the suprachiasmatic nucleus in the brain, which is important in regulation of the circadian clock.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

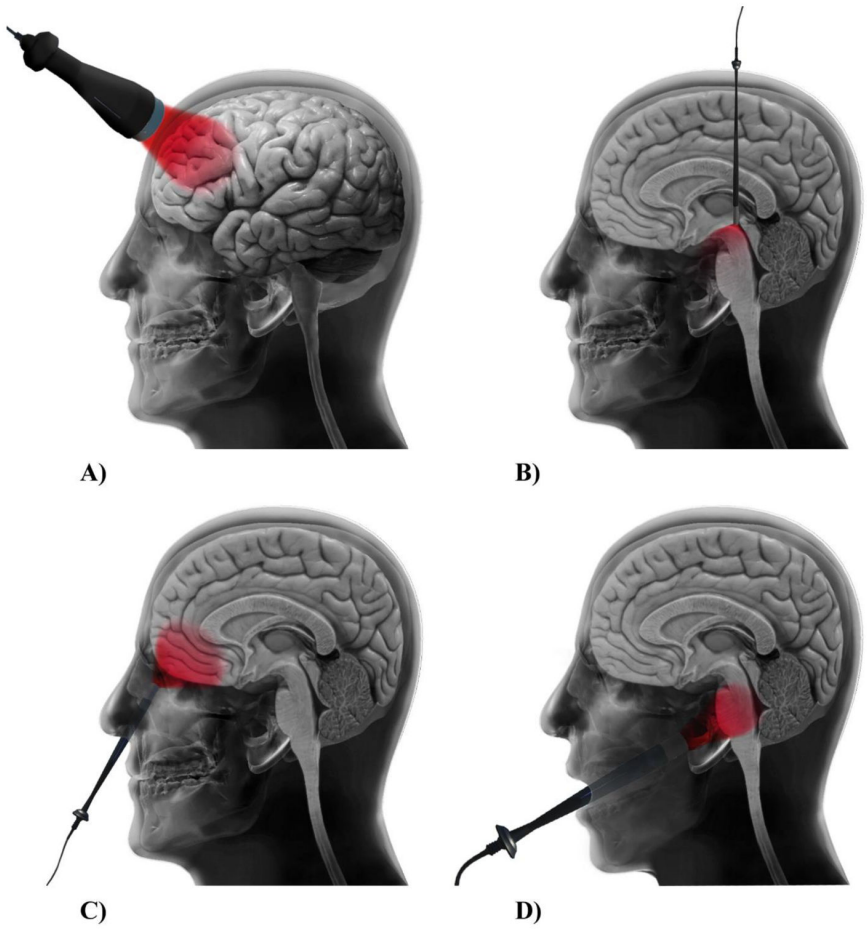


Fig. 3. Different approaches for light delivery to achieve brain photobiomodulation therapy
(A) Transcranial, (B) intracranial, (C) intranasal photobiomodulation therapy, (D) brain photobiomodulation via oral cavity.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

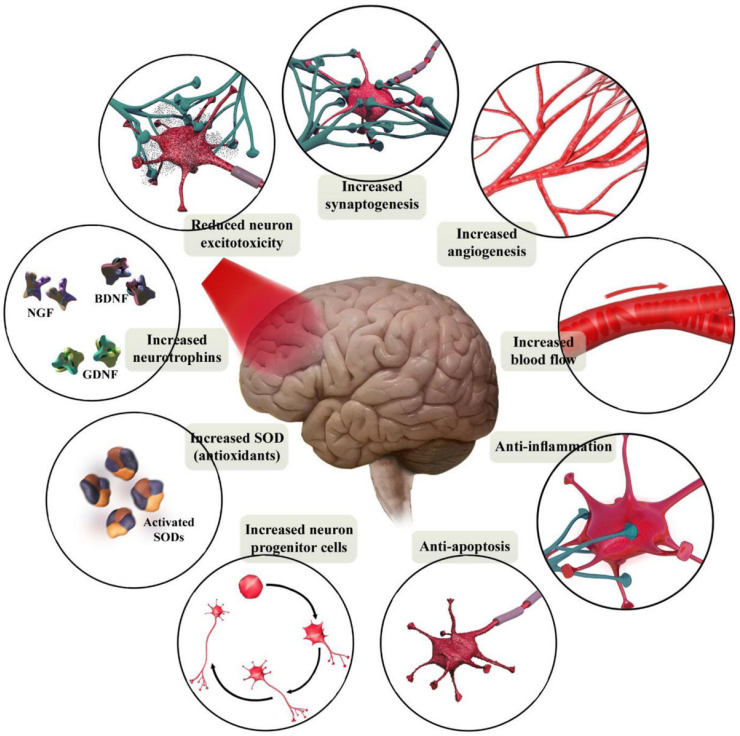


Fig. 4. Brain tissue-specific functional processes that occur after brain photobiomodulation therapy

On a cellular level, photobiomodulation can reduce apoptosis and excitoxicity, increase antioxidants, neurotrophins and stimulate neuroprogenitor cells. On a tissue level, photobiomodulation therapy can increase blood flow and angiogenesis, reduce inflammation and help neurons form new connections. BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; NGF, nerve growth factor; SOD, superoxide dismutase.

The Brain

Trauma

Neurodegenerative Diseases
- Alzheimer's
- Parkinson's
- Chronic Traumatic Encephalopathy
- Amyotrophic Lateral Sclerosis

Depression

Anxiety

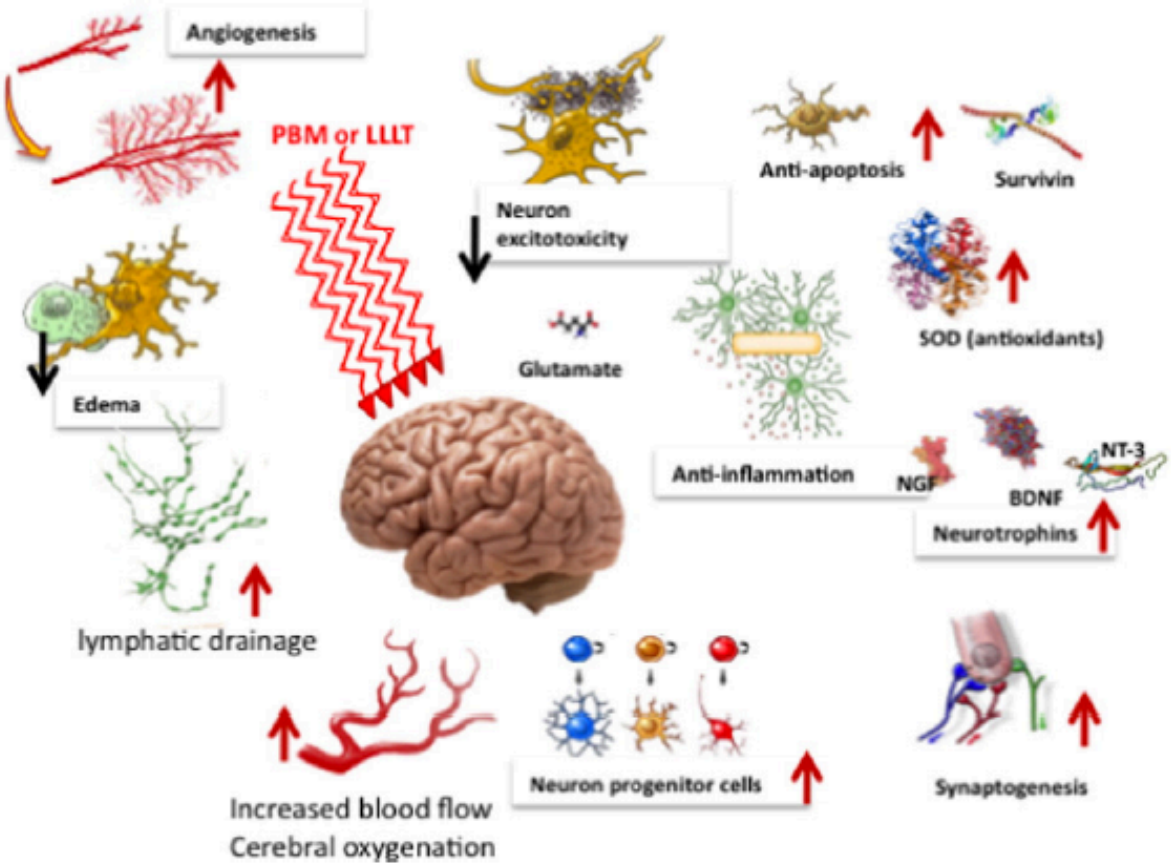
Stroke

Cognitive Enhancement

Etc.

Shining Light on the Head: Photobiomodulation for Brain Disorders
BBA Clinical (Biochimica et Biophysica Acta Journal)
2016; No. 6; pp. 113-124

Michael R. Hamblin
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston;
Department of Dermatology, Harvard Medical School, Boston;
Harvard-MIT Division of Health Sciences and Technology



Photobiomodulation (PBM) describes the use of red or near-infrared light to stimulate, heal, regenerate, and protect tissue that has either been injured, is degenerating, or else is at risk of dying.

One of the organ systems of the human body that is most necessary to life, and whose optimum functioning is most worried about by humankind in general, is the brain.

The brain suffers from many different disorders that can be classified into three broad groupings: traumatic events (stroke, traumatic brain injury, and global ischemia), degenerative diseases (dementia, Alzheimer's and Parkinson's), and psychiatric disorders (depression, anxiety, post traumatic stress disorder). There is some evidence that all these seemingly diverse conditions can be beneficially affected by applying light to the head.
There is even the possibility that PBM could be used for cognitive enhancement in normal healthy people.

NIH Public Access
Author Manuscript
PM R. Author manuscript; available in PMC 2011 December 1.

Published in final edited form as:
PM R. 2010 December ; 2(12 Suppl 2): S292–S305. doi:10.1016/j.pmrj.2010.10.013.

Role of Low-Level Laser Therapy in Neurorehabilitation

Javad T. Hashmi, MD,
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA Disclosure: nothing to disclose

Ying-Ying Huang, MD,
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Aesthetic and Plastic Center, Guangxi Medical University, Nanning, PR China Disclosure: nothing to disclose

Bushra Z. Osmani, MD,
Aga Khan Medical College, Karachi, Pakistan Disclosure: nothing to disclose

Sulbha K. Sharma, PhD,
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA Disclosure: nothing to disclose

Margaret A. Naeser, PhD, LAc, and
VA Boston Healthcare System, Boston, MA; Department of Neurology, Boston University School of Medicine, Boston, MA Disclosure: nothing to disclose

Michael R. Hamblin, PhD
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, 40 Blossom St BAR414, Boston, MA 02114 ; Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA. Address correspondence to: M.R.H.; hamblin@helix.mgh.harvard.edu

Abstract

This year marks the 50th anniversary of the discovery of the laser. The development of lasers for medical use, which became known as low-level laser therapy (LLLT) or photobiomodulation, followed in 1967. In recent years, LLLT has become an increasingly mainstream modality, especially in the areas of physical medicine and rehabilitation. At first used mainly for wound healing and pain relief, the medical applications of LLLT have broadened to include diseases such as stroke, myocardial infarction, and degenerative or traumatic brain disorders. This review will cover the mechanisms of LLLT that operate both on a cellular and a tissue level. Mitochondria are thought to be the principal photoreceptors, and increased adenosine triphosphate, reactive oxygen species, intracellular calcium, and release of nitric oxide are the initial events. Activation of transcription factors then leads to expression of many protective, anti-apoptotic, anti-oxidant, and pro-proliferation gene products. Animal studies and human clinical trials of LLLT for indications with relevance to neurology, such as stroke, traumatic brain injury, degenerative brain disease, spinal cord injury, and peripheral nerve regeneration, will be covered.

© 2010 by the American Academy of Physical Medicine and Rehabilitation
Disclosure key can be found on the Table of contents and at www.pmrjournal.org

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

also reported that, in patients with long-term peripheral nerve injury, 780-nm laser therapy (250 mW) can progressively improve nerve motor function, which leads to significant functional recovery [84].

Barbosa et al [85] observed that, compared with the 830-nm laser group and the sham group, rats in the 660-nm laser group had the best sciatic functional index scores on average, which indicates that the use of these parameters was more efficient. Differences in sciatic functional index were found among the 660-nm laser group and the other ones at the 14th day [85]. However, Gigo-Benato et al [86] found that pulsed (905 nm) continuous (808 nm) combined laser biostimulation showed the best effectiveness in promoting peripheral nerve regeneration.

CONCLUSION

LLLT is steadily moving into mainstream medical practice. As the Western populations continue to age, the incidence of the degenerative diseases of old age will only continue to increase and produce an evermore severe financial and societal burden. Moreover, despite the best efforts of "big pharma," distrust of pharmaceuticals is growing in general because of uncertain efficacy and troublesome adverse effects. LLLT has no reported adverse effects, and no reports of adverse events can be directly attributed to laser or light therapy. We believe that the high benefit:risk ratio of LLLT should be better appreciated by medical professionals in the rehabilitation and physical medicine specialties. The introduction of affordable LED devices powered by rechargeable batteries will lead to many home-use applications of LLLT. The concept of "wearable" light sources is not far off. Moreover, the particular benefits of LLLT to both the central and peripheral nervous systems suggest that much wider use of LLLT could or should be made in cases of both brain diseases and injuries.

Acknowledgments

Disclosure: research in the Hamblin laboratory supported by NIH grant R01AI050875, Center for Integration of Medicine and Innovative Technology (DAMD17-02-2-0006), CDMRP Program in TBI (W81XWH-09-1-0514), and Air Force Office of Scientific Research (FA9950-04-1-0079)

REFERENCES

1. Mester E, Szende B, Tota JG. Effect of laser on hair growth of mice. Kiserl Orvostud. 1967; 19:628–631.
2. Mester E, Spiry T, Szende B, et al. Effect of laser rays on wound healing. Am J Surg. 1971; 122:532–535. [PubMed: 5098661]
3. Mester E, Szende B, Spiry T, et al. Stimulation of wound healing by laser rays. Acta Chir Acad Sci Hung. 1972; 13:315–324. [PubMed: 4659882]
4. Huang YY, Chen AC, Carroll JD, et al. Biphasic dose response in low level light therapy. Dose Response. 2009; 7:358–383. [PubMed: 20011653]
5. Aimbire F, Albertini R, Pacheco MT, et al. Low-level laser therapy induces dose-dependent reduction of TNFalpha levels in acute inflammation. Photomed Laser Surg. 2006; 24:33–37. [PubMed: 16503786]
6. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol B. 1999; 49:1–17. [PubMed: 10365442]
7. Passarella S, Casamassima E, Molinari S, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. FEBS Lett. 1984; 175:95–99. [PubMed: 6479342]

NIH Public Access
Author Manuscript
Accepted for publication in a peer reviewed journal
About Author manuscripts | Submit a manuscript

From: PM R. Author manuscript; available in PMC 2011 December 1.
Published in final edited form as:
PM R. 2010 December; 2(12 Suppl 2): S292–S305.
doi: 10.1016/j.pmrj.2010.10.013

Copyright/License ► Request permission to reuse

<< Prev Figure 1 Next >>

Figure 1

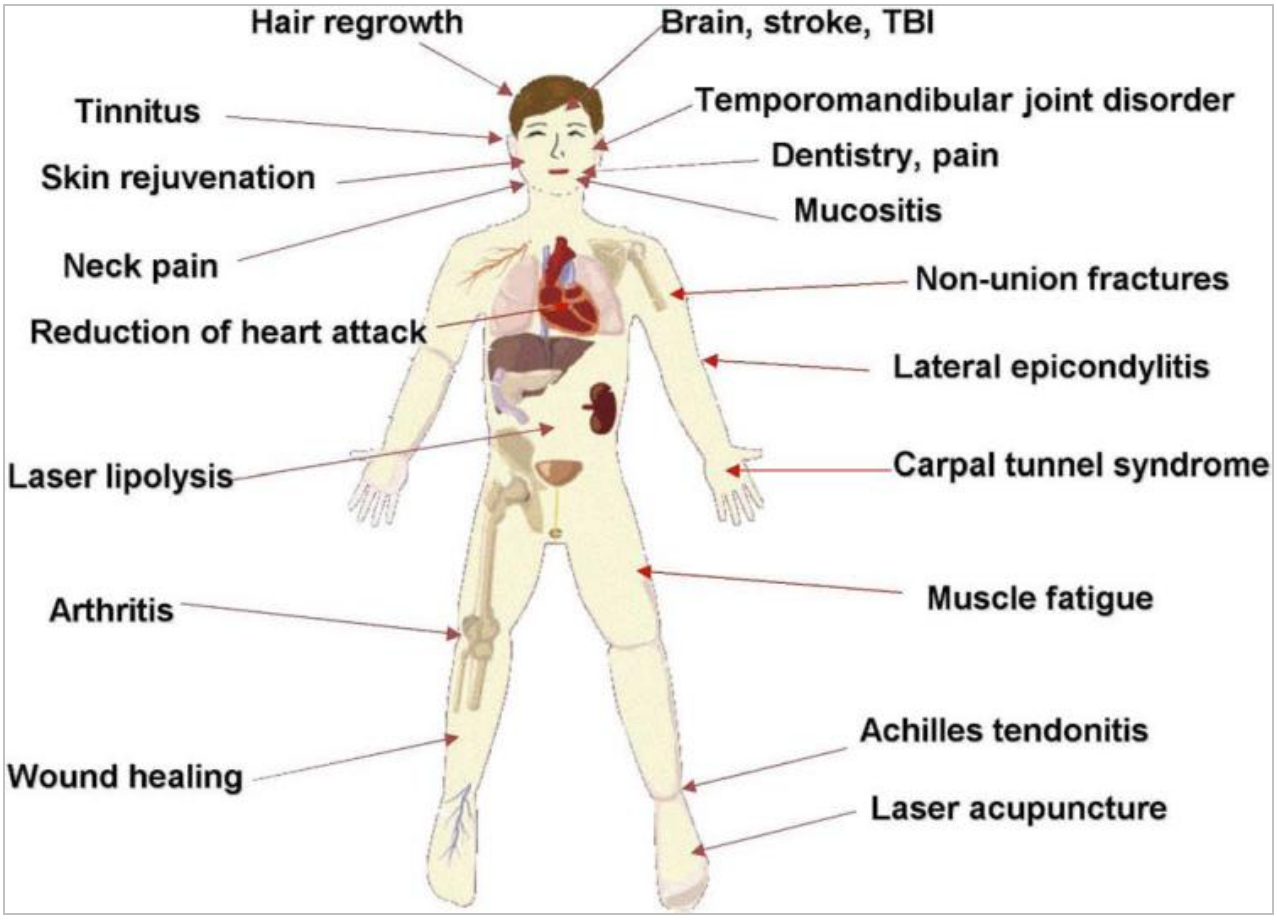


Diagram of the various medical applications of low-level light therapy.

Images in this article

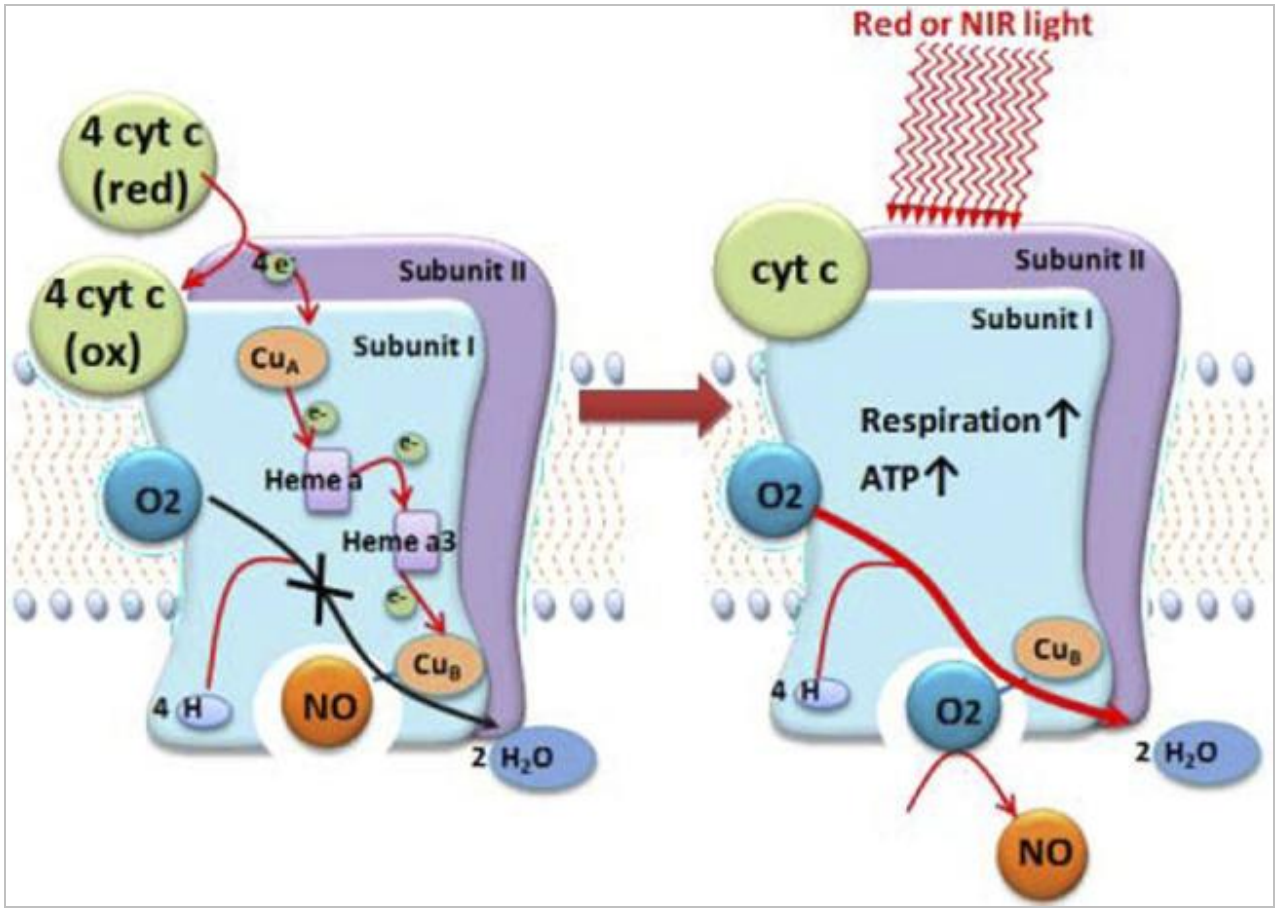
NIH Public Access
Author Manuscript
Accepted for publication in a peer reviewed journal
About Author manuscripts | Submit a manuscript

From: PM R. Author manuscript; available in PMC 2011 December 1.
Published in final edited form as:
PM R. 2010 December; 2(12 Suppl 2): S292–S305.
doi: 10.1016/j.pmrj.2010.10.013

Copyright/License ► Request permission to reuse

<< Prev Figure 4 Next >>

Figure 4



Nitric oxide can bind to copper (or heme) centers in cytochrome c oxidase and inhibit respiration. The nitric oxide may be photodissociated by absorption of red or near infrared light, allowing oxygen to return and sharply increasing respiration and adenosine triphosphate formation.

Lasers in Surgery and Medicine
Supplement 22, 2010

#185

THE APPLICATION OF LOW-LEVEL LASER THERAPY FOR THE SYMPTOMATIC CARE OF LATE STAGE PARKINSON'S DISEASE: A NON-CONTROLLED, NON-RANDOMIZED STUDY

Ryan Maloney, Steven Shanks, Jillian Maloney

Erchonia Medical, McKinney, TX; University of Arizona, Tucson, AZ

Background: Parkinson's Disease (PD) is the degeneration of dopaminergic neurons of the substantial nigra resulting in a reduction of strital dopamine content. The exact mechanism is not well understood; however, several pathophysiologic mechanisms such as oxidative stress, mitochondrial dysfunction, and and degradation of major intracellular proteins have been postulated to explain the progressive neuron loss. Numerous studies have revealed that LLLT can modulate cell bioenergetics influencing the intracellular redox state of a cell. With histological evidence suggesting that laser therapy can repair oxidatively damaged cells and increase neuronal axonal transport, the objective of this non-controlled, non-randomized study was to evaluate the improvement of symptoms associated with late stage PD.

Study: Eight volunteers between 18 to 80 years with late stage PD participated in a non-controlled, non-randomized study. Participants received LLLT treatments (PL5000, manufactured by Erchonia Medical Inc.) daily for two weeks. Each participant received treatment of the brain stem, bilateral occipital, parietal, temporal and frontal lobes, and treatment along the sagittal suture. Patients were asked, using the Visual Analog Scale (VAS), to record the severity of their symptoms of balance, gait, freezing, cognitive function, rolling in bed, and difficulties with speech pre-procedure and at study endpoint with 10 being most severe and 0 as no symptom.

Results: Compared with baseline, all participants demonstrated a numerical improvement in the VAS from baseline to study endpoint. A statistically significant reduction in VAS rating for gait and cognitive function was observed with average mean change of -1.87 ($p < 0.05$) for gait and a mean reduction of -2.22 ($p < 0.05$) for cognitive function. Further, freezing and difficulty with speech ratings were significantly lower at study endpoint with a mean reduction of -1.28 ($p < 0.05$) for freezing and -2.22 ($p < 0.05$) for difficult with speech.

Conclusion: These data suggest that laser therapy may serve as a non-invasive instrument for symptom reduction of PD.

Author of the *New York Times* bestseller

THE BRAIN THAT CHANGES ITSELF

The Brain's Way of Healing

REMARKABLE DISCOVERIES and RECOVERIES from the FRONTIERS of NEUROPLASTICITY

NORMAN DOIDGE MD

Alzheimer's (neurodegenerative) Prevention Protocol
Brain Rehabilitation Protocols

Stop consuming refined/glycating carbohydrates and ultra-processed foods

Balance omega-6/omega-3 ratio (1.5 – 4 /1)

Get vitamin D levels above 50 ng/ml

Take vitamin K2-4 and K2-7

Be mindful of cholesterol lowering drugs (optimum total cholesterol for brain physiology 200-240 mg/dl)

Supplement with magnesium, about 500 mg/day

No copper water or copper in supplements

Take antioxidant vitamin/mineral supplements (watch the iron and copper)

Take curcumin/resveratrol

Elevate glutathione (Undenatured Whey Protein / NAC supplementation / Sublingual)

Detoxify (passive sweating / oil pull)

Treat/Protect the gut/microbiome (especially prebiotics/probiotics)

Low Level Laser Therapy (XLR8 two 7.5mW diodes: 1-10-40-60 or 1-10-40-528) [while doing your goals, gratitude, and forgiveness lists] [laser works best with mitochondrial supplements] [Trevor, Michelle]

- 2 minutes prefrontal cortex (most important)
- 2 minutes cerebellum/atlas junction (for CSF)
- 2 minutes at frontal/parietal junction (vertex of skull)
- 2 minutes for each cymba conchae (ear): use 10-40-10-40, Trevor
- 2 minutes carotid sheath between mastoid and jaw: use 10-10-10-10, Trevor
- 2 minutes GI Vagus (above umbilicus): use 1-10-1-10, Trevor

Avoid brain trauma (especially repetitive sub-concussive blows)

Exercise

Do not smoke

Minimize television and other mindless activities

Do crossword puzzles and other challenging brain games/activities

Consume Medium Chain Saturated Triglycerides (coconut oil, 1 Tbs./meal)

Do not retire from work (increases risk 3% per year of retirement)

Minimize consumption of Anti-Cholinergic Drugs

Take Cholinergic supplements

Nobel Prize in Medicine Awarded for Work on Senses

10/5/2021

WSJ

By Denise Roland
And Brianna Abbott

The Nobel Prize in physiology or medicine was jointly awarded to David Julius and Ardem Patapoutian for their work on how the human body senses temperature, touch and movement.

The Nobel Assembly said Monday that the scientists' discoveries had unlocked one of the secrets of nature by explaining the molecular basis for sensing heat, cold and mechanical force.

This basic understanding of how temperature and touch signal the nervous system is now being harnessed to research potential treatments for chronic pain and other medical conditions, the Nobel Assembly said.

JONATHAN NACKSTRAND/AGENCE FRANCE-PRESSE/GETTY IMAGES

David Julius and Ardem Patapoutian were honored for explaining the molecular basis for sensing heat, cold and mechanical force. Above right, Thomas Perlmann, secretary of the Nobel Assembly.

"These sensations of heat and pain and touch, if those are all converted to electrical signals and sent to the brain, that opens up a whole new world of potential treatments," said Chad Bouton, a professor at the Feinstein Institutes for Medical Research in New York, whose work includes the use of stimulation of the brain to restore the sense of touch to patients who have lost it as a result of a stroke or injury. "It's all made possible by these critical discoveries," he added.

Dr. Julius was born in 1955 in New York and is now a professor and chairman of the department of physiology at the University of California, San Francisco. Dr. Patapoutian was born in 1967 in Beirut. He moved to the U.S. in his youth and is currently a professor at Scripps Research in La Jolla, Calif.

While at UCSF in the late 1990s, Dr. Julius used capsaicin, a compound in chili peppers that causes a burning sensation, to identify a chemical receptor in nerve endings of the skin that responds to heat. In separate research, Dr. Patapoutian used pressure-sensitive cells to discover new receptors that respond to touch in the skin and internal organs.

Both the scientists' work involved identifying the specific genes involved in sensing either heat or touch and then figuring out what those genes did within cells.

Dr. Julius and his team assembled a library of millions of DNA fragments from sensory neurons and found a single gene that made cells sensitive to capsaicin. That gene directs nerve cells to make a so-called ion channel that opens up in response to capsaicin and high temperatures, allowing electrically charged particles called ions to flood into cells and send a pain message to the brain. That receptor was later named TRPV1.

"There is a time when you make a discovery where you are the only person on the planet, or at least you think you're the only person on the planet, who knows the answer to a particular question," Dr. Julius said in a media event. "And that's a really thrilling moment."

That discovery, published in a 1997 paper, sparked a wave of research by large drugmakers hopeful that blocking the TRPV1 receptor could treat chronic pain.

The work also paved the way for the discovery of other ion channels.

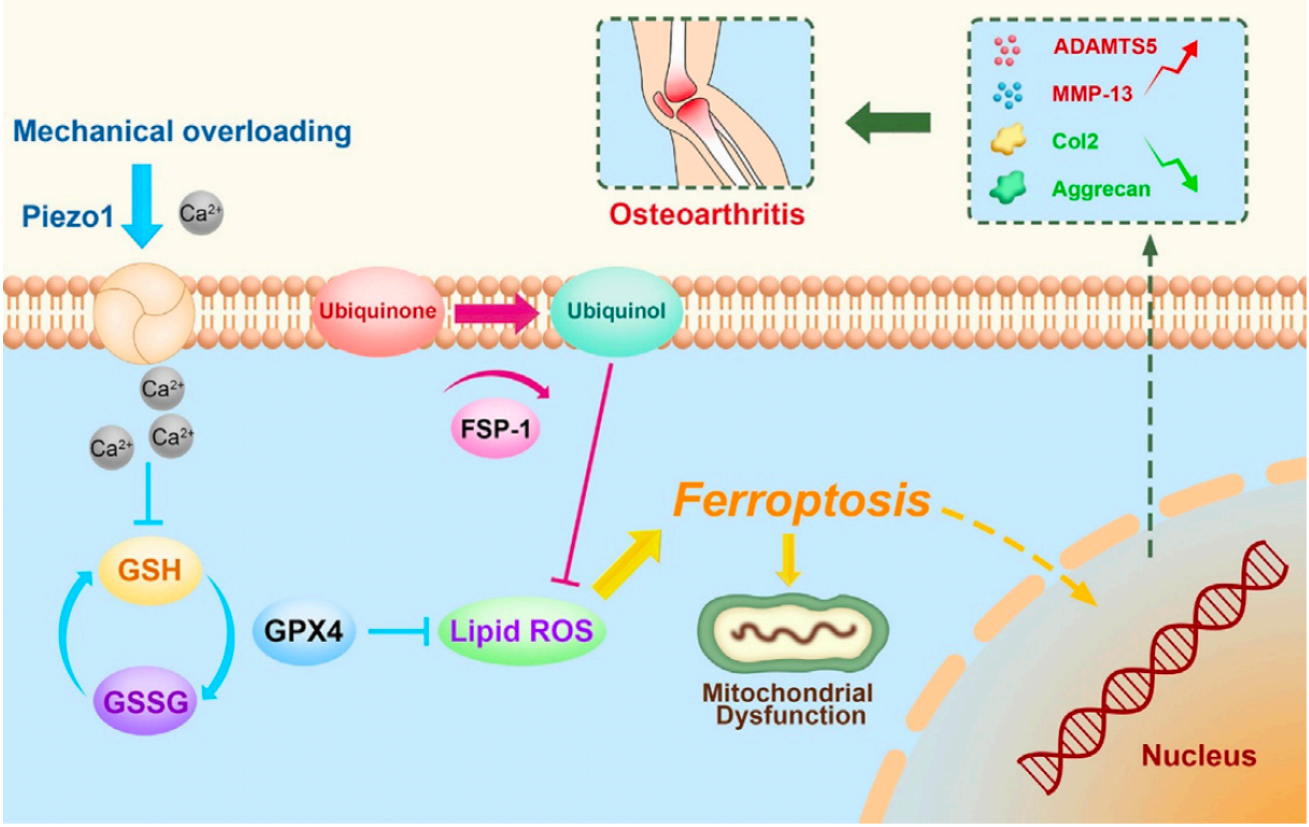
One of those channels was a cold-sensing receptor called TRPM8, which Drs. Julius and Patapoutian uncovered independently of one another, using menthol.

Dr. Patapoutian's work on touch uncovered two ion channels, named Piezo1 and Piezo2 after the Greek word for pressure, that open up in response to touch. He later showed that Piezo2 played a key role in how the body senses its position and movement. Subsequent work demonstrated how Piezo1 and Piezo2 help regulate bodily functions such as blood pressure and bladder control.

Dr. Patapoutian said that work was under way to find molecules that block the Piezo channels as these could form the basis of drugs for different types of pain.

Mechanical Overloading Induces Glutathione-Regulated Chondrocyte Ferroptosis in Osteoarthritis via Piezo1 Channel Facilitated Calcium Influx

Journal of Advanced Research
November 2022



A Simplified Model from Dan Murphy

Piezo1 is a **mechanoreceptor** that was mentioned in the **2021 Nobel Prize** in physiology or medicine.

Piezo1 receptors are found in the membrane of chondrocytes.

Mechanical loading (overloading) opens the Piezo1 receptor which allows excessive influx of Ca++ to enter into the cell. **[consider magnesium]**

The excessive intracellular Ca++ inhibits glutathione which increases chondrocyte oxidative stress, leading to osteoarthritis. **[consider glutathione supplements]**

CoQ10 blocks the oxidative stress driven ferroptosis cartilage damage.
[consider CoQ10; consider donating blood]

In an integrative narrative, this article has applications for the chiropractic subluxation and adjustment, Ca++ excess, Mg++ deficiency, glutathione status, and free radical damage. As such it would support not only the chiropractic adjustment, but also diet, nutrition, supplements, and laser therapy.

Excessive Mechanical Stress-induced Intervertebral Disc Degeneration is Related to Piezo1 Overexpression Triggering the Imbalance of Autophagy/Apoptosis in Human Nucleus Pulposus

Arthritis Research & Therapy
May 23, 2022; Vol. 24; No. 1; Article 119

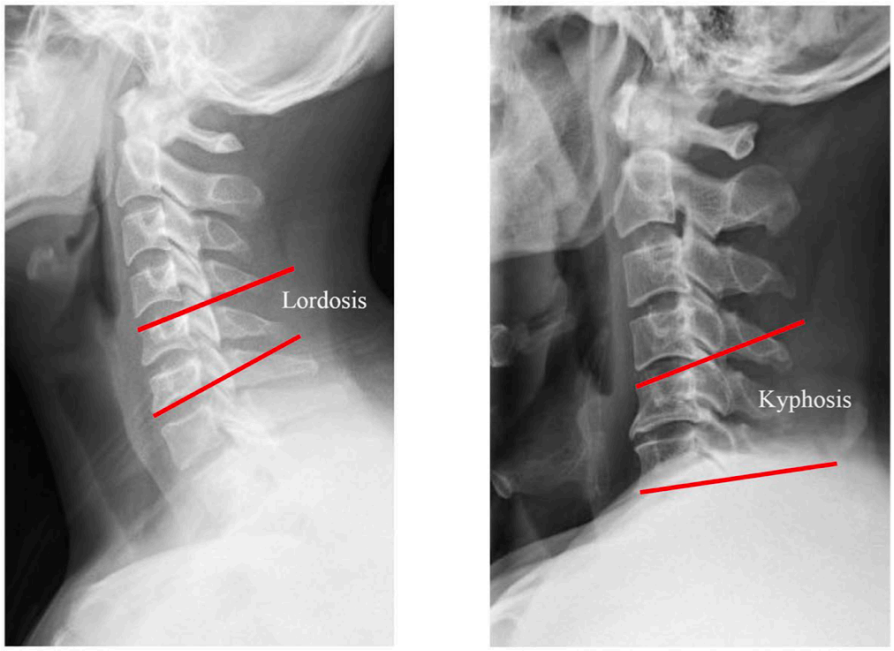
Sheng Shi, Xing-Jian Kang, Zhi Zhou, Zhi-Min He, Shuang Zheng, Shi-Sheng He

This study aimed to investigate the effect of the ***Piezo1*** mechanoreceptor on the mechanical stress-induced intervertebral disc degeneration (IVDD) and explore the possible mechanism. Immunohistochemistry staining antibodies against ***Piezo1*** were used in the analysis.

Cervical nucleus pulposus (NP) samples were collected via surgery from 26 patients (12 men and 14 women; age range: 22–65 years).

"In order to explore whether mechanical stress treatment can affect Piezo1 expression and cell function of NP cells, a mechanical compression with different intensity and/or duration was conducted on human NP cells."

Cervical lordosis was assessed with x-rays using the protocol established by Deed Harrison, DC, and colleagues in the journal *Clinical Biomechanics* in 2001: [Harrison DE, Harrison DD, Janik TJ, William Jones E, Cailliet R, Normand M. Comparison of axial and flexural stresses in lordosis and three buckled configurations of the cervical spine; Clinical Biomechanics; May 2001; Vol.16; No. 4; pp. 276–784.]



The angle between the superior endplate of the rostral vertebra and the inferior endplate of the caudal vertebra on the lateral x-ray was measured.

See the following picture:

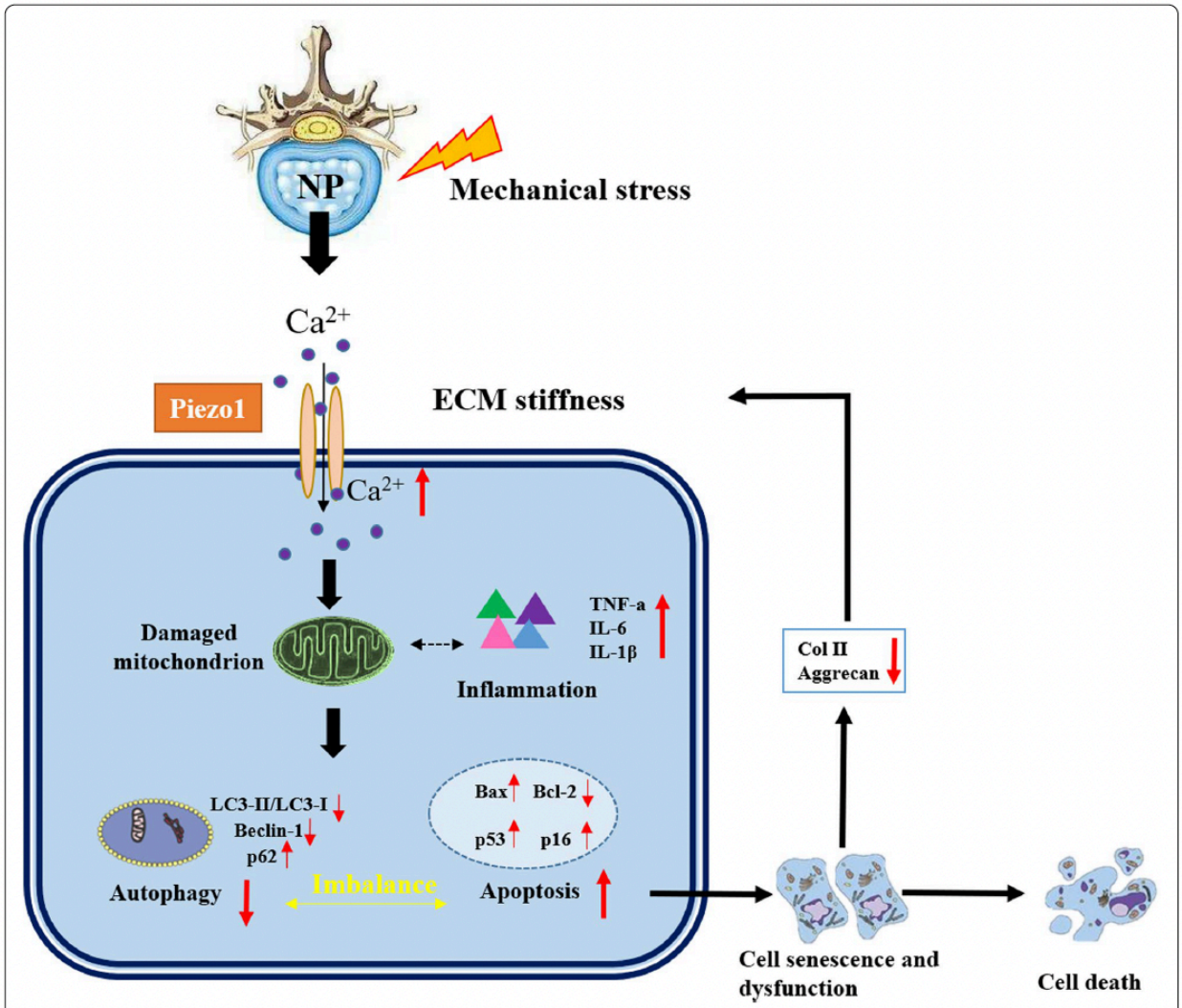


Fig. 5 Excessive mechanical stress stimulates mechanosensitive channel protein Piezo1 overexpression in human nucleus pulposus cells, which aggravates mitochondrial damage and inflammatory response in NP cells and further triggers the reduction of autophagy and the intensification of apoptosis. The imbalance between autophagy and apoptosis may result in cell senescence and dysfunction, weaken the synthesis of collagen II and Aggrecan in NP cells, and consequently precipitate cell death and exacerbate disc degeneration

Other *Article Reviews* on Piezo1 mechanoreceptors include:
Article Review 16-23:
Mechanical Loading Induces Piezo1 Calcium Influx and Osteoarthritis

Article Review 42-23:
Injury Initiates Disc Degeneration Through Piezo1 Mediated Inflammation

Other *Article Reviews* on cervical kyphosis include:
Article Review 24-11:
Is the Kyphosis Cause or Effect of Disc Degenerative Disease

Article Review 52-13:
Focal Kyphosis correction and Neurological Outcomes

Article Review 2-23:
Improvement in Cervical Curve in the Management of Lumbar Radiculopathy

RESEARCH ARTICLE

THE FASEB JOURNAL

Blood contains circulating cell-free respiratory competent mitochondria

Zahra Al Amir Dache[1] | Amaëlle Otandault[1] | Rita Tanos[1] | Brice Pastor[1] | Romain Meddeb[1] | Cynthia Sanchez[1] | Giuseppe Arena[2] | Laurence Lasorsa[1] | Andrew Bennett[3] | Thierry Grange[3] | Safia El Messaoudi[1] | Thibault Mazard[1] | Corinne Prevostel[1] | Alain R. Thierry[1]

Blood Contains Circulating Cell-free Respiratory Competent Mitochondria

The FASEB Journal
[Federation of American Societies for Experimental Biology]

March 2020; Vol. 34; No. 3; pp. 3616-3630

We believe that circulating cell-free intact mitochondria have crucial biological and physiological roles because mitochondria are already known as systemic messengers in cell-cell communication by transferring hereditary and nonhereditary constituents.

Mitochondria were recently discovered to translocate from one cell to the other.

Indeed, intercellular mitochondria trafficking was observed in vitro and in vivo, both in physiological and pathophysiological conditions including tissue injury and cancer.

We speculate that mitochondrial clearance and degradation occurs principally by phagocytosis.

This study is the first showing free structurally intact mitochondria in plasma.

•••••••••

The presence of mitochondria in unicellular to mammalian organisms originates from an ancient symbiosis between primitive eukaryotic cells and free-living aerobic prokaryotes.

Mitochondria are crucial organelles for central cell functions, and they are the principal nutrient-up-taking and energy-producing cell organelle; they also take part in calcium signaling, reactive oxygen species (ROS) production, cell death, and diverse cell signaling events.

Call-derived mitochondrial components, including mitochondrial DNA, have been found in the extracellular space.

Mitochondrial DNA has a small circular genome, without protective histones, and thus is more sensitive to degradation in the circulation.

There are approximately 50,000-fold more copies of the mitochondrial genome than the nuclear genome in the plasma of healthy individuals.

Our work demonstrates for the first time the presence in blood of circulating cell-free respiratory competent mitochondria.

In view of the potential roles of mitochondria in cell to cell communication, immune response, and inflammation, our discovery has broad implications in homeostasis and disease, and paves the way for new paths toward the treatment and prevention of diseases.

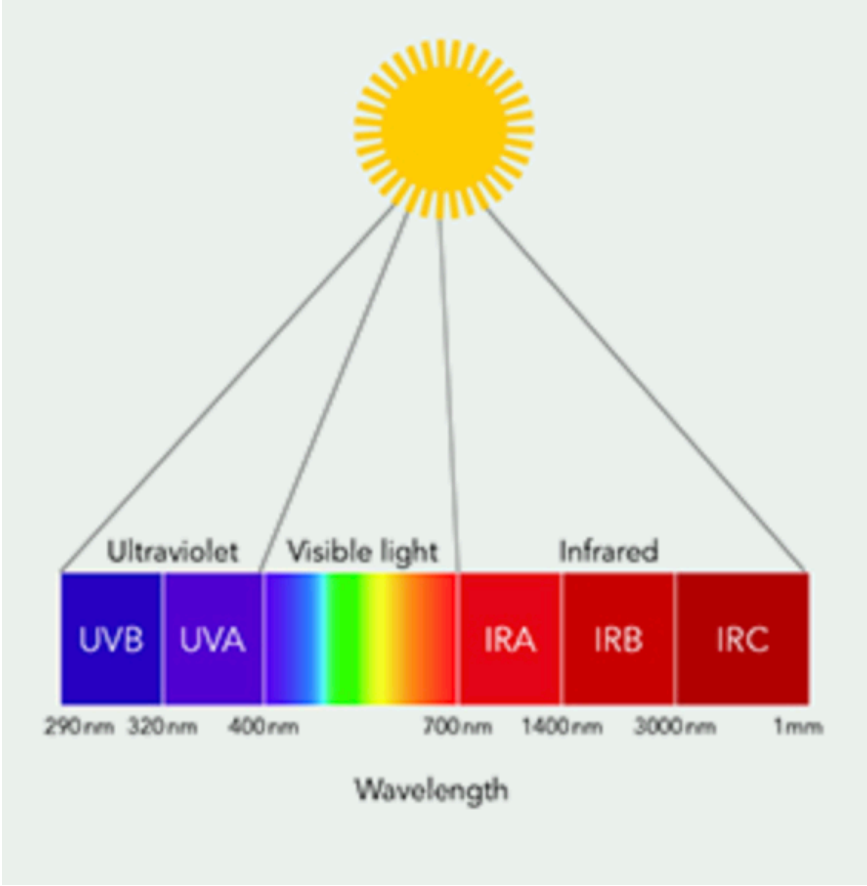
Wavelengths

A nanometer (nm) is equal to one-billionth of a meter

10,000 nanometers (nm) = 1 millimeter (mm)

IR = Infrared
Wavelengths *begin* at about 700 nm *to* 760 nm

- **IR-A = 700 nm *to* 1,400 nm = near infrared = NIR**
- **IR-B = 1,400 nm *to* 3,000 nm = mid infrared = MIR**
- **IR-C = 3,000 nm *to* 10,000 nm = far infrared = FIR**



Effects of Infrared Radiation and Heat on Human Skin Aging *in vivo*

Soyun Cho[1,2,3], Mi Hee Shin[1,2,3], Yeon Kyung Kim[1,2,3], Jo-Eun Seo[1,2,3], Young Mee Lee[1,2,3], Chi-Hyun Park[1,2,3] and Jin Ho Chung[1,2,3]

Sunlight damages human skin, resulting in a wrinkled appearance. Since natural sunlight is polychromatic, its ultimate effects on the human skin are the result of not only the action of each wavelength separately, but also interactions among the many wavelengths, including UV, visible light, and infrared (IR). In direct sunlight, the temperature of human skin rises to about 40°C following the conversion of absorbed IR into heat. So far, our knowledge of the effects of IR radiation or heat on skin aging is limited. Recent work demonstrates that IR and heat exposure each induces cutaneous angiogenesis and inflammatory cellular infiltration, disrupts the dermal extracellular matrix by inducing matrix metalloproteinases, and alters dermal structural proteins, thereby adding to premature skin aging. This review provides a summary of current research on the effects of IR radiation and heat on aging in human skin *in vivo*.

Journal of Investigative Dermatology Symposium Proceedings (2009) **14**, 15–19; doi:10.1038/jidsymp.2009.7

INTRODUCTION

Infrared (IR) radiation consists of wavelengths from 760 nm to 1 mm, and it is subdivided into three regions of increasing wavelength, IR-A (760–1400 nm), IR-B (1400–3000 nm), and IR-C (3000 nm–1 mm). Given that almost half of the solar energy reaching the earth's surface is in the IR range, solar IR is expected to have significant biological effects on human skin.

Heat is a form of energy that may be transmitted by IR radiation, which results in raised skin temperature. Human skin is exposed daily to natural sunlight. We found that the temperature of human skin can increase to more than 40°C under direct IR irradiation (Lee *et al.*, 2006) due to the conversion of IR into heat. There is clinical evidence indicating that chronic heat exposure of human skin may cause alterations. The skin disease called erythema ab igne is known to be caused by chronic heat exposure. It is characterized clinically by reticular pigmentation of the skin and histologically by the presence of solar elastosis in the dermis similar to what is seen in photoaged skin. Furthermore, severe skin aging may develop occasionally on bakers' arms, because of exposure to hot ovens, and on the faces of glass blowers.

However, the effects of IR radiation and heat on cutaneous aging are still largely unknown. This review provides an overview of the current knowledge of contributions of IR radiation and heat exposure to aging in human skin.

EFFECTS OF IR RADIATION ON AGING IN HUMAN SKIN *IN VIVO*

It has been reported that IR-A can penetrate epidermal and dermal layers and reach subcutaneous tissues without increasing the skin temperature significantly, whereas IR-B and IR-C are absorbed mostly in the epidermal layers and increase skin temperature significantly (Schieke *et al.*, 2003). The few studies conducted on IR collectively have concluded that IR radiation produces heat upon exposure. Considering the general principle that all biochemical processes are affected by temperature, the effects of IR on human skin can no longer be ignored.

Effects of IR on the expression of collagen and MMPs in human skin *in vivo*

Alterations and deficiencies of collagen, the major structural component of the skin, have been suggested to be a cause of the skin wrinkling observed in both photoaged and naturally aged skin (Fisher *et al.*, 1997; Varani *et al.*, 2000). Because collagen fibrils are responsible for the strength and resilience of skin, their disarrangement during photoaging causes the skin to appear aged. Excessive matrix degradation by UV-induced matrix metalloproteinases (MMPs) secreted by various cells, including keratinocytes, fibroblasts, and inflammatory cells, contributes substantially to the connective tissue damage that occurs during photoaging (Fisher *et al.*, 1996; Chung *et al.*, 2001, 2002). Although human skin is frequently exposed to IR radiation, little is known about the

[1]Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea; [2]Laboratory of Cutaneous Aging Research, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea and [3]Institute of Dermatological Science, Seoul National University, Seoul, Korea

Correspondence: Dr Jin Ho Chung, Department of Dermatology, Seoul National University Hospital, 28 Yongon-dong, Chongno-Gu, Seoul 110-744, Korea. E-mail: jhchung@snu.ac.kr

Abbreviations: IR, infrared; MMP, matrix metalloproteinase; ROS, reactive oxygen species; TRPV, transient receptor potential vanilloid

Received 14 November 2008; accepted 8 January 2009

© 2009 The Society for Investigative Dermatology

biological effects of IR on collagen metabolism. We reported the effects of acute and chronic IR exposure on type I procollagen expression (Kim *et al.*, 2006b). To investigate the effects of IR irradiation, we exposed human buttock skin to near-IR radiation. Previously, we had proposed the minimal heating dose as a standard unit to measure IR energy incident on human skin (Lee *et al.*, 2006). When we irradiated volunteers' skin with IR, skin temperature rose to a certain point and then plateaued. We defined this radiation dose where the skin temperature plateaued as the minimal heating dose. Three minimal heating doses were irradiated on human buttock skin once or three times a week for 4 weeks. It was found that although single IR irradiation increased type I procollagen expression, multiple irradiations reduced its expression (Kim *et al.*, 2006b). Single IR irradiation increased the expression of TGF-β1, -β2, and -β3 in human skin *in vivo*, whereas repeated IR irradiation reduced the expression of these TGF-βs. It is well known that TGF-β potently stimulates the proliferation of fibroblasts in the dermis and induces the synthesis and secretion of procollagen (Massague, 1998). Therefore, alterations in TGF-β may have influenced type I procollagen expression in IR-exposed human skin.

It was reported that a single treatment of human dermal fibroblasts with IR-A-induced MMP-1 (Schieke *et al.*, 2002). However, we demonstrated that MMP-1 was not induced by single IR irradiation in human skin *in vivo* (Kim *et al.*, 2006b). In contrast to the effects of a single IR irradiation, multiple IR irradiations significantly increased MMP-1 expression. Therefore, repeated IR exposure might induce premature skin aging (photoaging) in human skin *in vivo*.

To determine whether IR can induce wrinkles *in vivo*, mice were irradiated with IR five times a week for 15 weeks ($30\,J\,day^{-1}$) (Kim *et al.*, 2005). We observed that IR can cause skin wrinkling and augment UV-induced wrinkle formation through induction of MMPs (Kim *et al.*, 2005).

IR exposure turns on an angiogenic switch in human skin *in vivo*

Photoaging is the process whereby skin is prematurely aged by repeated exposure to solar UV radiation, and skin angiogenesis plays a critical role in this process (Yano *et al.*, 2002). Acute UV exposure of human skin is known to induce angiogenesis, that is, to form new blood vessels, in human skin. These new vessels are immature and leaky, resulting in cutaneous inflammation by extravasation of inflammatory cells and by the inflammatory mediators produced by these cells. These events may contribute to further degradation of extracellular matrix proteins, providing an adverse, less permissive environment for the maintenance of normal vessel structure and function, leading to progressive loss of cutaneous vessels in photoaged skin (Chung and Eun, 2007). As is the case with UVB, exposure of human skin to near-IR induces dermal angiogenesis and alters the balance between epidermal angiogenic factor (that is, VEGF) and endogenous angiogenic inhibitor (that is, TSP-2) (Kim *et al.*, 2006a).

Acute exposure of human skin to IR radiation increases mast cell number and tryptase expression in human skin *in vivo*

Mast cells are present in tissues throughout the body but are most prevalent at sites that are exposed to the environment, such as skin, airways, and gastrointestinal tract (Metcalfe *et al.*, 1997). Two types of mature human mast cells have been described, based on differences in their neutral protease composition (Irani *et al.*, 1986). MC_T cells contain tryptase alone, whereas MC_{TC} cells contain tryptase, chymase, and cathepsin G. UV radiation is considered an extrinsic factor that can alter the prevalence of mast cells (Grimbaldeston *et al.*, 2003). Several studies have demonstrated that sun-exposed human skin has more mast cells than sun-protected skin (Bhawan *et al.*, 1992; Bosset *et al.*, 2003). Recently, we also found that the number of mast cells in sun-exposed facial skin is always significantly higher than that in sun-protected buttock skin within the same individual (Kim *et al.*, 2009). On the other hand, the effect of IR on dermal mast cell prevalence remains unclear at present. We demonstrated that human skin mast cells are activated and recruited by IR as well as by UV. After IR irradiation of the buttock skin of young subjects, the number of MC_{TC} was significantly increased at 24 h post-IR, while the number of MC_T was not affected significantly. Tryptase expression was also clearly upregulated by IR treatment in human skin *in vivo* (Kim *et al.*, 2009).

EFFECTS OF HEAT ON AGING PROCESSES IN HUMAN SKIN *IN VIVO*

Effects of heat on the expression of MMP-12 in human skin *in vivo*

We demonstrated that heat shock induced the expression of MMP-1 and MMP-3, but not MMP-2, at the mRNA and protein levels in a dose-dependent manner in cultured normal human skin fibroblasts through activation of ERK and JNK and an autocrine IL-6 loop (Park *et al.*, 2004). This increased expression of MMPs by heat leads to degradation of extracellular matrix proteins such as collagen and elastic fibers. Heat is also known to induce MMP-12, which is capable of destroying the pre-existing elastic fiber network, thereby contributing to the accumulation of elastotic material in photoaged skin (Chen *et al.*, 2005). Therefore, heat, like UV, is a major environmental stimulus that probably plays an important role in the development of solar elastosis and premature skin aging.

Effects of heat on the expressions of tropoelastin and fibrillin-1 in human skin *in vivo*

It has been reported that chronic IR exposure can cause pronounced elastosis in mouse skin, changes that mimic the damage caused by UV (Kligman, 1982). It is known that repeated and prolonged exposure to heat insufficient to produce a burn causes erythema ab igne, which is characterized histologically by the basophilic degeneration of connective tissue and the alteration of elastic fibers, which resembles elastotic changes in photoaged skin (Hurwitz and Tisserand, 1987).

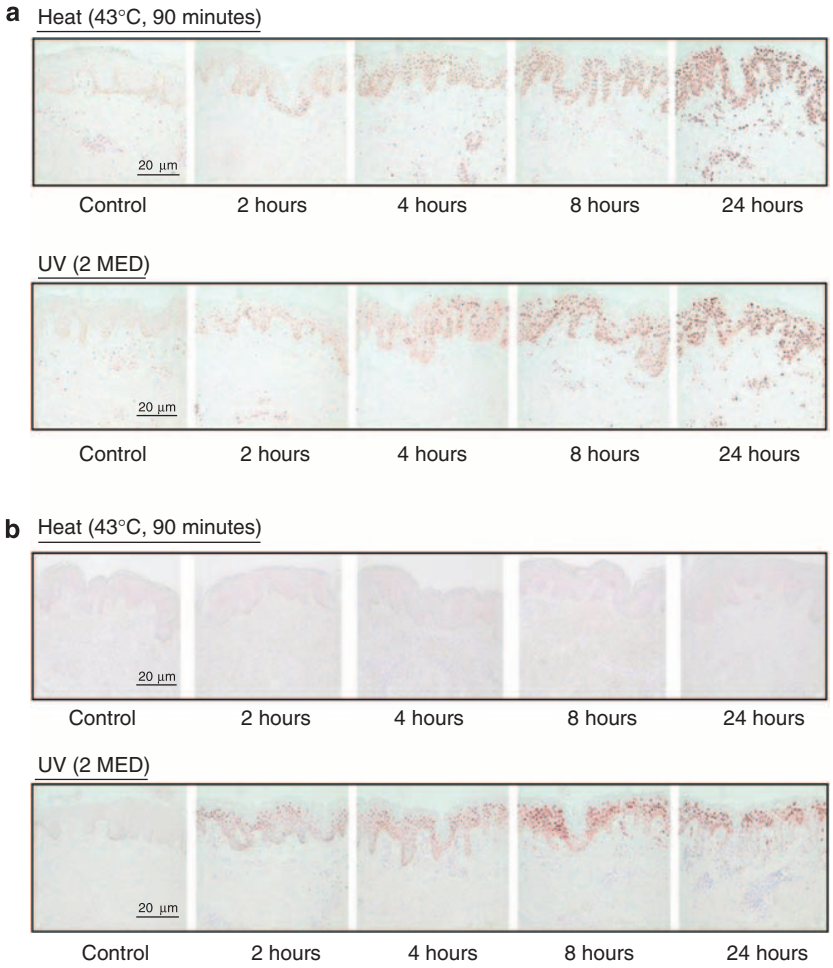


Figure 1. **The effects of heat shock and UV on DNA damage in human skin *in vivo*.** Human buttock skin was treated with heat shock at 43°C for 90 minutes or 2 MED of UV, and then obtained at indicated time points. The skin specimens were stained immunohistochemically using (**a**) anti- 8-hydroxy-2′-deoxyguanosine (Oxis International Inc., Foster City, CA) and (**b**) anti-thymidine dimer antibodies (Kamiya Co., Seattle, WA), respectively ($n = 5$). Bar = 20 μm.

CONCLUSION

Recent evidence indicates that IR and heat may induce premature skin aging, just like UV radiation: (1) IR exposure of human skin stimulates the expression of MMP-1 and decreases type I procollagen expression *in vivo*. Acute IR irradiation also increases new, leaky vessel formation and induces inflammatory cellular infiltration. (2) Heat energy, which increases skin temperature, also increases MMP-1, -3, and -12, and modulates elastin and fibrillin synthesis, resulting in the development of solar elastosis. Acute heat shock in human skin stimulates new vessel formation, recruits inflammatory cells, and causes oxidative DNA damage. Based on these observations, it can be concluded that IR and heat are important physical stimuli that may cause aging in human skin. Therefore, in addition to sunscreen to block the effects of UV, novel strategies to block IR- and heat-induced skin aging need to be developed to prevent skin aging more completely. TRPV-1 may be a good target for preventing heat-induced skin aging (thermal skin aging) in human skin *in vivo*.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

This research was supported by a Grant (R11-2002-097-06001-0) through the Center for Aging and Apoptosis Research at Seoul National University from the Korean Science & Engineering Foundation (KOSEF).

REFERENCES

Bhawan J, Oh CH, Lew R, Nehal KS, Labadie RR, Tsay A *et al.* (1992) Histopathologic differences in the photoaging process in facial versus arm skin. *Am J Dermatopathol* 14:224–30

Bosset S, Bonnet-Duquennoy M, Barre P, Chalon A, Kurfurst R, Bonte F *et al.* (2003) Photoageing shows histological features of chronic skin inflammation without clinical and molecular abnormalities. *Br J Dermatol* 149:826–35

Chen Z, Seo JY, Kim YK, Lee SR, Kim KH, Cho KH *et al.* (2005) Heat modulation of tropoelastin, fibrillin-1, and matrix metalloproteinase-12 in human skin *in vivo*. *J Invest Dermatol* 124:70–8

Cho S, Lee MJ, Kim MS, Lee S, Kim YK, Lee DH *et al.* (2008) Infrared plus visible light and heat from natural sunlight participate in the expression

An official website of the United States government
Here's how you know

FULL TEXT LINKS

Karger Final Version

Skin Pharmacol Physiol. 2010;23(1):15-7. doi: 10.1159/000257259. Epub 2010 Jan 14.

Photoprotection beyond ultraviolet radiation--effective sun protection has to include protection against infrared A radiation-induced skin damage

P Schroeder [1], C Calles, T Benesova, F Macaluso, J Krutmann

Affiliations

Affiliation

1 Institut für umweltmedizinische Forschung (IUF) an der Heinrich-Heine-Universität Düsseldorf gGmbH, Düsseldorf, Deutschland.

PMID: 20090404 DOI: 10.1159/000257259

Abstract

Solar radiation is well known to damage human skin, for example by causing premature skin ageing (i.e. photoageing). We have recently learned that this damage does not result from ultraviolet (UV) radiation alone, but also from longer wavelengths, in particular near-infrared radiation (IRA radiation, 760-1,440 nm). IRA radiation accounts for more than one third of the solar energy that reaches human skin. While infrared radiation of longer wavelengths (IRB and IRC) does not penetrate deeply into the skin, more than 65% of the shorter wavelength (IRA) reaches the dermis. IRA radiation has been demonstrated to alter the collagen equilibrium of the dermal extracellular matrix in at least two ways: (a) by leading to an increased expression of the collagen-degrading enzyme matrix metalloproteinase 1, and (b) by decreasing the de novo synthesis of the collagen itself. IRA radiation exposure therefore induces similar biological effects to UV radiation, but the underlying mechanisms are substantially different, specifically, the cellular response to IRA irradiation involves the mitochondrial electron transport chain. Effective sun protection requires specific strategies to prevent IRA radiation-induced skin damage.

2010 S. Karger AG, Basel.

Related information

MedGen

LinkOut - more resources

Full Text Sources
S. Karger AG, Basel, Switzerland

Other Literature Sources
The Lens - Patent Citations

Sreedhar et al. *Cell Death and Disease* (2020)11:444
https://doi.org/10.1038/s41419-020-2649-z

Cell Death & Disease

REVIEW ARTICLE Open Access

Mitochondria in skin health, aging, and disease

Annapoorna Sreedhar[1], Leopoldo Aguilera-Aguirre[1] and Keshav K. Singh[2,3]

Abstract

The skin is a high turnover organ, and its constant renewal depends on the rapid proliferation of its progenitor cells. The energy requirement for these metabolically active cells is met by mitochondrial respiration, an ATP generating process driven by a series of protein complexes collectively known as the electron transport chain (ETC) that is located on the inner membrane of the mitochondria. However, reactive oxygen species (ROS) like superoxide, singlet oxygen, peroxides are inevitably produced during respiration and disrupt macromolecular and cellular structures if not quenched by the antioxidant system. The oxidative damage caused by mitochondrial ROS production has been established as the molecular basis of multiple pathophysiological conditions, including aging and cancer. Not surprisingly, the mitochondria are the primary organelle affected during chronological and UV-induced skin aging, the phenotypic manifestations of which are the direct consequence of mitochondrial dysfunction. Also, deletions and other aberrations in the mitochondrial DNA (mtDNA) are frequent in photo-aged skin and skin cancer lesions. Recent studies have revealed a more innate role of the mitochondria in maintaining skin homeostasis and pigmentation, which are affected when the essential mitochondrial functions are impaired. Some common and rare skin disorders have a mitochondrial involvement and include dermal manifestations of primary mitochondrial diseases as well as congenital skin diseases caused by damaged mitochondria. With studies increasingly supporting the close association between mitochondria and skin health, its therapeutic targeting in the skin—either via an ATP production boost or free radical scavenging—has gained attention from clinicians and aestheticians alike. Numerous bioactive compounds have been identified that improve mitochondrial functions and have proved effective against aged and diseased skin. In this review, we discuss the essential role of mitochondria in regulating normal and abnormal skin physiology and the possibility of targeting this organelle in various skin disorders.

Facts

- Skin is the largest organ with high turnover rate in the human body.
- Mitochondria play a vital role in the skin.
- Mitochondrial dysfunction induces skin aging.
- Skin disorders manifest mitochondrial dysfunction.
- Targeting mitochondria may help rejuvenate skin.

Open Questions

- How do mitochondria regulate skin aging?
- Is mitochondrial dysfunction a primary or a secondary cause of skin aging?
- Does targeting mitochondria prevent or slow down skin aging?

Introduction

The skin is the outer sheath of the body, which interfaces with the external environment. It is a complex structure made of several tissue layers, each with a distinct cellular composition. It has crucial functions like sensation, heat insulation and prevention of water loss, and acts as a physical barrier to pathogens. The upper layer of the skin is the epidermis, a stratified structure interspersed with hair follicles. The outer epidermal surface is made of

Correspondence: Keshav K. Singh (kksingh@uab.edu)
[1]Yuva Biosciences, 1500 1st Avenue N, Birmingham, AL 35203, USA
[2]Department of Genetics, University of Alabama at Birmingham, Birmingham, AL 35294, USA
Full list of author information is available at the end of the article
Edited by E. Candi

© The Author(s) 2020
Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

SPRINGER NATURE
CDDpress

“In addition to the UV radiation, infrared (IR) rays have also been associated with photo-aging of human skin.

Schieke et al. showed that exposure to IR dysregulated the expression of metalloproteases in primary human fibroblasts.

Similar changes were observed in situ in human skin exposed to IR, while chronic exposure to IR also resulted in the typical clinical signs of photo-aging in animal models.

Schauen et al. detected a significant increase in the intra-mitochondrial levels of ROS in primary human skin fibroblasts exposed to IR, indicating a direct role of the mitochondria in IR-induced photoaging.

The underlying mechanism of IR-induced mitochondrial damage was elucidated by Karu et al. who showed that the IR rays are absorbed by the copper atoms of ETC complex IV, leading to disturbed electron flow and ‘leakage,’ and increased ROS production.”

June 13, 2023

FROM: Chiropractor in Tennessee

TO: Michelle Schaer, DC and Dan Murphy, DC

Hello to both of you. I am a DC in ••••••••••, TN. My father developed a massive blood clot in his basilar artery/brain stem in February that caused him to have repeated strokes over the course of several weeks. The doctors had no answer and he gradually got so bad that he was placed on hospice and death seemed near. I drove up to see him (for what appeared to be our final goodbyes). I left behind my Erchonia PLT red laser and showed my mom your brain protocol. She used to the laser 4-6 times per day on my dad for 2 min in each region (nasal, vertex, cerebellum and temporal). He has done nothing but improve since starting with the laser. He was released from hospice two weeks ago and his md's are shocked at his results . . . so are we. His medical doctors are all left scrambling to figure out what the laser is and how it works. Wanted to thank you for your guidance and help with this. If you'd like a more formal testimony to share I'm happy to write one up.

Unfortunately my PLT is now in Wisconsin with my dad so I'm going to need to invest in a new laser to replace it. I'm a little unsure of if I should get a red/violet (EVRL) or the green/violet (GVL). I do not have another red laser here so I'm concerned that I won't have all three types of lasers to stimulate all 4 complexes in the electron transport chain as explained in your webinar. Is there an advantage to the green vs red in regards to mitochondrial health/function or ATP production? If I get the GVL will I be missing out a lot on not having that red laser to effect complex 4? Just not sure if their is an advantage to one over the other in terms of brain/mitochondrial function? I could really use help from the two of you . . . have tremendous faith in your clinical experience and research. Any thoughts or recommendations for me on this one?

Thank you so much for helping me with my dad! I really am so very thankful for any guidance you can give me on this.

Dermatologists say red light therapy works, but use care

Charles Trepany
USA TODAY 9/11/23

Is the secret to glowing, youthful skin zapping your face with red light?

Quite a few TikTokers think so, with videos tagged #redlighttherapy garnering more than 96 million views on the app. In the videos, users expose their skin to red light to treat a wide range of cosmetic conditions, including acne, signs of aging and hair loss.

It turns out, the TikTokers may be on to something – and red light has been on dermatologists' radars for a while.

"Red light is something dermatologists have been using for quite some time now," says Dr. Anthony Rossi, a New York-based dermatologist. "I'm a big proponent of red light therapy, because I use it in a clinical setting."

What is red light therapy?

Skin care enthusiasts might recoil at the idea of intentionally exposing their skin to a form of radiation. After all, ultraviolent rays from the sun cause a host of problems, including accelerating signs of aging and, at worst, skin cancer.

But red light – a spectrum of visible light around 600 nanometers in wavelength – shows promise as a safe way of healing the skin of many problems, says Dr. Danilo Del Campo, a Chicago-based dermatologist, adding that scientists began researching the effects of red light on the body in the 1960s and found it helpful in healing wounds.

That's because red light, he says, stimulates the production of adenosine triphosphate, or ATP, a compound he describes as "the gasoline of our body."

By boosting ATP, red light therapy can heal wounds and stimulate hair growth, he says. Though the largest and most robust studies have shown red light therapy's effectiveness in these two areas, Dr. Del Campo adds smaller studies have shown potential for red light in regulating the skin's oil production, thereby reducing acne, as well as boosting the skin's collagen production, which can reduce signs of aging.

"It's still an exciting field that hasn't been explored in large trials yet," he says.

What do doctors say about red light therapy?

Still, dermatologists say clinical evidence indicates red light therapy is safe to try, and it's offered at many dermatologists offices. Here's what to know:

- **Consult your dermatologist:** It's important to first meet with a board-certified dermatologist and let them know you're interested in red light therapy. Most dermatologists can administer the treatment in their offices, which Rossi recommends over at-home devices. "Seeing a board-certified dermatologist who does red light therapy ... is probably your best bet, because the tools that they're using are medical grade, they're standardized, they know how to use them, they know how to properly place them," he says.
- **Not all at-home red light therapy devices are created equal:** If you do seek out an at-home red light therapy device, such as a mask, Del Campo advises buying one from a reputable company or one that your dermatologist recommends. He says you should follow all directions that come with the device or that are given to you, especially when it comes to frequency and duration of exposure, to avoid burning your skin.
- **Protect your eyes:** Keep in mind that what's good for your skin may not be good for your eyes. "I do like to tell my patients that if they're going to use a red light panel at home, they should wear proper eye protection," Rossi says. "They shouldn't look directly at the light, because you don't want to cause any eye issues."
- **Don't throw out the rest of your skin care routine:** Red light therapy is a supportive, not primary therapy, so don't use it in place of your skin care regimen, medication or regular sunscreen application, Del Campo says.

Most of all, remember red light therapy is something that can enhance your skin care, but it's not a necessity for healthy skin – and it's certainly no magic cure for every condition.

Elite Athletes' Therapies Go Mainstream

Longevity researchers look at cutting-edge treatments to improve health and wellness among the general population

clock, and what medical experts think about them.

Light therapy

Some liken it to photosynthesis in plants: Photobiomodulation uses specific wavelengths of red or near-infrared light in treatments for humans, aimed at promoting speedier healing and other benefits. Red light occupies the long end of the visible light spectrum with wavelengths between 630 and 700 nanometers. Near-infrared light lies on the invisible spectrum with wavelengths ranging from 800 to 2,500 nanometers.

The idea has been used in efforts to stimulate hair growth since the early 1960s. NASA started experimenting with it in the 1980s to prevent muscle atrophy in astronauts. Now longevity researchers are taking a look.

Studies suggest photobiomodulation could stimulate collagen growth, decrease inflammation and even improve cognitive function. Olympic athletes lie in Thor Photomedicine's NovoThor red-light therapy bed—which looks like a tanning bed and retails for $130,000—for 15-minute sessions, hoping to boost performance and recovery. Also used by sports pros, Vielight's headband-and-nose-clip combination, at $1,800-$2,400, emits pulsed near-infrared light waves into the nostril toward the brain.

Photobiomodulation is believed to work through cell components known as mitochondria—our body's battery packs that give us energy, says Margaret Naeser, a research professor of neurology at Boston University School of Medicine who also works at the Boston VA Medical Center. When red or near-infrared light within a wavelength range of 600 to 1,200 nanometers is applied to tissue, it is absorbed by mitochondria, especially in damaged or compromised cells, where it triggers repair signals, she says. This appears to increase blood flow to the brain and help repair damaged cells.

Naeser was an author of a 2023 study published in the Journal of Alzheimer's Disease Reports that found photobiomodulation could be a management therapy for people suffering chronic traumatic encephalopathy, Alzheimer's and strokes.

Praveen Arany, an associate professor of oral biology at the University at Buffalo and an expert on therapeutic uses of lasers and light, says photobiomodulation clearly has benefits. But he questions speedy adoption in clinical and wellness realms. "How can you use the same light for any-

The Key To Understanding Clinical Laser

Energy v. Power

Background

μ = "micro" = one millionth of the *unit*:

μW = microwatt

m = "milli" = one thousandth of the *unit*.

mW = milliwatt

1 mW = 1000 μW

Erchonia Handheld Lasers use 7.5 mW = 7500 μW

https://www.kmlabs.com/en/wavelength-to-photon-energy-calculator

Wavelength nm	Power μW	Electron Volt=eV = Photon Energy	Photons/Second = Flux
405 nm violet	**7500 μW (7.5 mW)**	**3.06 eV**	**15+ Quadrillion**
520 nm green	**7500 μW (7.5 mW)**	**2.38 eV**	**19+ Quadrillion**
635 nm red	**7500 μW (7.5 mW)**	**1.95 eV**	**23+ Quadrillion**
830 nm IR	1,000,000 μW (1W)	1.49 eV	4172+ Quadrillion

Energy *does* the work.
Energy is dependent on the wavelength.
Shorter wavelengths have more energy.
Shorter wavelengths have greater frequency.

Power controls the *rate* of the work
Power is dependent in watts, milliwatts.

Dose-Response, 7:358–383, 2009
Formerly Nonlinearity in Biology, Toxicology, and Medicine
Copyright © 2009 University of Massachusetts
ISSN: 1559-3258
DOI: 10.2203/dose-response.09-027.Hamblin

International Dose-Response Society
www.Dose-Response.org

BIPHASIC DOSE RESPONSE IN LOW LEVEL LIGHT THERAPY

Ying-Ying Huang □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Aesthetic and Plastic Center of Guangxi Medical University, Nanning, P.R. China

Aaron C.-H. Chen □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Boston University School of Medicine, Graduate Medical Sciences, Boston, MA

James D. Carroll □ THOR Photomedicine Ltd, 18A East Street, Chesham, HP5 1HQ, UK

Michael R. Hamblin □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA

□ The use of low levels of visible or near infrared light for reducing pain, inflammation and edema, promoting healing of wounds, deeper tissues and nerves, and preventing cell death and tissue damage has been known for over forty years since the invention of lasers. Despite many reports of positive findings from experiments conducted in vitro, in animal models and in randomized controlled clinical trials, LLLT remains controversial in mainstream medicine. The biochemical mechanisms underlying the positive effects are incompletely understood, and the complexity of rationally choosing amongst a large number of illumination parameters such as wavelength, fluence, power density, pulse structure and treatment timing has led to the publication of a number of negative studies as well as many positive ones. A biphasic dose response has been frequently observed where low levels of light have a much better effect on stimulating and repairing tissues than higher levels of light. The so-called Arndt-Schulz curve is frequently used to describe this biphasic dose response. This review will cover the molecular and cellular mechanisms in LLLT, and describe some of our recent results in vitro and in vivo that provide scientific explanations for this biphasic dose response.

1. INTRODUCTION

1.1. Brief history

Low level laser therapy (LLLT) is the application of light (usually a low power laser or LED in the range of 1mW – 500mW) to a pathology to promote tissue regeneration, reduce inflammation and relieve pain. The light is typically of narrow spectral width in the red or near infrared

Address correspondence to Professor Michael R. Hamblin, BAR 414, Wellman Center for Photomedicine, Massachusetts General Hospital, 40 Blossom Street, Boston, MA 02114; Phone: 617-726-6182, Fax: 617-726-8566, E-mail: hamblin@helix.mgh.harvard.edu

(NIR) spectrum (600nm – 1000nm), with a power density (irradiance) between 1mw-5W/cm^2. It is typically applied to the injury for a minute or so, a few times a week for several weeks. Unlike other medical laser procedures, LLLT is not an ablative or thermal mechanism, but rather a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change.

The phenomenon was first published by Endre Mester at Semmelweis University, Budapest, Hungary in 1967 a few years after the first working laser was invented (Mester *et al.* 1967). Mester conducted an experiment to test if laser radiation might cause cancer in mice. He shaved the hair off their backs, divided them into two groups and irradiated one group with a low powered ruby laser (694-nm). The treatment group did not get cancer and to his surprise, the hair grew back more quickly than the untreated group. He called this "Laser Biostimulation".

1.2. Evidence for effectiveness of LLLT

Since 1967 over 100 phase III, randomized, double-blind, placebo-controlled, clinical trials (RCTs) have been published and supported by over 1,000 laboratory studies investigating the primary mechanisms and the cascade of secondary effects that contribute to a range of local tissue and systemic effects.

RCTs with positive outcomes have been published on pathologies as diverse as osteoarthritis (Bertolucci and Grey 1995; Ozdemir *et al.* 2001; Stelian *et al.* 1992), tendonopathies (Bjordal *et al.* 2006b; Stergioulas *et al.* 2008; Vasseljen *et al.* 1992), wounds (Caetano *et al.* 2009; Gupta *et al.* 1998; Ozcelik *et al.* 2008; Schubert *et al.* 2007), back pain (Basford *et al.* 1999), neck pain (Chow *et al.* 2006; Gur *et al.* 2004), muscle fatigue (Leal Junior *et al.* 2008a; Leal Junior *et al.* 2008b), peripheral nerve injuries (Rochkind *et al.* 2007) and strokes (Lampl *et al.* 2007; Zivin *et al.* 2009); nevertheless results have not always been positive. This failure in certain circumstances can be attributed to several factors including dosimetry (inadequate or too much energy delivered, inadequate or too much irradiance, inappropriate pulse structure, irradiation of insufficient area of the pathology), inappropriate anatomical treatment location and concurrent patient medication (such as steroidal and non-steroidal anti-inflammatories which can inhibit healing) (Aimbire *et al.* 2006; Goncalves *et al.* 2007).

1.3. The medicine and the dose

As with other forms of medication, LLLT has its active ingredients or "medicine" (irradiation parameters) and a "dose" (the irradiation time). Table 1 lists the key parameters that define the medicine and Table 2 defines the dose. It is beyond the scope of this paper to exhaustively list and discuss every conceivable aspect of laser radiation or other light

Science News 7/29/2023

CHEMISTRY

One photon kicks off photosynthesis

Laboratory experiments confirm a long-held hypothesis

BY EMILY CONOVER

For photosynthesis, one photon is all it takes.

Only a single particle of light is required to spark the first steps of the biological process that converts light into chemical energy, scientists report June 14 in *Nature*.

Researchers have long assumed that the reactions of photosynthesis begin upon the absorption of just one photon, but it had never been demonstrated, says physical chemist Graham Fleming of the University of California, Berkeley. He and colleagues decided "we would just look to see was it really true that one photon was enough to start the whole thing off."

The sunlight that falls on Earth's surface seems brilliant to human eyes. But on small scales, that light translates to a dribble of photons. Every second, only a few tens of photons of the appropriate wavelengths of sunlight fall on a square nanometer, the scale of the tiny chlorophyll and bacteriochlorophyll molecules that are central to photosynthesis in plants and bacteria.

Many experiments on photosynthesis use lasers, much more powerful light sources, to kick off the reactions. Instead, Graham and colleagues used a source of light that produces just two photons at a time. One photon served as a herald, going off to a detector to let researchers know when the photons were released. The other photon went into a solution containing light-absorbing structures from the bacterium *Rhodobacter sphaeroides*. These structures—called light-harvesting 2 complexes, or LH2—are made up of two rings of bacteriochlorophyll and other molecules.

In a normal photosynthesis reaction, it's thought that LH2 absorbs a photon and passes its energy to another LH2 complex, and then another, like a game of hot potato. Eventually, the energy reaches another type of ring, LH1, which then passes the energy to the reaction center where it is finally converted into a form that the bacterium can use.

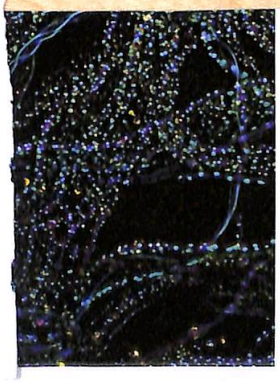
In the experiment, the solution contained no LH1, so LH2 emitted a photon instead of passing its energy on to LH1. The emitted photon had a different wavelength than the absorbed photon, a sign that energy had been transferred between LH2's two rings, a first step of photosynthesis. The team detected that second photon and, by comparing the detection time with that of the initial herald photon, confirmed that LH2 needed to absorb only one photon to kick things off.

Though plants and bacteria use different processes for photosynthesis, the initial steps are similar enough that a single photon would kick off the process in plants as well, Fleming says. However, plants require multiple independently absorbed photons to complete the reactions.

The role of single photons isn't surprising, says Richard Cogdell, a biochemist at the University of Glasgow in Scotland who was not involved in the research. The important thing, he says, is the new technique. With it, "you're able to essentially interrogate what will be happening in nature," Cogdell says.

Some researchers suspect that photosynthesis relies on quantum physics (SN: 2/27/10, p. 10). While it's not clear whether the new technique could resolve the role of quantum effects, it could help researchers disentangle natural effects from artifacts of using intense sources of light in studies of photosynthesis.

"You can really work out what's happening in the early reactions," Cogdell says, "[as if] you could shrink yourself down and watch these photons moving around." ■



NASA, ESA AND J. OLMSTED/STSCI

In *Rhodobacter sphaeroides* bacteria (shown fluorescing in this microscope image), one particle of light can initiate photosynthesis.

Einstein and the Photoelectric Effect, 1905

The Nobel Prize in Physics 1921 was awarded to Albert Einstein "for his services to Theoretical Physics, and especially for his discovery of the law of the photoelectric effect"

The Key Concept

Energy = (Planck's Constant) X (Frequency)
Therefore, as frequency increases, healing energy increases

(Wavelength) X (Frequency) = 186,282 miles/second

Increase Wavelength *Must* Decrease Frequency
and
Therefore Decreases Energy

Decrease Wavelength *Must* Increase Frequency
and
Therefore Increases Energy

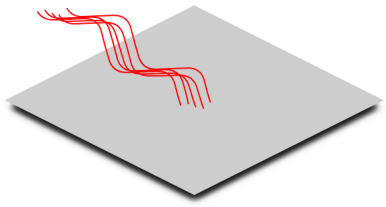
Shorter Wavelengths:	***Longer Wavelengths:***
Have *More* Energy	Have *Less* Energy
Have *Higher* Frequencies (Hertz)	Have *Lower* Frequencies (Hertz)
Do *Not* Penetrate as Deep	Penetrate Deeper
Do *Not* Generate Heat	Increase Molecular Motion and thus Generate Heat

The experimental results show that electrons are dislodged *only* when the light exceeds a certain *frequency*—regardless of the light's *intensity* or duration of exposure.

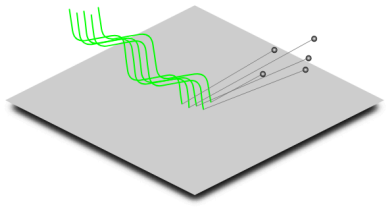
A low-frequency beam at a high intensity does *not* build up the energy required to produce photoelectrons.

Light with frequencies *below* a certain cutoff value, called the *threshold frequency*, would *not* eject photoelectrons from the metal surface *no matter how bright* the source was. These results were completely unexpected.

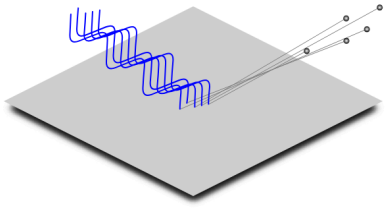
Given that it is possible to move electrons with light and given that the energy in a beam of light is related to its intensity, classical physics would predict that a more intense beam of light would eject electrons with greater energy than a less intense beam *no matter what the frequency*. This was *not* the case, however.



Red light does not eject photoelectrons (even if it is very bright).



Green light does eject photoelectrons (even if it is very dim).



Blue light ejects photoelectrons with more energy than green light (even if it is very dim).

The instant that light with an appropriate frequency of *any* intensity strikes a photoemissive surface, at least one electron will always pop out immediately.

The genius that figured out what was going on here was none other than the world's most famous physicist *Albert Einstein*.

In 1905, Einstein realized that light was behaving as if it was composed of tiny particles (initially called *quanta* and later called *photons*) and that the *energy* of each particle was proportional to the *frequency* of the electromagnetic radiation that it was a part of.

What we perceive as a continuous wave of electromagnetic radiation is actually a stream of discrete particles.

491. To Otto H. Warburg

Berlin W., 5 Haberland St., 23 March 1918

Highly esteemed Colleague,

You are probably surprised at receiving a letter from me, because until now we have only walked past each other, without actually ever getting to know each other. I must even fear rousing some form of indignation in you with this letter; but it *has* to be.

I hear that you are one of Germany's most talented younger biologists with great promise[1] and that presently representatives in your particular field are quite mediocre here. I also hear, though, that you are stationed there at a very vulnerable outpost[2] so your life is constantly hanging by a thread! Now, please step out of your shoes and into those of another discerning creature and ask yourself: Is this not madness? Can this post of yours out there not be filled by an unimaginative average person of the type that come 12 to the dozen? Is it not more important than all that big scuffle out there that valuable people stay alive? You know it yourself very well and must admit that I am right. Yesterday I spoke with Prof. Krauss, who is also entirely of my opinion and is also ready to arrange to have you recalled for another task.[3]

My plea to you, which arises from what has been said above, is therefore that you support our efforts in securing your personal safety. Please, after a few hours of serious reflection, write me a couple of words so that we here know that our efforts will not founder on your attitude.

In the ardent hope that in this matter, for once, reason will exceptionally prevail, I am, with cordial regards, yours truly,

A. Einstein.

Health

We may know how exercise fights cancer

CREATIVEPHOTOTEAM/ALAMY

EXERCISE can slow tumour growth in mice by shifting the body's metabolism so that muscle cells, rather than cancer cells, take the glucose and grow. A similar process may occur in people.

It is well known that exercise is linked to a lower risk of cancer, but the mechanisms behind this are only partly understood. Some of exercise's influence seems to come via impacts on the community of microbes in our guts and through its effects on the immune system.

To examine another possible route, Rachel Perry at Yale School of Medicine and her colleagues have injected breast cancer cells into 18 mice – 12 of which were fed a diet that caused obesity, which worsens the progression of several types of cancer – and let half the animals run as much or as little as they wanted on an exercise wheel.

They found that after four weeks, tumours in obese mice that chose to exercise were 60 per cent smaller than those in obese mice that didn't have access to a working wheel – and also slightly smaller than those of sedentary mice fed a normal diet (*PNAS*, doi.org/hbdbnz). A 30-minute bout of exercise was tied to increased uptake of oxygen and the key energy source glucose in skeletal and cardiac muscles, and decreased glucose uptake in tumours.

Being active has long been linked to a lower risk of cancer

"This work reveals that aerobic fitness fundamentally reshapes metabolic competition between muscle and tumours," says Perry. "Importantly, the exercise intervention was voluntary. We're not talking about training for a marathon-type exercise, just what the mice wanted to do."

The researchers analysed gene activity and identified 417 genes in key metabolic pathways in mice that change as a result of exercise, essentially meaning the muscle tissues metabolise glucose more and the tumour tissues metabolise it less.

In particular, the researchers say down-regulation in cancer cells of mTOR, a protein involved in cell growth, may be restricting tumour growth.

Perry says these metabolic pathways are very similar across mammals, so she would expect the same process to happen in people.

"We need a clinical trial in people, but I really can't see any reason why you wouldn't have a similar effect in humans," says Rob Newton at Edith Cowan University in Perth, Australia. ▮ CS

Select Concepts from Otto Warburg, PhD

[from Dan Murphy]

Fermentation is the process of anaerobically breaking down molecules such as glucose. [can also occur aerobically]
It occurs in the cytoplasm of the cell.

In an era prior to insulin, diabetics would spill excess glucose into the urine. However, if they developed cancer, urinary glucose would stop, indicating cancer patients increased glucose consumption.

Also, in cancer patients, lactate levels would increase 70-fold. This would indicate a dramatic increase in the cytoplasmic anaerobic *fermentation* of glucose into pyruvate (and then into lactate) in cancer patients. This is also known as *anaerobic glycolysis* and is required for tumor growth (Warburg Effect).

The fermentation of glucose is *10-100 times faster* than the complete respiratory oxidation of glucose. This is a *rapid* production of ATP. This is a *higher rate* but a *lower yield* of ATP, giving cancer cells a *short-term* selective advantage.

Cancer cells can develop and live in the absence of oxygen.

"All normal cells have an absolute requirement for oxygen, but cancer cells can live without oxygen, a rule without exception."

"The [mitochondrial] respiration of all cancer cells is damaged." "Damage in [mitochondrial] respiration leads to carcinogenesis." "Chronic hypoxia damages mitochondria."

[Interestingly, for low-level laser users, blockage or inefficiency of mitochondrial electron transport chain enzyme IV {*cytochrome c oxidase*} reduces mitochondrial respiratory

production of ATP, increasing cytoplasmatic fermentation of glucose to pyruvate and then to lactate. Warburg was the discoverer of *cytochrome c oxidase*].

"The primary cause of the replication of cancer cells is replacement of cell respiration with fermentation (lactate formation from glucose)."

In a 1966 lecture to the meeting of Nobel Laureates, Warburg commented:

"Cancer, above all other diseases, has countless secondary causes."

"The prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar."

"All normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation."

"All normal body cells are thus obligate aerobes, whereas all cancer cells are partial anaerobes."

"From the standpoint of the physics and chemistry of life this difference between normal and cancer cells is so great that one can scarcely picture a greater difference. Oxygen gas, the donor of energy in plants and animals is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose."

In 1927, while studying respiration, Warburg knew that both *cyanide* and *carbon dioxide* were respiratory poisons because they "bind to iron and prevent the meeting of iron and oxygen in our cells." 95

"In the dark, carbon monoxide would react with the iron in hemoglobin, the molecule that carries oxygen in blood, but shining a simple beam of light on the hemoglobin could cause the gas to lose its deadly power. It was as if the light, like a security guard, were stepping in carbon dioxide's way before it could attach to the iron." 95-96

"Warburg understood that if light was preventing the carbon monoxide from binding to the iron in blood cells, it might have the same effect in every cell. And if the phenomenon did hold true for every cell, then light could provide Warburg with an entirely new way of identifying his invisible respiratory ferment." 96

"Warburg's insight was based on a principle that had been appreciated for decades. Every molecule in a cell absorbs light differently according to its chemical properties. If Warburg could figure out exactly how much light, at each wavelength, would block the carbon monoxide from attacking iron, it would reveal his respiratory ferment's unique 'absorption spectrum'." 96

"Iron was the chemical match in our cells that made it possible to burn food without fire." 96

"Warburg immediately went to work shining lights of different wavelengths on cells until he had his ferment's fingerprint." 97 [February 22, 1928]

"By linking cellular breathing to a specific part of a specific molecule, Warburg had launched a new era in science." "Warburg had identified the mechanism of life itself." 97

"In the 1930s, Otto Warburg embarked on his own war against cancer, even as his entire world unraveled around him. He had spent much of the previous decade examining cancer cells that overeat and ferment glucose. The next step seemed straightforward: Warburg would cure cancer either by preventing the switch from respiration to fermentation or by interfering with the fermentation process and starving cancer cells. It was a perfectly logical plan but one far ahead of its time. Warburg had already identified the respiratory ferment." 143

Before Warburg could cure cancer "he would need a better understanding of enzymes, the microscopic machines that carry out the work of metabolism." 144

"Enzymes rip hydrogen atoms off of the fat and carbohydrate molecules that we eat. The hydrogen atoms are then stripped of their electrons, which are passed from one

molecule to the next on a journey to meet oxygen at Warburg's respiratory ferment." 145

"It's clear why evolution arrived at a multistep system for cellular breathing, rather than allowing hydrogen and oxygen to react. A direct reaction between hydrogen and oxygen would release too much energy at once, as the Nazis were reminded when their prized *Hindenburg* zeppelin turned into a ball of fire and left 36 people dead." 145

"Specific enzymes function like movers—taking the hydrogen from one molecule and transferring it to another." 145

Warburg had "discovered why vitamins are so critical for our health. Most vitamins function as coenzymes that make respiration and fermentation possible. Because our bodies can't produce these critical engine parts, we need to obtain them from food." 147

"Warburg had already moved on to another enzyme. He called it the "between ferment" because it appeared to function as a link between the hydrogen reaction that takes place at the trunk of the elephant and the oxygen reaction that takes place at the tail." 147

"In 1933, Warburg successfully isolated the "between ferment" and saw that it, too, relied on a coenzyme." 147 "It was nicotinamide." 148

Nicotinamide, "is the critical component of two hydrogen-transferring coenzymes—now known as NAD and NADP—that are central to both respiration and fermentation. Today, the molecules are an increasingly popular area of interest in both cancer and aging studies." 148 "Warburg discovered that nicotinamide played a critical role in respiration." 149

"Nicotinic acid, or niacin, is also known as vitamin B_3." "Nicotinic acid, the precursor molecule that turns into nicotinamide in our bodies." "Warburg seems never to have appreciated that his research on coenzymes was the world-changing discovery he had always hoped to make. In 1938, 400,000 people were thought to be suffering from pellagra in the American South (Some 100,000 Americans died from the disease between 1906 and 1940.) That the little white tablets of nicotinic acid could wipe out the disease was deemed a "miracle" by the *New York Times* in 1939." 149-150

Warburg "believed that cancer arose from damaged respiration. Having found that coenzymes were necessary for a cell to breathe, he wondered if he had also arrived at a major cancer discovery. He wondered, specifically, if feeding cells the key components of coenzymes could keep respiration humming along so that the transition to fermentation would never take place."

Warburg "had long believed that chemicals and radiation caused cancer by damaging a cell and leaving it unable to use oxygen properly. The new research suggested that a disruption in the delivery of oxygen to a cell could cause cancer, even if the cellular

machinery itself wasn't damaged. The origins of a deadly cancer might be as innocuous as a plugged gland." 198 When "the use of oxygen was impaired, the result would be the same: a need for more energy from fermentation." 199

"When cells turned to fermentation to generate enough energy to survive, it would lead to a 'struggle for existence'. The cells least capable of replacing the power of respiration with fermentation might die quickly, but the more flexible cells would cling to life, even as they gasped for air." 199

"The 'struggle' to survive in the suffocating environment might be a prolonged process, which explained why cancers often arose years after someone had been exposed to carcinogens. But over time, as the cells took up glucose and divided, the best fermenters would win the Darwinian competition and multiply until they came to dominate." 199

"The victory of the superior fermenters, as Warburg had argued from the start, would come at a terrible price. Because the energy supplied by fermentation alone cannot maintain the structure of a 'differentiated' cell—a cell that is specialized for a particular tissue—the survivors of the oxygen drought end up as primitive 'undifferentiated' cells that eat and grow without pause." 199

"Warburg believed that all cells had lived by fermentation alone before the earth's atmosphere had filled with oxygen. The return to fermentation amounted to evolution in reverse. Cancer was a cell's journey backward in time to its deepest origins." 199

"Cancer cells swallow more glucose and ferment more than noncancerous cells." 200

In 1913, Warburg had made an important observation. "Cells were able to breathe oxygen thanks to small particles he could see inside the cells under his microscope. Warburg called the particles 'grana' and refused to call them anything but 'grana' for the rest of his life—long after the rest of the scientific world had begun to refer to them as mitochondria." 253-254

"... the remarkable origins of the mitochondria: they are descendants of ancient bacteria that moved inside another unicellular organism more than a billion years ago. It turned out to be a symbiotic relationship, and it would give rise to the eukaryotic cells that form the building blocks of all plants and animals. The mitochondria could burn food with oxygen; the host cell could ferment. This is why our cells, as Warburg put it, have 'two' engines. Though the two organisms evolved together, the mitochondria held on to a small number of their own genes." 256

Cytochrome c is the enzyme that allows us to breathe by passing electrons to oxygen. "And cytochrome c, of all molecules, is critical to activating the death signal [apoptosis]." "The very same protein that gives us life had been revealed to also be an assassin." 255-256

“It became clear that the mitochondria were directing apoptosis.” “If a mitochondrion was too damaged or unable to obtain food or oxygen, ... the entire system would collapse, allowing cytochrome c to escape and alerting the cell that a brownout was underway. A single failing mitochondrion wouldn't trigger cell death, but if enough of the mitochondria began to fail, the brownout would become a blackout and the cell would self-destruct.” 256

“The Cambridge researcher David Keilin made clear in the 1920s, electrons travel along a chain of molecules, now known as the electron transport chain, before reaching oxygen at Warburg's respiratory ferment. (Warburg never forgave Keilin for changing the name of his ‘respiratory ferment’ to ‘cytochrome c oxidase’.” [1925] 294

“Electron transport chains, found throughout the inner membranes of our mitochondria, are essentially tiny electrical wires containing copper and iron. (We need to eat, first and foremost, because we need electrons to supply the electricity for this system.) The wires are one of evolution's most remarkable inventions, but they also create one of life's great vulnerabilities: as electrons are passed along the chain, some will inevitably leak, leading to the formation of molecules that are commonly known as ‘free radicals’ or ‘reactive oxygen species’. Such molecules are unstable and hungry for electrons. They will take them from whatever nearby molecules they can, including from our DNA.” 294

“Problems tend to arise only when the electron processing machinery malfunctions. Sometimes a damaged mitochondrion will lack the appropriate components to handle the electron flow. But other times, such as when a cell has more glucose than it should, there will be more electrons than the system can handle. More of the electrons will leak and more reactive oxygen species will form.” “The excess fuel that a cell takes up and burns ‘actually creates a way to mutagenize itself’.”

Reactive oxygen species compare to “muggers stealing a handbag.” “The molecules that are mugged are now short an electron and become highly reactive. It is as if having your handbag snatched deranges your mind and turns you into a mugger yourself, restless until you have snatched someone else's bag.”

“That reactive oxygen species can cause cancer is well understood. Radiation drives mutations by splitting the water molecules inside an organism. The splitting gives rise to the same reactive oxygen molecules and the same chain reaction of electron snatching. And the reactive molecules don't have to make it all the way to the nucleus of the cell to attack our DNA. The radicals form in the mitochondria, which has its own genes that might now become damaged.”

“The damage to the mitochondria that ensues can have far-reaching effects, including making it harder for a cell to use oxygen—which is very much in keeping with Warburg's vision of how cancer arises.”

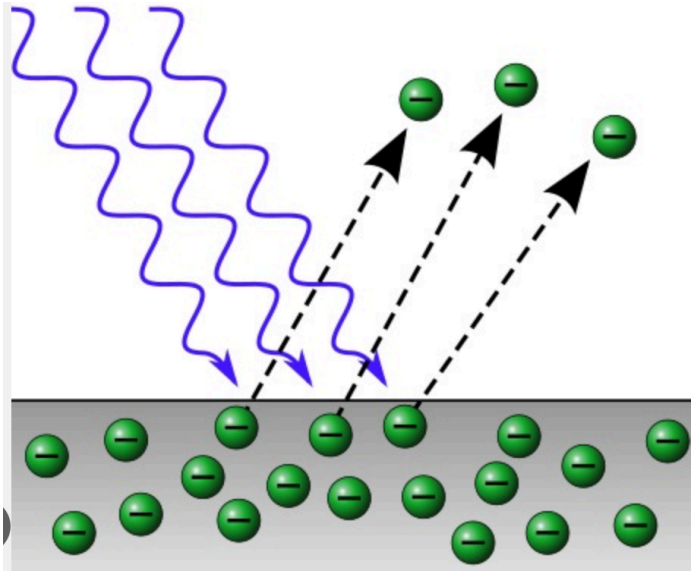
From Quantum Physics for Dummies

The photoelectric effect was one of many experimental results that made up a crisis for classical physics around the turn of the 20th century. It was also one of Einstein's first successes, and it provides proof of the quantization of light. Here's what happened.

Electrons were emitted as soon as someone shone light on the metal. In fact, *no matter how weak the intensity of the incident light*, electrons were immediately emitted.

Experiments with the photoelectric effect showed that the kinetic energy of the emitted electrons depended only on the *frequency* — *not the intensity* — of the incident light.

The results were hard to explain classically, so entered Einstein. This was the beginning of his heyday, around 1905. Encouraged by the success of Max Planck, Einstein postulated that not only were oscillators quantized but so was light — into discrete units called *photons*. Light, he suggested, acted like particles as well as waves.



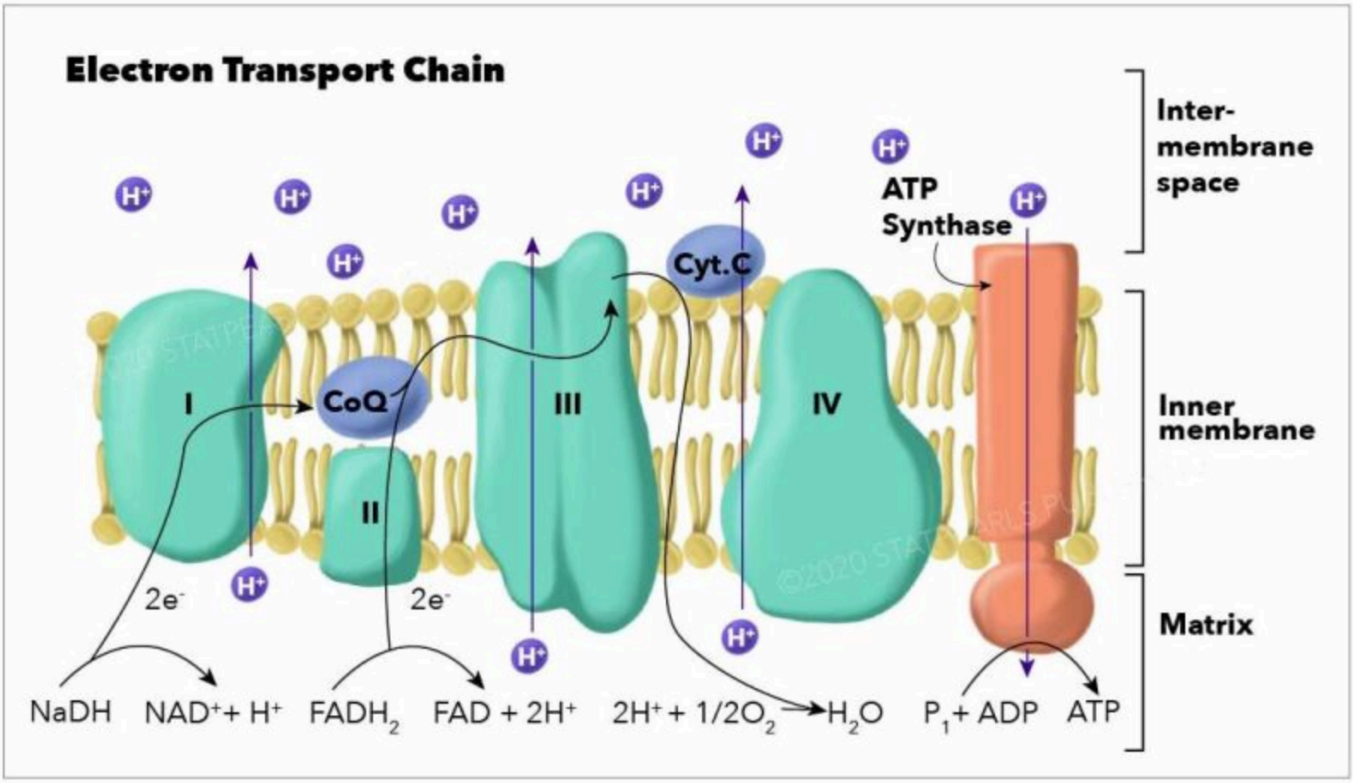
From StatPearls; January 2025
National Library of Medicine

Biochemistry, Electron Transport Chain

Maria Ahmad, Georgia Institute of Technology

Adam Wolberg, Lake Erie College of Osteopathic Medicine

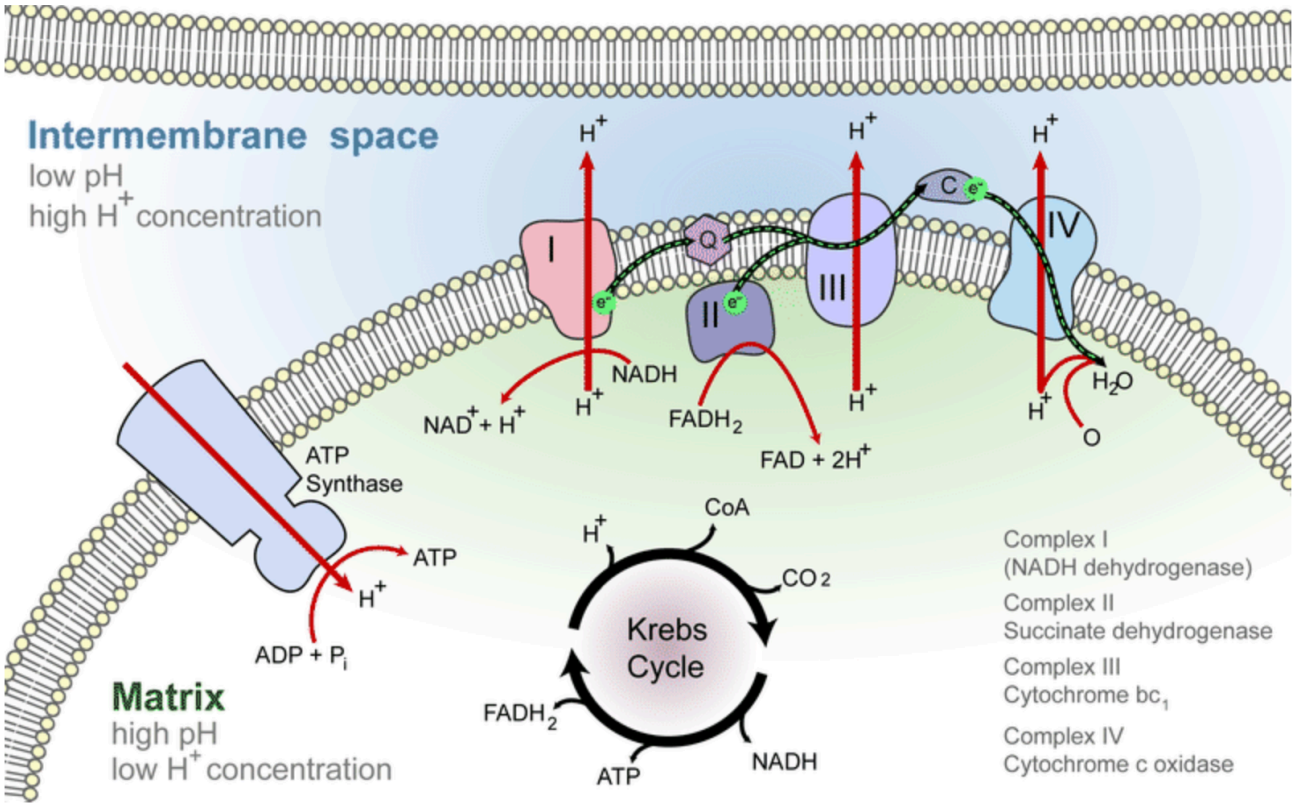
Chadi I. Kahwaji, University of California, Irvine



To remove an electron from a hydrogen atom, you need to supply enough energy to overcome the attraction between the single electron and the proton in the nucleus.

Light can remove the electron, by providing the electron with enough energy to overcome the attraction it has for the nucleus. This happens when the hydrogen atom absorbs a photon with sufficient energy, according to Bohr's model.

https://www.youtube.com/watch?v=zJNx1DDqIVo

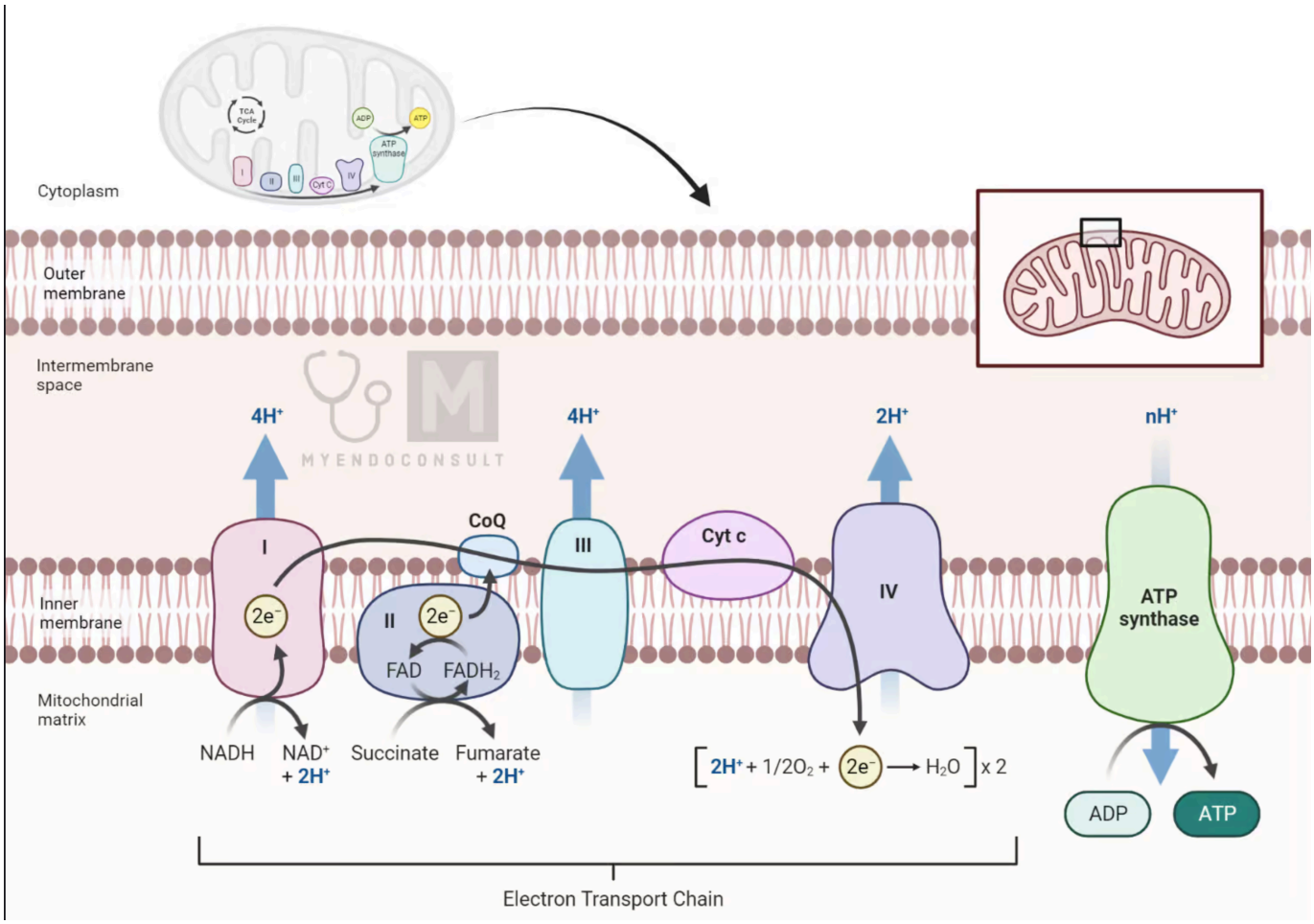


2022

TRANSFORMER

The Deep Chemistry of Life and Death

NICK LANE


TCA Cycle
ADP
ATP
ATP synthase
I
II
III
Cyt C
IV
Cytoplasm
Outer membrane
Intermembrane space
MYENDOCONSULT
4H+
4H+
2H+
nH+
CoQ
I
II
III
Cyt c
IV
ATP synthase
2e-
2e-
Inner membrane
FAD
FADH2
Mitochondrial matrix
NADH
NAD+ + 2H+
Succinate
Fumarate + 2H+
[2H+ + 1/2O2 + 2e- → H2O] x 2
ADP
ATP
Electron Transport Chain

PubMed

Display Settings: Abstract

Support Care Cancer. 2009 Nov;17(11):1409-15. doi: 10.1007/s00520-009-0603-9. Epub 2009 Feb 22.

Cyclooxygenase-2 and vascular endothelial growth factor expression in 5-fluorouracil-induced oral mucositis in hamsters: evaluation of two low-intensity laser protocols.

Lopes NN, Plapler H, Chavantes MC, Lalla RV, Yoshimura EM, Alves MT.

Department of Experimental Surgery, Federal University of São Paulo, São Paulo, Brazil, CEP 04023-062. nnflopes@terra.com.br

Abstract

GOAL OF WORK: The aim of this study was to investigate the mechanisms whereby low-intensity laser therapy may affect the severity of oral mucositis.

MATERIALS AND METHODS: A hamster cheek pouch model of oral mucositis was used with all animals receiving intraperitoneal 5-fluorouracil followed by surface irritation. Animals were randomly allocated into three groups and treated with a 35 mW laser, 100 mW laser, or no laser. Clinical severity of mucositis was assessed at four time-points by a blinded examiner. Buccal pouch tissue was harvested from a subgroup of animals in each group at four time-points. This tissue was used for immunohistochemistry for cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and factor VIII (marker of microvessel density) and the resulting staining was quantified.

MAIN RESULTS: Peak severity of mucositis was reduced in the 35 mW laser group as compared to the 100 mW laser and control groups. This reduced peak clinical severity of mucositis in the 35 mW laser group was accompanied by a significantly lower level of COX-2 staining. The 100 mW laser did not have an effect on the severity of clinical mucositis, but was associated with a decrease in VEGF levels at the later time-points, as compared to the other groups. There was no clear relationship of VEGF levels or microvessel density to clinical mucositis severity.

CONCLUSION: The tissue response to laser therapy appears to vary by dose. Low-intensity laser therapy appears to reduce the severity of mucositis, at least in part, by reducing COX-2 levels and associated inhibition of the inflammatory response.

PMID: 19234862 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

Cytokines

Cytokines are small proteins that function as singling molecules for intercellular communication.

Virtually all nucleated cells can produce cytokines, but they are primarily produced by endothelial cells (vascular system cells) and macrophages (innate immune cells).

Cytokines can be either inflammatory or anti-inflammatory. The primary inflammatory cytokines are Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-a).

Interleukin-1 plays a central role in the regulation of immune and inflammatory responses to infections or trauma.

Interleukin-6 is secreted by T cells and macrophages to stimulate immune response during infection or after trauma, leading to inflammation.

Tumor necrosis factor (cachexin or cachectin) is involved in systemic inflammation as a portion of the acute phase response. It is produced by macrophages. Dysregulation of TNF production is implicated in a variety of human diseases, including Alzheimer's, cancer, major depression, and inflammatory bowel disease.

PubMed hwang and shin and kim and yoo and choi and light therapy

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov .
Get the latest research from NIH: https://www.nih.gov/coronavirus.

Full text links
WILEY Full Text Article

The new PubMed site will become the default in mid-May.
Click here to try it now!
Frequently asked questions

Format: Abstract

See 1 citation found using an alternative search:

Photochem Photobiol. 2015 Mar-Apr;91(2):403-10. doi: 10.1111/php.12415. Epub 2015 Jan 26.

Low level light therapy modulates inflammatory mediators secreted by human annulus fibrosus cells during intervertebral disc degeneration in vitro.

Hwang MH[1], Shin JH, Kim KS, Yoo CM, Jo GE, Kim JH, Choi H.

Author information

1 Department of Medical Sciences, Graduate School of Medicine, Korea University, Seoul, South Korea.

Abstract

Intervertebral disc degeneration (IVD) is one of the important causes of low back pain and is associated with inflammation induced by interaction between macrophages and the human annulus fibrosus (AF) cells. Low-level light therapy (LLLT) has been widely known to regulate inflammatory reaction. However, the effect of LLLT on macrophage-mediated inflammation in the AF cells has not been studied till date. The aim of this study is to mimic the inflammatory microenvironment and to investigate the anti-inflammatory effect of LLLT at a range of wavelengths (405, 532 and 650 nm) on the AF treated with macrophage-like THP-1 cells conditioned medium (MCM) containing proinflammatory cytokines and chemokines (interleukin-1beta, tumor necrosis factor-alpha, interleukin-6 and 8). We observed that AF cells exposed to MCM secrete significantly higher concentrations of IL-6, IL-8, IL-1β and TNF-α. LLLT markedly inhibited secretion of IL-6 at 405 nm in a time-dependent manner. Level of IL-8 was significantly decreased at all wavelengths in a time-dependent manner. We showed that MCM can induce the inflammatory microenvironment in AF cells and LLLT selectively

suppressed IL-6 and 8 levels. The results indicate that LLLT is a potential method of IVD treatment and provide insights into further investigation of its anti-inflammation effect on IVD.

© 2015 The American Society of Photobiology.

PMID: **25557915** DOI: 10.1111/php.12415

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

The New Science of the *Vagus Nerve* and How to Harness Its *Healing Reflexes*

THE GREAT NERVE

2025

KEVIN J. TRACEY, MD

2023

How the Immune System Works

Seventh Edition

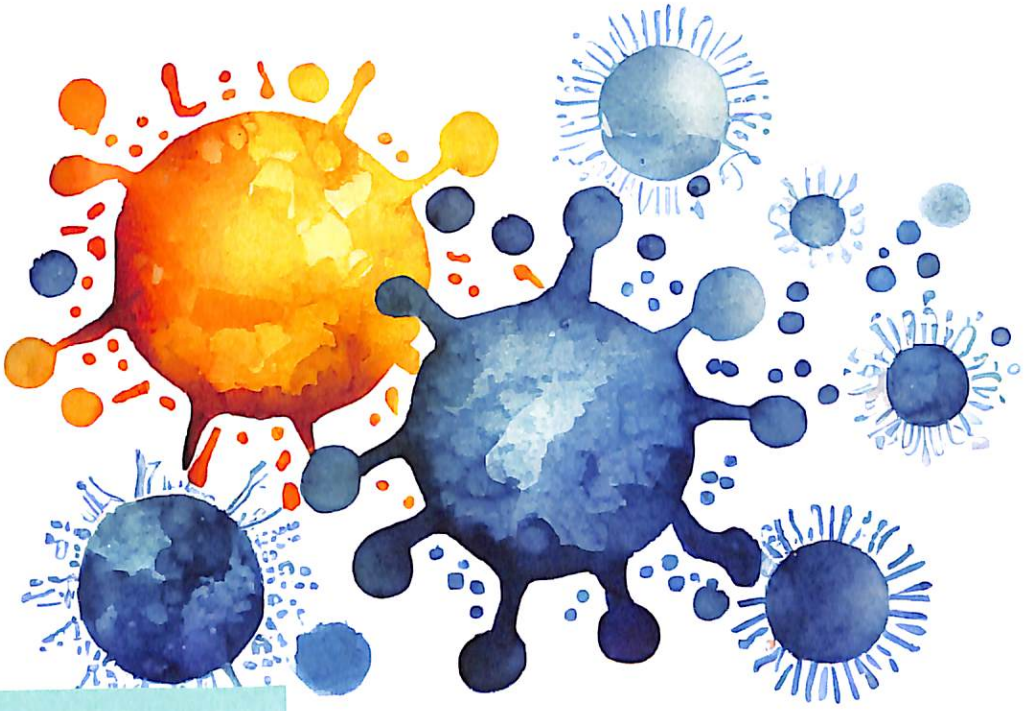
Lauren Sompayrac

with website

WILEY Blackwell

The Logic of Immunity

Deciphering an Enigma



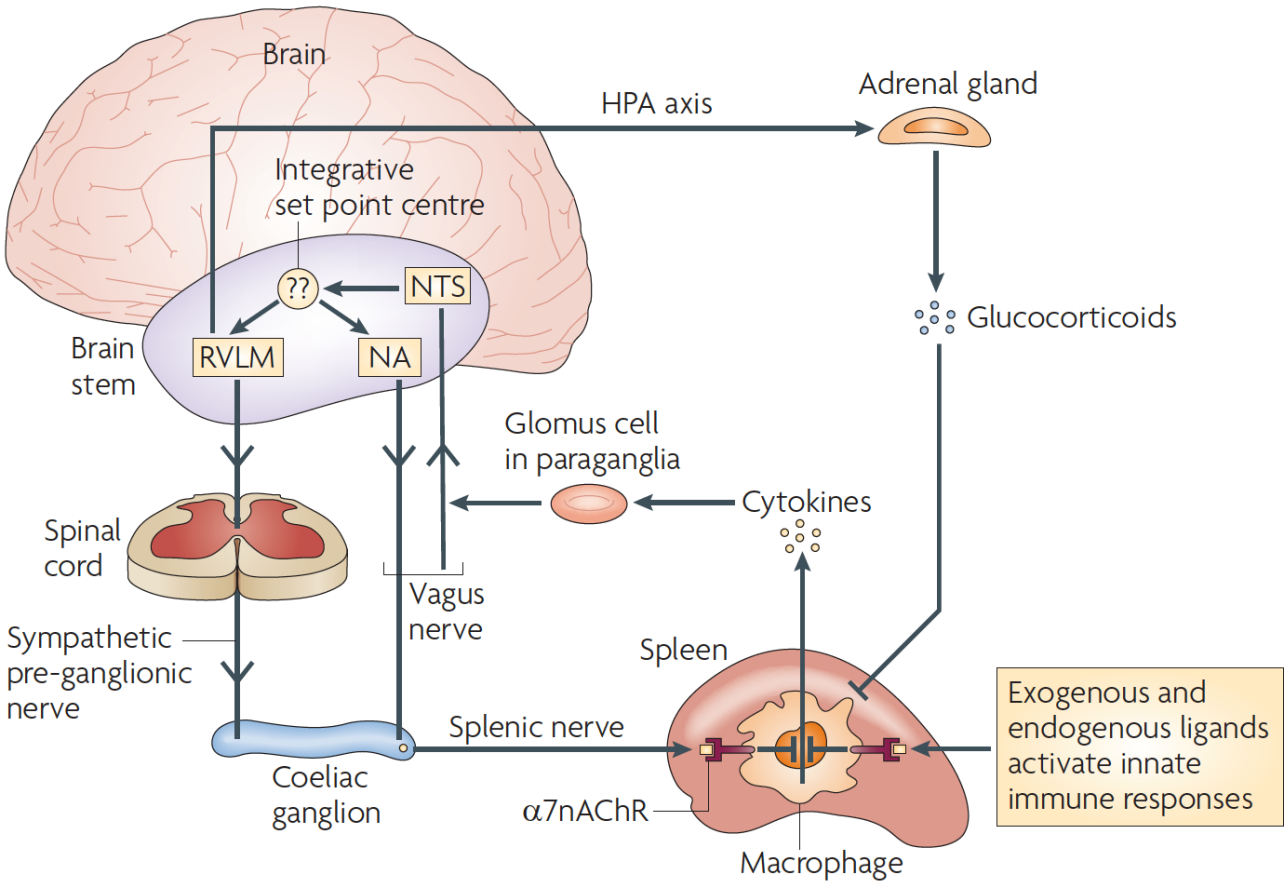
2024

B. J. Cherayil

Reflex Control of Immunity

Nature Immunology
June 2009

Kevin Tracey



Dan Murphy, DC
PO Box 7044
Auburn, CA 95604
Phone: (530) 878-6869
Fax: (530) 878-6559
www.danmurphydc.com
Email: dan@danmurphydc.com

Seminar Coordinator
General Contact and
Professional Assistant:
Michelle Schaer DC
(602) 826-2277
michelle@danmurphydc.com

Life Chiropractic College West
(510) 780-4500
Bookstore Extension: 4502

Dan Murphy's

Article Review Service

Studies are reviewed and summarized and the Key Points pertinent to chiropractic are listed

The Most Relevant Studies Pertaining to Chiropractic Clinical Practice

Adjusting/Neurology/Orthopedics/Whiplash /Posture/Headaches/Pediatrics/Vaccines/ Nutrition/Exercise/Risks/Outcomes/ Benefits/ Maintenance/ and More

52 Articles Every Year
$120.00 Per Year

24 Years of Archives
$200.00

Sign Up At
www.danmurphydc.com

I am very grateful for keeping me in the loop of knowledge. These article reviews are priceless.

KB, San Francisco, March 15, 2023

Stay Informed

BRAINSPAN®

Practice Guidelines: Fatty Acid Testing

What are your metrics?

Learn more and receive your free trial opportunity by scanning the image below.

If you have any difficulty, simply go to www.brainspan.com/murphy

DAN MURPHY DC
KNOWLEDGE FOR LIFE SET 5
DVD or Thumb Drive
$299.00 plus $10.00 s&h

Disc 1

Levers
Children and Phones
Ultraprocessed Foods and Health
Scientific Evidence

Disc 2

Plastic Brains
Glymphatic Brain Wash
Aggression Violence Homicide
Chiropractic Basic Neurology

●●●