Mitochondria

Erchonia Webinar
Four Hours

2026

Dan Murphy, DC

Questions

What Do the Following Activities Have in Common?

Infrared Saunas

Cold Water Plunge

Regular Moderate Exercise

High Intensity Interval Training

Intermittent Fasting

Avoidance of Fructose

Low Level Laser Therapy

Methylene Blue

All of these Activities are Dependent Upon?

Peter Mitchell, British Biochemist
Nobel Prize 1978
Mitochondria Chemiosmotic Theory

AI Overview

First proposed by Mitchell in 1961, the chemiosmotic theory solved a decades-long mystery of how living cells produce energy.

The Energy Currency: Cells require adenosine triphosphate (ATP) to power their chemical processes.

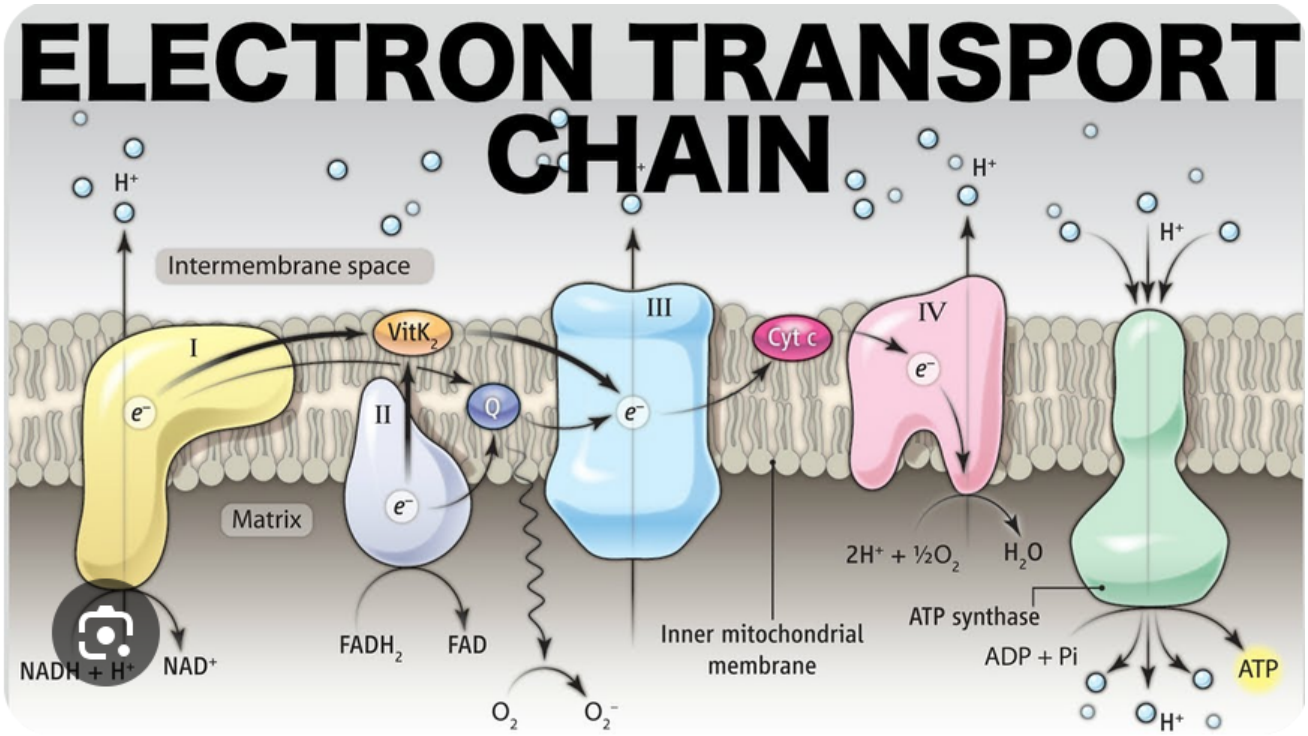
Proton Translocation: Mitchell discovered that as electrons pass through respiratory chains (embedded in inner mitochondrial membranes), the energy released is used to pump hydrogen ions (protons) across the membrane.

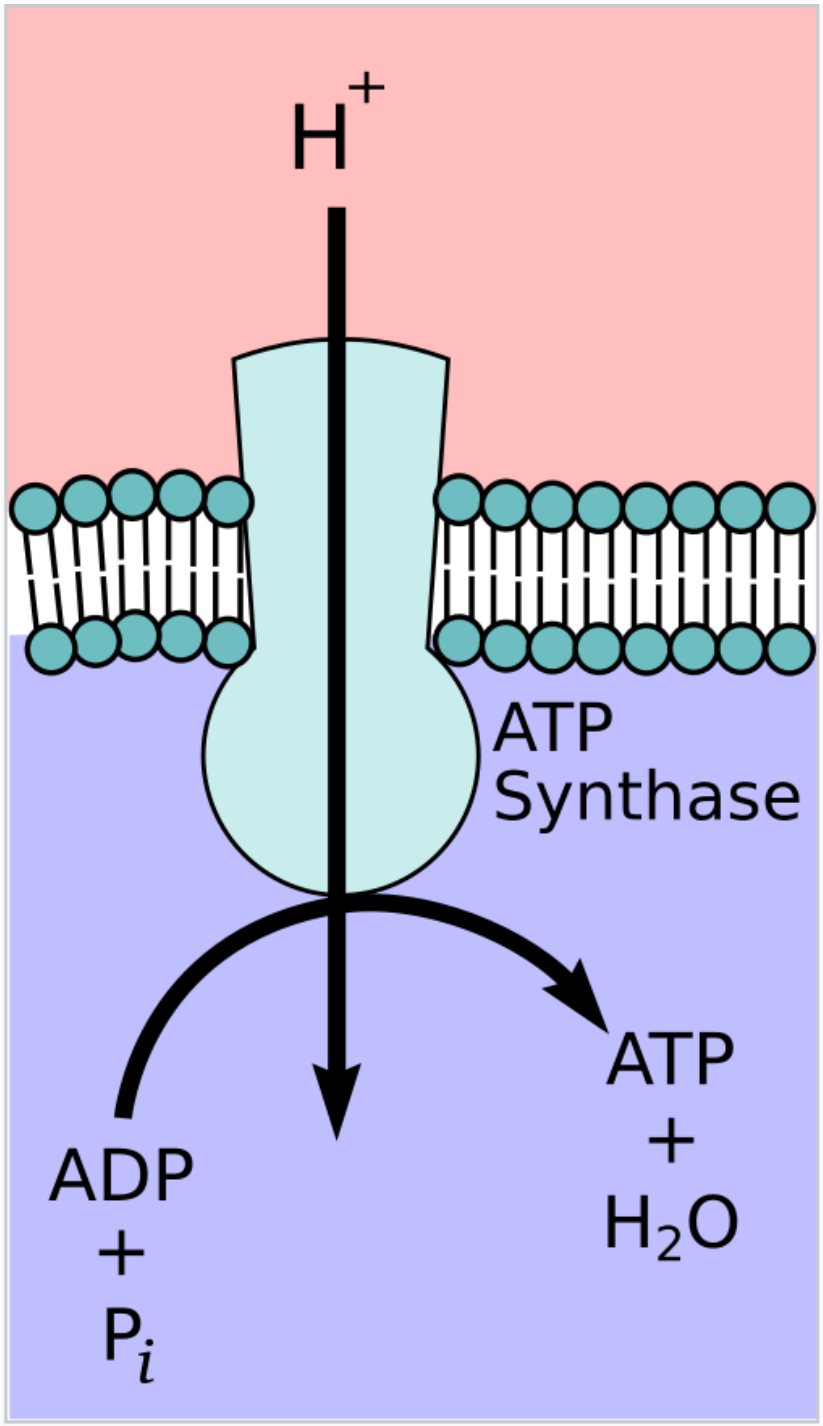
Protonmotive Force: This pumping creates an electrochemical concentration gradient, which Mitchell called the **protonmotive force**.

ATP Synthesis: Protons flow back across the membrane down their electrochemical gradient through a specialized enzyme complex called ATP synthase. This drives the chemical synthesis of ATP from ADP and inorganic phosphate.

Paradigm Shift: By the mid-1970s, experimental proof using reconstituted membrane systems and enzymatic studies confirmed his model.

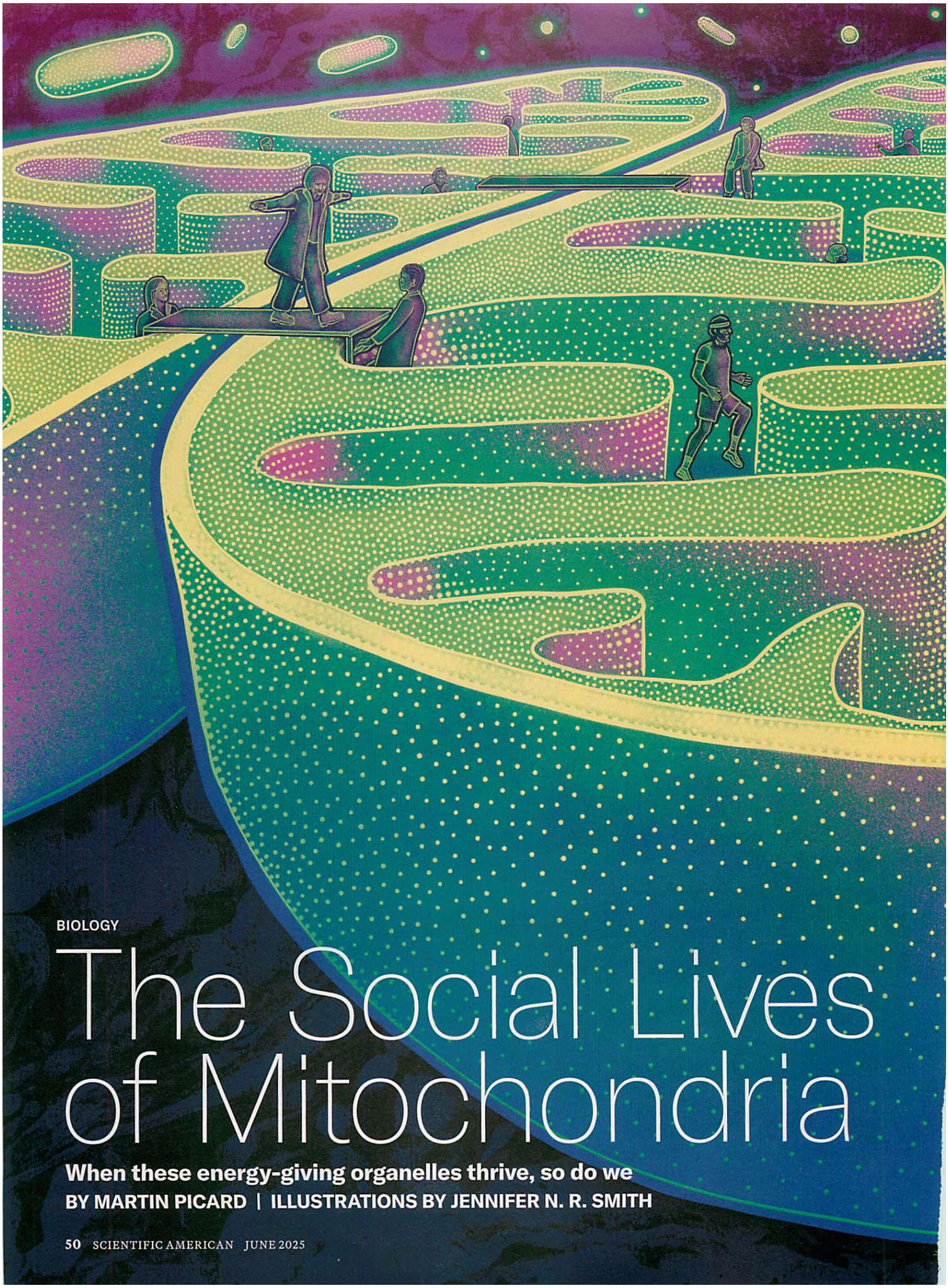
Universal Application: Today, the chemiosmotic theory is a foundational pillar of modern biology, explaining oxidative phosphorylation in mitochondria.


ELECTRON TRANSPORT CHAIN
H+
Intermembrane space
I
e−
VitK2
II
Q
e−
III
e−
Cyt c
IV
e−
H+
H+
Matrix
NADH + H+
NAD+
FADH2
FAD
O2
O2−
Inner mitochondrial membrane
2H+ + ½O2
H2O
ATP synthase
ADP + Pi
ATP
H+



The discovery of ATP synthase vindicated Mitchell's hypothesis. Today, it is well-accepted that chemiosmosis of H+ ions power the synthesis of ATP, and other biochemical processes.

Mitochondria

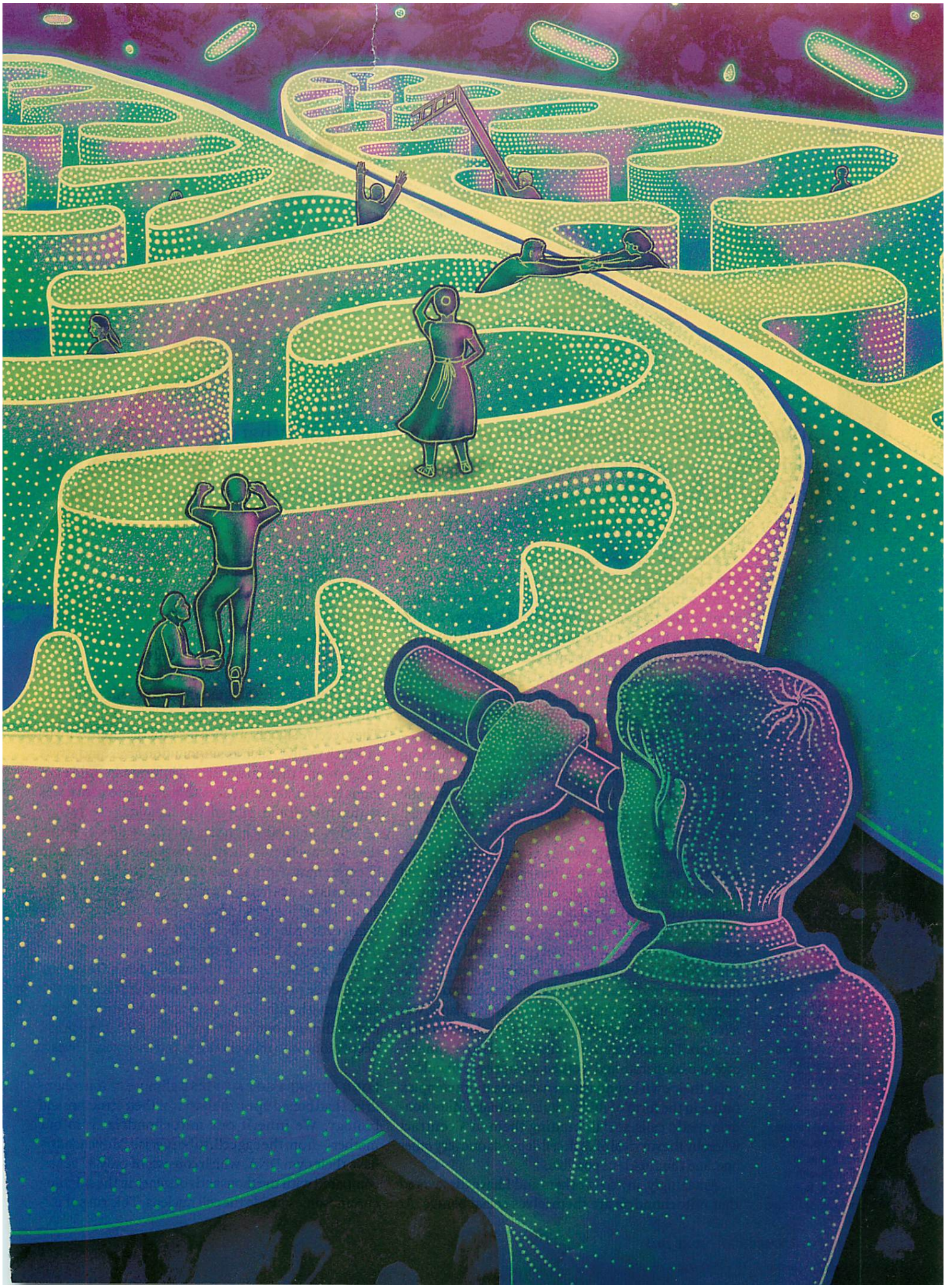


BIOLOGY

The Social Lives of Mitochondria

When these energy-giving organelles thrive, so do we

BY MARTIN PICARD | ILLUSTRATIONS BY JENNIFER N. R. SMITH



ALWAYS WANTED TO UNDERSTAND LIFE. What moves us? What allows us to heal and thrive? And what goes wrong when we get sick or when we eventually stop breathing and die? My search for answers to these stupendously ambitious questions led me, it now seems inexorably, to mitochondria.

In biology classes from high school through university, I learned that mitochondria are little objects that reside within each cell and serve as "powerhouses," combining oxygen and food to yield energy for the body. This idea of mitochondria being little batteries with a built-in charger, about as interesting as the one in my phone, left me unprepared for the vital reality of these organelles when I first saw them under a microscope in 2011. They were luminous because of a glowing dye I had put in them, and they were dynamic—constantly moving, stretching, morphing, touching one another. They were beautiful. That night, a graduate student alone in a dark laboratory in Newcastle upon Tyne in England, I became a mitochondriac: hooked on mitochondria.

A profound insight by biologist Lynn Margulis helped me make some sense of what I was seeing. She postulated in 1967 that mitochondria descend from a bacterium that was engulfed by a larger ancestral cell about 1.5 billion years ago. Instead of consuming this tidbit, the larger cell let it continue living within. Margulis called this event endosymbiosis, which means, roughly, "living or working together from the inside." The host cell had no energy source that used oxygen—which, thanks to plants, was already abundant in the atmosphere; mitochondria filled this gap. The unlikely union allowed cells to communicate and cooperate and let their awareness expand beyond their own boundaries, enabling a more complex future in the form of multicellular animals. Mitochondria made cells social, binding them in a contract whereby the survival of each cell depends on every other one, and thus made us possible.

Amazingly, my co-workers and I have discovered that mitochondria are themselves social beings. At least, they foreshadow sociality. Like the bacterium they descended from, they have a life cycle: old ones die out, and new ones are born out of existing ones. Communities of these organelles live within each cell, usually clustered around the nucleus. Mitochondria communicate, both within their own cells and among other cells, reaching out to support one another in times of need and generally helping the community flourish. They produce the heat that keeps our bodies warm. They receive signals about aspects of the environment in which we live, such as air pollution levels and stress triggers, and then integrate this information and emit signals such as molecules that regulate processes within the cell and, indeed, throughout the body.

When our mitochondria thrive, so do we. When they malfunction—when, for instance, their ability to change energy into forms required for biochemical reactions is impaired—we may experience conditions as diverse as diabetes, cancer, autism and neurodegenerative disorders. And as mitochondria accumulate defects over a lifetime of stress and other insults, they contribute to aging and, ultimately, death. To understand these processes—to see how to sustain physical and mental health—it helps to understand how energy moves through our bodies and minds. That requires a deeper look into mitochondria and their social lives.

LONG BEFORE I GOT MY FIRST glimpse of mitochondria, I had boned up on the basics of their structure and biology. We inherit our mitochondria from our mother—from the egg cell, to be precise. Mitochondria have their own DNA, which consists of only 37 genes, compared with the thousands of genes in the spiraling chromosomes inside the cell nucleus. This ring of mi-

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tochondrial DNA, or mtDNA, is sheltered within two membranes. The outer shell, shaped like the skin of a sausage, encases the mitochondrion and selectively allows molecules to enter or exit. The inner membrane is made of densely packed proteins and has many folds, called cristae, which serve as a site for chemical reactions, much like the plates suspended inside a battery.

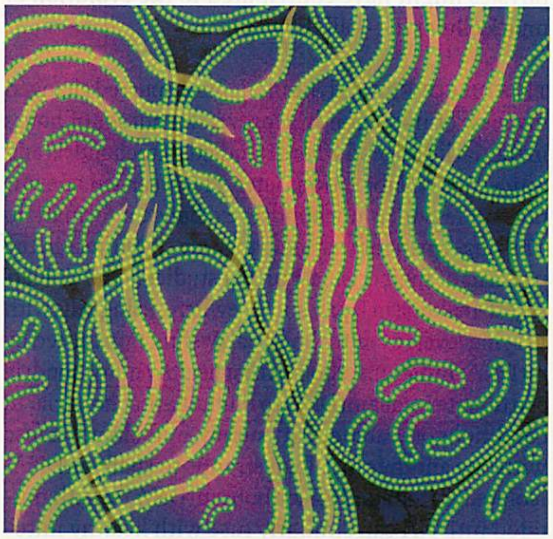
In the 1960s British biochemists Peter Mitchell and Jennifer Moyle discovered how electrons derived from carbon in food combine with oxygen in the cristae, releasing a spark of energy that is captured as a gradient in electrical voltage across the membrane. This voltage provides the driving force for all processes in the body and brain, from warming to manufacturing molecules to thinking. Mitochondria also produce a molecule called adenosine triphosphate, which serves as a portable unit of energy that powers hundreds of biochemical reactions within each cell.

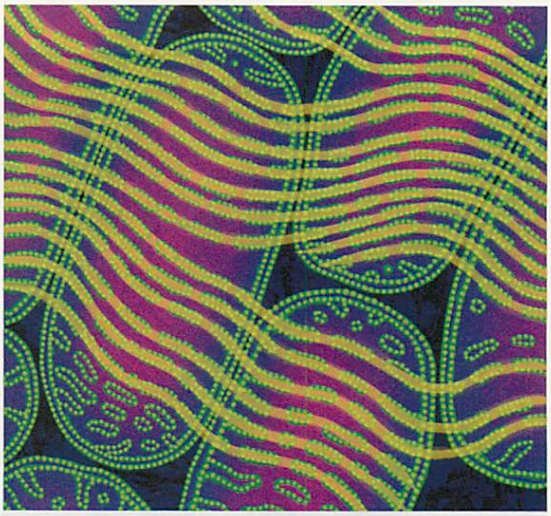
Returning from the U.K., I started a postdoctoral fellowship with geneticist and evolutionary biologist Douglas Wallace at the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia. In 1988 Wallace had discovered the first-ever link between a mutation in mtDNA and a human disease. He had gone on to map some of mitochondrial biology's fundamental connections to various diseases and the aging process, laying the foundation of the field of mitochondrial medicine. In Philadelphia, I began working with a fellow postdoc, Meagan McManus, who wanted to understand how defective mitochondria could cause cardiovascular and neurological diseases. McManus asked me to photograph with an electron microscope the mitochondria in the hearts of mice with a specific mtDNA mutation that led to heart failure.

Our team was also experimenting with three-dimensional imaging using electron tomography, the same technology that allows a radiologist to see a patient's internal organs in 3D. Weeks later, the director of this project, Dewight Williams of the University of Pennsylvania, brought me to a room where the million-dollar tomography microscope stood, as high as the ceiling, to show me reconstructed movies of mitochondria.

The tomography gave us a 3D view of the cristae. Some mitochondria in the hearts of the sick mice had jagged, highly irregular cristae—the unhealthy look I had been seeing in the 2D pictures. But one thing showed up in 3D that we had never seen in the flat images: even when mitochondria looked unhealthy, their cristae looked healthy at places where the mitochondria touched one another. They were interacting, helping one another's internal organization. These mito-mito junctions also had more cristae than any other part of the same mitochondrion. "Meagan has to see this!" I thought, rushing to the lab across campus.

As I restarted the movie for McManus, I narrated what I had seen a few minutes earlier: "Mitochondria are influencing one another!" We watched the looping video a few times. Then McManus said, her voice pitched high with excitement, "And the cristae line up! The cristae line up between mitochondria!" She drew a line with her extended finger across a junction between mitochondria.



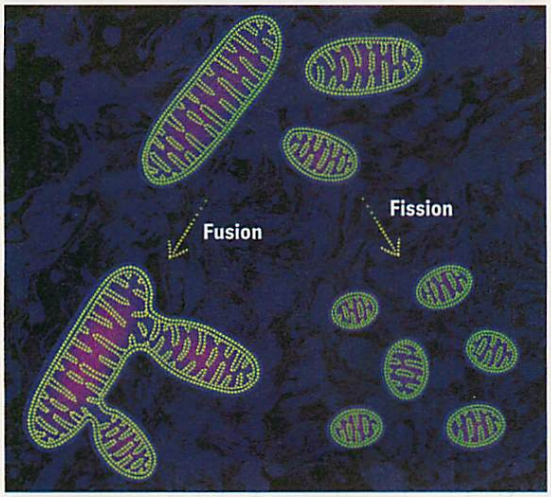


I had pored over thousands of electron microscopy images from the best microscopists. Never had I heard about cristae in one mitochondrion aligning with the cristae of another mitochondrion. While in Newcastle, I had seen a 1983 paper by Russian scientists Lora E. Bakeeva and Vladimir P. Skulachev describing "intermitochondrial contacts," and I had demonstrated that these contacts increased after exercise—perhaps increasing energy efficiency. How had we all missed the alignment? Yet instead of lying there as parallel plates, like textbooks often portrayed them, the cristae formed parallel ribbons undulating across mitochondria. It almost looked like the cristae were helping their neighbors organize to achieve the typical, healthy, regular array.

At the next lab meeting, I suggested that these patterns looked like iron filings aligned around a magnet. Cristae are full of iron-sulfur clusters that may be paramagnetic. If they are, maybe there were electromagnetic fields induced by the flow of electrical charge across the cristae? Could they induce the cristae to line

up? So far this hypothesis appears to be the best one for how cristae align across mitochondria. For me, it also opened the door to thinking about how the forces of physics might have contributed to the evolution of multicellular life—all the way to us.

THIS DISCOVERY and the thoughts it spurred changed my view of mitochondria forever. Hundreds of hours in the dark dungeon where I studied mitochondria and numerous collaborations later, I had learned one important lesson: mitochondria exchange information. The fingerprint of that exchange lay right there in the patterns of their cristae. Further studies at the University of Tsukuba in Japan and elsewhere, using cells with varying levels of mitochondrial dysfunction caused by mtDNA mutations, showed that healthy mitochondria can donate intact mtDNA to mutant mitochondria. In conditions of scarce energy supply, mitochondria fuse with one another into long strands to share mtDNA. Isolated mitochondria without mtDNA or with mutated mtDNA can similarly fuse with healthy mitochondria, restoring their normal function.

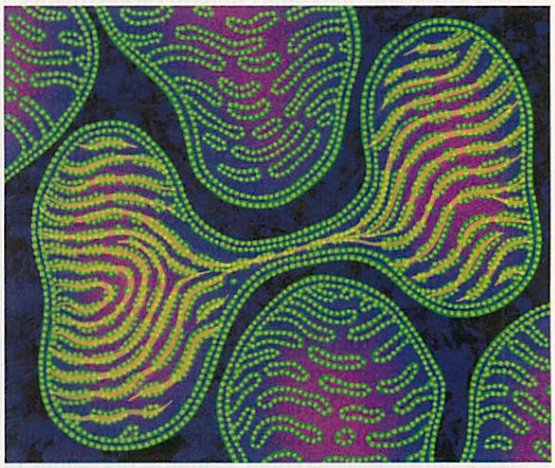


Fusion enhances the resilience not only of mitochondria but also of cells; interfering with these interactions leads to isolated mitochondria that accumulate mtDNA defects and ultimately die, along with the cells they live in. In people, decreased levels of mitofusin 2, a protein located in the outer mitochondrial membrane that helps with fusion, are correlated with neurodegeneration. And mice with mitochondria that have been engineered to impede fusion in the nucleus accumbens, a brain region involved in regulating reward, are more anxious.

Could there be yet other ways in which mitochondria communicate? Could they act like their bacterial ancestors, which build biofilms and use membrane protrusions, electrical fields and secreted molecules to cooperate and conquer the living world with their versatile collective behaviors? Could mitochondrial communication reveal a broader internal universe of energy and information exchange? Could mitochondrial junctions and aligned cristae operate like neuronal synapses, with the resulting mitochondrial collective behaving essentially like an intracellular brain?

IN 2016, SHORTLY AFTER STARTING my own lab at Columbia University, I was back in Newcastle on a visit to Doug Turnbull's Wellcome Center for Mitochondrial Research. I was again sitting at the electron microscope, this time with a stellar British graduate student, Amy Vincent. We were imaging muscle from the calf of a woman with an mtDNA mutation that caused a rare mitochondrial disease. By coincidence, her mutation was similar to the one McManus's mice had had.

What Vincent and I found that afternoon opened another avenue of inquiry. In front of our eyes lay mitochondrial nanotunnels: thin membrane protrusions—the same kind that bacteria use to share their circular DNA! For the first time in humans, Vincent and I saw that mitochondria send thin tubular structures out toward one another, like feelers that some solitary cells use to search for a more hospitable environment or a healthy fellow cell. By imaging dozens of other muscle samples, we found that people whose mitochondria don't work well have more nanotunnels. It was as if unhealthy mitochondria with mtDNA mutations were reaching out for help.



Perhaps the most remarkable aspect of the mitochondrial collective, however, is that mitochondria from different parts of the body talk to one another, using hormones as their language. Mitochondria produce the steroid hormones we use for sustaining and reproducing life. Cortisol, the hormone that increases blood glucose levels to fuel the stress response, is made in the mitochondria of the adrenal glands, which sit on top of the kidneys. Testosterone, estrogen and progesterone are synthesized mainly by mitochondria in the reproductive organs. Interestingly, brain mitochondria have receptors to sense both stress and sex hormones. So we have a population of mitochondria in the adrenal glands that signal directly, via the blood, to mitochondria in the brain.

Further, mitochondria are not all created equal. In the same way that humans develop specialties in different social and economic roles and organs specialize

in executing complementary functions (the liver feeds other organs, the heart pumps, the brain integrates information and issues directives), mitochondria also specialize. Across organs and cell types, mitochondria look different. Their protein contents are different. They move differently. And their ability to sense, integrate and signal specific information varies according to the cell they inhabit. Mitochondrial specialization most likely affords gains in efficiency, allowing an organism to survive at a lower overall energy cost.

My co-workers and I recently built the first map of mitochondria in the human brain. Even within this single organ there are different types of mitochondria in different parts of the cortex and in deeper, subcortical brain regions. The brain uses 20 percent of the body's energy, despite constituting only 2 percent of the body's mass, so an efficient source of power is critical to its functioning. My colleagues, notably, Michel Thiebaut de Schotten of the French National Center for Scientific Research and Eugene V. Mosharov of Columbia, and I found that the more recently evolved brain areas, which have the highest energy expenditure, have mitochondria that are more strongly specialized for energy transformation.

Mitochondria within a cell may also look very different from one another. For example, in neurons, "dendritic" mitochondria are found in the fibers, or dendrites, through which neurons receive signals from other cells. These mitochondria are stable filaments that stretch over 10 to 30 microns—a stupendously long distance for this type of structure—and have several mtDNA copies. "Axonal" mitochondria move along the linear axons, which conduct signals to other neurons, as if they were cellular highways. They are generally short and stubby (up to a micron in length), and many lack mtDNA. "Cytoplasmic" mitochondria cluster around the nucleus and look like something between the dendritic and axonal types. Similar grouping and specialization of mitochondria exists in muscle and fat cells.

These findings, taken together, led behavioral neuroscientist Carmen Sandi of the Swiss Federal Institute of Technology and me to propose in 2021 that mitochondria are social organelles. If you are like me and your eyebrow rises when you hear the term "social" applied to a subcellular organelle, you are having a normal reflex. Nevertheless, Sandi and I argue that mitochondria show all the features of social beings—a shared environment inside the cell or body, communication, formation of groups or types, synchronization of behavior, interdependence, and specialization in the tasks they perform.

In a subsequent paper, which required a painfully long review of more than 400 studies, Orian S. Shirihai of the University of California, Los Angeles, and I established that the mitochondrial collective operates as a mitochondrial information-processing system, or MIPS. Like the animals they exist within and support, which must respond flexibly to the environment, the mitochondria sense signals, integrate this information in the membrane potential of their cristae, and produce signals that regulate the genes of the cell and shape cell behavior.

Your eyes transform light into electrical impulses that coalesce into an image in your visual field, and your ears transform air-pressure waves into electrical pulses that you eventually perceive as sounds. Likewise, mitochondria transform dozens of hormonal, metabolic, chemical, and other information streams into their electrical membrane potential. This "bioenergetic" state then leads to the production of secondary messenger molecules that are intelligible to the nucleus. So in the same way you read messages on your phone, which receives signals, transforms them and projects decipherable information onto its screen, the nucleus of your cells can "read" the environment through the MIPS that surrounds it.

Rather than having supplementary roles like those of battery chargers, mitochondria are more like the motherboard of the cell. Genes sit inert in the nucleus until energy and the right message come along to turn some of them on and some others off. Mitochondria provide these messages, speaking the language of the epigenome—the malleable layer of regulation that sits on top of the genome to regulate its expression.

My colleague Timothy Shutt of the University of Calgary likes to call mitochondria the "CEO of the cell": the chief executive organelle. This metaphor captures how mitochondria not only are involved in integrating information but also give orders. They dictate whether the cell divides, differentiates or dies. Indeed, mitochondria have a veto on cell life or death. If the MIPS deems it necessary, it triggers programmed cell death, or apoptosis—a form of self-sacrifice for the greater good of the organism.

So vital are mitochondria that in difficult times cells may donate entire mitochondria to other cells. "In cellular emergencies, newly arrived mitochondria might kick-start tissue repair, fire up the immune system or rescue distressed cells from death," journalist Gemma Conroy noted in a *Nature* news story last April. Inside tumors, cancer cells and immune cells appear to compete for mitochondria, using them as a kind of bioweapon. An international effort I participated in, led by Jonathan R. Brestoff of the Washington University School of Medicine in St. Louis, recently created an entirely new lexicon to guide the emerging field of mitochondria transfer and transplantation.

ALL WELL AND GOOD, you may think. What does all this mean for my health or how long I'm going to live?

The short answer is that it may have everything to do with human health. Diabetes, neurodegenerative conditions, cancer and even mental health illnesses are all emerging as metabolic disorders involving malfunctioning mitochondria. And these findings are indicating new routes for intervention.

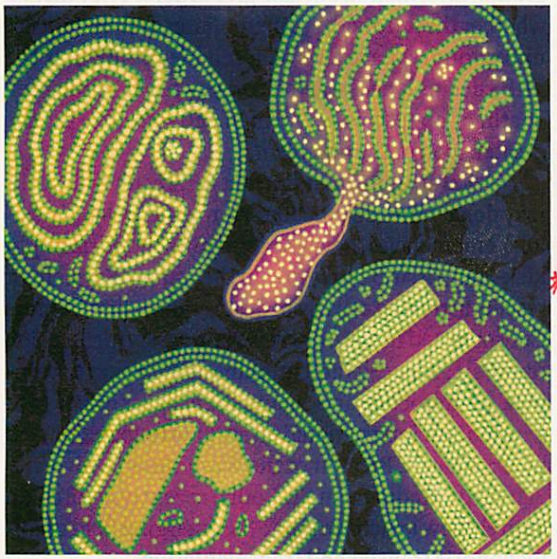
Mitochondria drive health—or disease—in several

ways. One route derives from their role as energy processors. In an electrical circuit, if we crank up the input voltage too much, we can blow it out. Similarly, if our cells are exposed to too much glucose or fat—or, worse, both together, causing what doctors refer to as glucolipotoxicity—the mitochondria undergo fission and fragment into little bits, accumulate mtDNA defects, and produce signals that end up prematurely aging or killing the cell. Experiments in cells and in mice have shown that pharmacologically or genetically preventing mitochondrial fission induced by excessive glucose and fats may protect against insulin resistance.

Cancer, too, may be a disorder of cellular metabolism. Cancer cells can burn glucose without oxygen, which suggests either that something is wrong with their mitochondria or that they prefer to reserve mitochondria for use in cell division—and proliferation.

A second pathway is through mitochondria's influence on gene expression. Mitochondrial signals alter the expression of more than 66 percent of genes in the nuclear chromosomes. By changing which genes are expressed and to what extent, mutations in mtDNA may completely alter the nature, behavior and stress resilience of cells and ultimately of the whole organism.

Mitochondria can look terribly odd when sick. In people with mtDNA defects that cause rare mitochondrial diseases, such as the person in whose mitochondria we first saw nanotunnels, the cristae in particular can look somewhat alien—like crop circles with regular angles, paracrystalline inclusions, and other weird shapes.



Notably, abnormal mitochondrial shape and function are emerging as biomarkers and potential causes of cognitive and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and others. Clinically, a neurobiological subtype of autism spectrum disorder involves defects in mitochondrial biology.

A third pathway is inflammation. When cells are injured or stressed, they may leak mtDNA into the cell's interior, the cytoplasm, or even into the blood. Along with Caroline Trumpff of Columbia, Anna Marsland and Brett Kaufman of the University of Pittsburgh, and other co-workers, I found that mental stress induced by having to speak in public for five minutes increased the amount of free-floating mtDNA in the blood. People in intensive care units who are grievously ill tend to have very high levels of mtDNA in their blood. Because mtDNA rings resemble bacterial DNA, immune cells see them as pathogens and mount an attack that can develop into inflammation. And inflammation, clinicians know well, is linked to the onset and progression of a host of chronic health conditions.

Just how defective mitochondria lead to illness in the body and mind is a question that has yet to be answered. But there are simple ways to ensure our mitochondria stay healthy. One is exercise. When you move vigorously, your cells consume energy rapidly, powering up the membrane potential of your mitochondria. If your exercise leaves you feeling out of breath, it is a sign that your mitochondria are working hard. Because the brain-body entity is expert at anticipating and preparing for the future, if you move in a way that activates your mitochondria, your body thinks, "Next time this happens, I'll be ready!" To get ready, it makes more mitochondria and keeps them working at their best.

Surprisingly, social connections, too, may promote the health of our brain mitochondria. In a major study led by David A. Bennett of Rush Medical College in Chicago, researchers asked hundreds of individuals aged 65 and older in the Chicago area to fill out surveys, take cognitive tests and give blood every year until they died. After death their brains were collected to enable analysis of their mitochondria. My colleague Trumpff used those data to ask whether positive mental states such as feeling purpose in life, optimism and a sense of connectedness—or, in contrast, negative mental states such as perceived stress, depression and social isolation—could be related to the mitochondria's ability to transform energy.

What Trumpff learned was remarkable: the amount of energy-transforming proteins in mitochondria in the prefrontal cortex was significantly correlated with how many positive and negative experiences people reported in the year before they died. This finding aligned with previous studies relating early-life adversity or daily mood markers such as feelings of love, closeness or trust to mitochondria in blood immune cells. Our states of mind might affect the biology of our mitochondria, modulating how well they transform energy.

Another intervention that can be remarkably effective is diet. Medical ketogenic therapy or "nutritional ketosis," which involves cutting out all refined sugars, limiting intake of carbohydrates, and making up the calorie difference with more proteins and fats, has been shown to sustainably reverse insulin resistance and type 2 diabetes. The ketogenic diet has been used for decades to ward off seizures and thereby "stabilize" the brain in children and adults with intractable and otherwise incurable epilepsy. A ketogenic diet can even ameliorate the mental state and cognitive function of people with Alzheimer's. It enhances brain-network

stability, a marker of brain aging—and this function may explain why some people on the diet sleep better.

The ketogenic diet can have astonishing effects in other diseases as well, as evinced by the story of Lauren Kennedy West, a Canadian woman diagnosed with schizophrenia and bipolar disease at the age of 25. Her life progressively felt too difficult to navigate, "like there was no space for me in the world," she explained in a moving account of her journey posted on YouTube last year. In December 2023 West began nutritional ketogenic therapy. A couple of weeks later, she noticed she had more energy. Many of her symptoms lessened. After about nine months she was symptom-free, had tapered her medication in collaboration with her care team, and continued to feel better. Late in 2024 she took her last dose of antipsychotic medication.

West's experience parallels initial positive results from a pilot trial of 21 people with bipolar disease and schizophrenia. Numerous other clinical trials of the ketogenic diet for people with severe mental illnesses such as schizophrenia, depression, anxiety and obsessive compulsive disorder are currently in progress around the world. (Many of these trials are by funded by the Baszucki Group, a philanthropic foundation formed after Matt Baszucki, the son of the group's founders, successfully treated his bipolar disease with the ketogenic diet. In 2024 I received the Baszucki Prize in Science, which helps to fund my lab at Columbia.)

A new study of 28,995 people in the U.S., 4,484 of whom had significant depression symptoms, also supports the protective effects of low-sugar diets on mental health. People whose diet was "more ketogenic"—low in carbohydrates and sugars relative to lipids and proteins—were less than half as likely to develop depression compared with people whose diet was fairly rich in sugars.

How does it work? From a mitocentric perspective, the ketogenic diet does three things. First, it leads to the supply of an efficient fuel source by the liver, which feeds other organs in the body. If you fast or eat a ketogenic diet, your liver takes the fats from your love handles or your food and breaks them down into smaller bits called ketone bodies. This process happens inside the liver's mitochondria. Second, after entering the blood, ketone bodies reach the organs, some of which, including the brain, prefer ketone bodies over other fuels such as glucose, proteins and fats. So in the presence of various fuel sources, the brain will preferentially burn ketones.

The third thing may have to do with efficiency—and might explain why ketone bodies are the preferred fuel for the brain. Glucose has to traverse a number of hurdles before getting to neuron mitochondria—it detours through astrocytes, crosses several membranes and goes through several enzymatic reactions. In contrast, ketone bodies are taken up directly by the mitochondria in neurons, where they are burned. It's a far less convoluted path.

So ketosis, or the burning of ketone bodies, may exert its effects on the brain by enabling energy to directly flow between mitochondria. Ketones in your blood open a stream of communication between producer and consumer mitochondria, fostering their sociality throughout your body.

Rather than being like battery chargers, mitochondria are more like the motherboard of the cell.

ONCE WE REGARD MITOCHONDRIA as dynamic energy and information processors, an entirely new perspective of life emerges. Think of yourself as a waterfall. The waterfall exists only insofar as the water molecules keep flowing down. You learn as much about the waterfall when you scoop up a few inert H_2O molecules as you learn about how healthy a person is by sequencing their genome: close to nothing.

The waterfall cannot be understood from its parts, only from its movement. And once the flow stops, there is no more waterfall. The waterfall is not a thing that appears and disappears. It is a *process*—a process that flows and stops flowing. Like a waterfall, you are not a thing. You are a process—an energetic process, to be precise.

Your fundamentally energetic nature has two main implications. The first is that as a dynamic process, you are bound to change. Your body continually sheds, kills and makes cells. Your mind also changes. Some parts of your mind, such as your personality, are relatively stable. But then again, that can change, too—when you are "hangry," for instance, and become less than your best self. That's an energy deficit changing your mind.

Some drugs can dramatically change your mind. Psychedelics, for example, act on the serotonin system to desynchronize the human brain. They also dissolve the sense of self, or "ego." Change brain-energy patterns, change the mind. The mind, then, may essentially be an energy pattern. Further, energy flowing through your brain somehow *feels* like something. As Nirosha Murugan of Wilfrid Laurier University in Ontario and I recently postulated in a paper, humans may be wired to experience excessive resistance to energy flow as aversive. In contrast, smoothly flowing energy, as occurs after an enjoyable exercise session or when you are working on a stimulating project, feels good. When energy ceases flowing to your brain—if your heart stops, for example—your conscious awareness quickly fades, and you no longer are.

Does all this say anything useful about my original questions? I suspect we now have answers. The key to life and health may lie in how easily energy flows through your mitochondria with each breath you take. So next time you skip that appealing sugary treat, go outside for a stroll, hit the gym or decide to spend time with someone you care about, know that you are supporting your mitochondria. Keeping energy flowing through your mitochondrial collective may be the key to good health and a meaningful life. ●

FROM OUR ARCHIVES

A New Understanding of the Cell. Philip Ball; February 2025. ScientificAmerican.com/archive

BIOLOGY

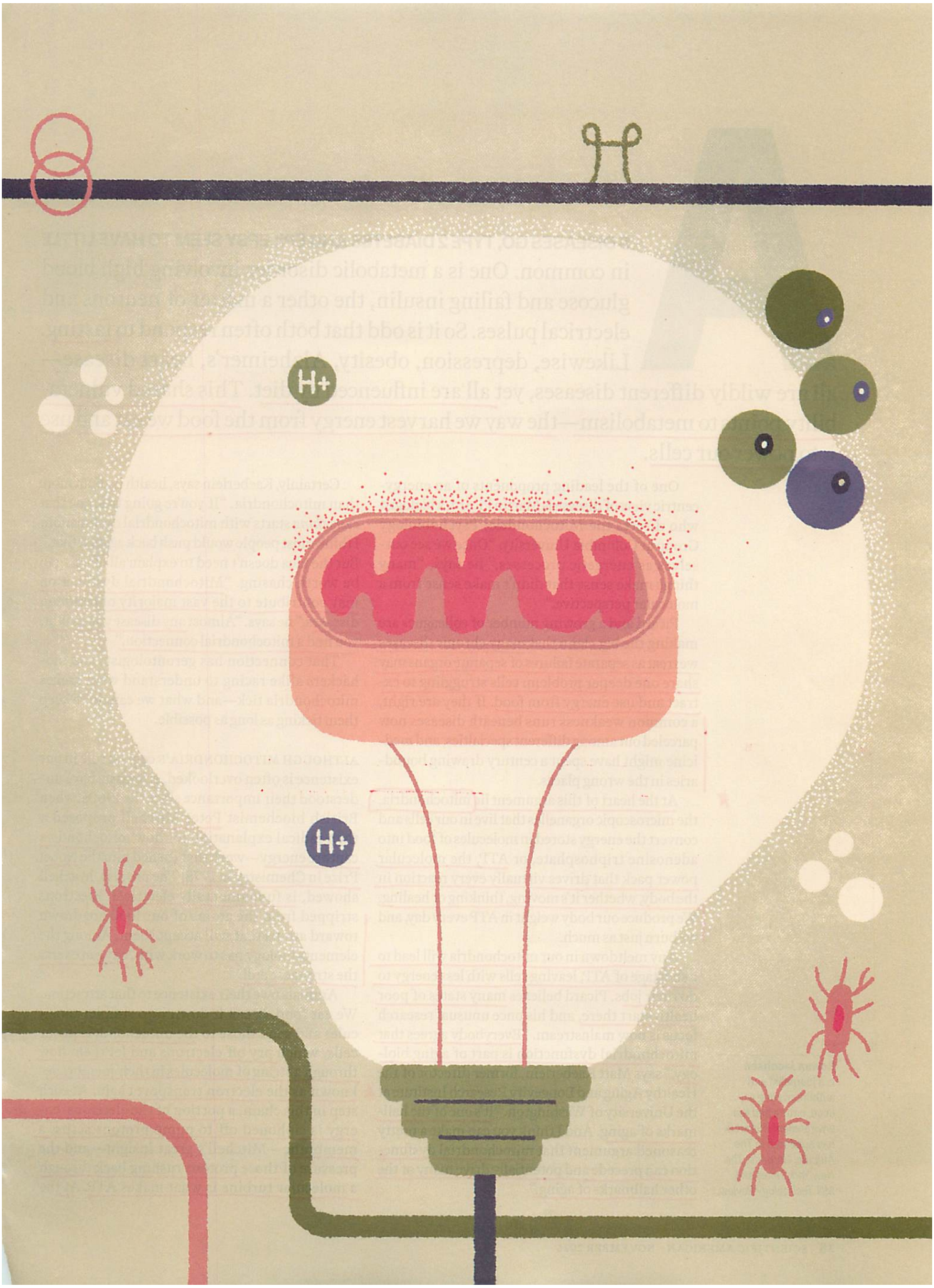
Power Play

Could a new theory of cellular energy help explain why we age and get sick?

BY ROWAN JACOBSEN

ILLUSTRATIONS BY NOEMI FABRA




H+
H+

AS DISEASES GO, TYPE 2 DIABETES AND EPILEPSY SEEM TO HAVE LITTLE in common. One is a metabolic disorder involving high blood glucose and failing insulin, the other a matter of neurons and electrical pulses. So it is odd that both often respond to fasting. Likewise, depression, obesity, Alzheimer's, heart disease—all are wildly different diseases, yet all are influenced by diet. This shared vulnerability points to metabolism—the way we harvest energy from the food we eat and use it to power our cells.

One of the leading proponents of an energy-centric view of disease is Martin Picard, a biologist who directs the Mitochondrial Psychobiology Group at Columbia University. "Once we see ourselves as energetic processes," he says, "many things make sense that didn't make sense from a molecular perspective."

Picard and a growing number of colleagues are making the big claim that many chronic diseases we treat as separate failures of separate organs may share one deeper problem: cells struggling to extract and use energy from food. If they are right, a common weakness runs beneath diseases now parceled out among different specialties, and medicine might have spent a century drawing boundaries in the wrong places.

At the heart of this argument lie mitochondria, the microscopic organelles that live in our cells and convert the energy stored in molecules of food into adenosine triphosphate, or ATP, the molecular power pack that drives virtually every reaction in the body, whether it's moving, thinking or healing. We produce our body weight in ATP every day, and we burn just as much.

Any meltdown in our mitochondria will lead to a shortage of ATP, leaving cells with less energy to do their jobs. Picard believes many states of poor health start there, and his once unusual research focus is now mainstream. "Everybody agrees that mitochondrial dysfunction is part of aging biology," says Matt Kaeberlein, former director of the Healthy Aging and Longevity Research Institute at the University of Washington. "It's one of the hallmarks of aging. And I think you can make a pretty reasoned argument that mitochondrial dysfunction can precede and potentially drive many of the other hallmarks of aging."

Certainly, Kaeberlein says, health is about more than mitochondria. "If you're going to argue that *everything* starts with mitochondrial dysfunction, I think most people would push back against that." But the idea doesn't need to explain all of aging to be worth chasing. "Mitochondrial dysfunction may contribute to the vast majority of common diseases," he says. "Almost any disease you look at, you find a mitochondrial connection."

That connection has gerontologists and biohackers alike racing to understand what makes mitochondria tick—and what we can do to keep them ticking as long as possible.

ALTHOUGH MITOCHONDRIA'S central role in our existence is often overlooked, scientists have understood their importance since the 1960s, when British biochemist Peter Mitchell proposed a then radical explanation for how mitochondria capture energy—work that earned him the Nobel Prize in Chemistry in 1978. The process, Mitchell showed, is fundamentally electrical. Electrons stripped from the atoms of our food are drawn toward atoms that will accept them. Among the elements biology has to work with, oxygen exerts the strongest pull.

Animals owe their existence to that attraction. We eat food, break it down into simpler molecules and send those to the mitochondria in our cells, which pry off electrons and let them flow through a string of molecules in their membranes known as the electron transport chain. At each step in this chain, a portion of the electrons' energy is siphoned off to pump protons across a membrane—Mitchell's great insight—and the pressure of those protons rushing back through a molecular turbine is what makes ATP. At the

Rowan Jacobsen is a journalist and author covering science, nature and the environment. His work has appeared in *The Atlantic*, *Harper's*, *The New York Times* and *MIT Technology Review*.

end of the chain, oxygen accepts the electrons and, together with protons, becomes water.

As many observers have noted, this flow of electrons through the body resembles the flow of electricity through the power grid. Power plants drive electricity through wires and into our homes, where our devices tap that energy to light our rooms and power our lives. The current has to meet the right amount of resistance in the right places. Too little, and the energy races past without doing any work, eventually damaging other components.

Something similar happens in our mitochondria. Under ideal conditions, electrons are slowed in their passage through the electron transport chain just enough that their energy can be transferred. But if the mitochondrial circuits are impaired or if there are simply more electrons from food pouring into the system than the mitochondria can handle, the flow can get bogged down. Electrons can then leak out of the chain, bonding with oxygen in the wrong parts of the mitochondria to form highly reactive free radicals that attack and deform neighboring molecules. These reactive oxygen species, or ROS, can do real damage to mitochondria, cells and organs.

No matter how smoothly electrons flow through mitochondria, a certain amount of ROS is unavoidable in everyday life. The classic free-radical theory of aging, first proposed in the 1950s, held that aging itself resulted from the relentless buildup of ROS in our cells, decade after decade, and the wear and tear this caused. Now we know the body is quite capable of repairing manageable amounts of ROS, which at lower levels can even act as signals, telling a cell to get to work. Only when the oxidative stress gets out of hand do mitochondria get dinged up, but when they do, they move electrons less efficiently, which leads to even more ROS and more damage. The brownouts spread. Eventually cells lose capacity, and the body follows.

Picard has written in this magazine about mitochondria's role in health. In November 2025 he and Nirosha Murugan, a biophysicist at Wilfrid Laurier University in Ontario, codified this concept in the journal *Cell Metabolism* as the energy resistance principle. If a major cause of chronic disease is simply too many food-derived electrons frying the mitochondrial wires, then a major goal of medicine should be to reduce that overload. "The secret to longevity," Picard says, "is to find ways to live at optimal energy resistance."

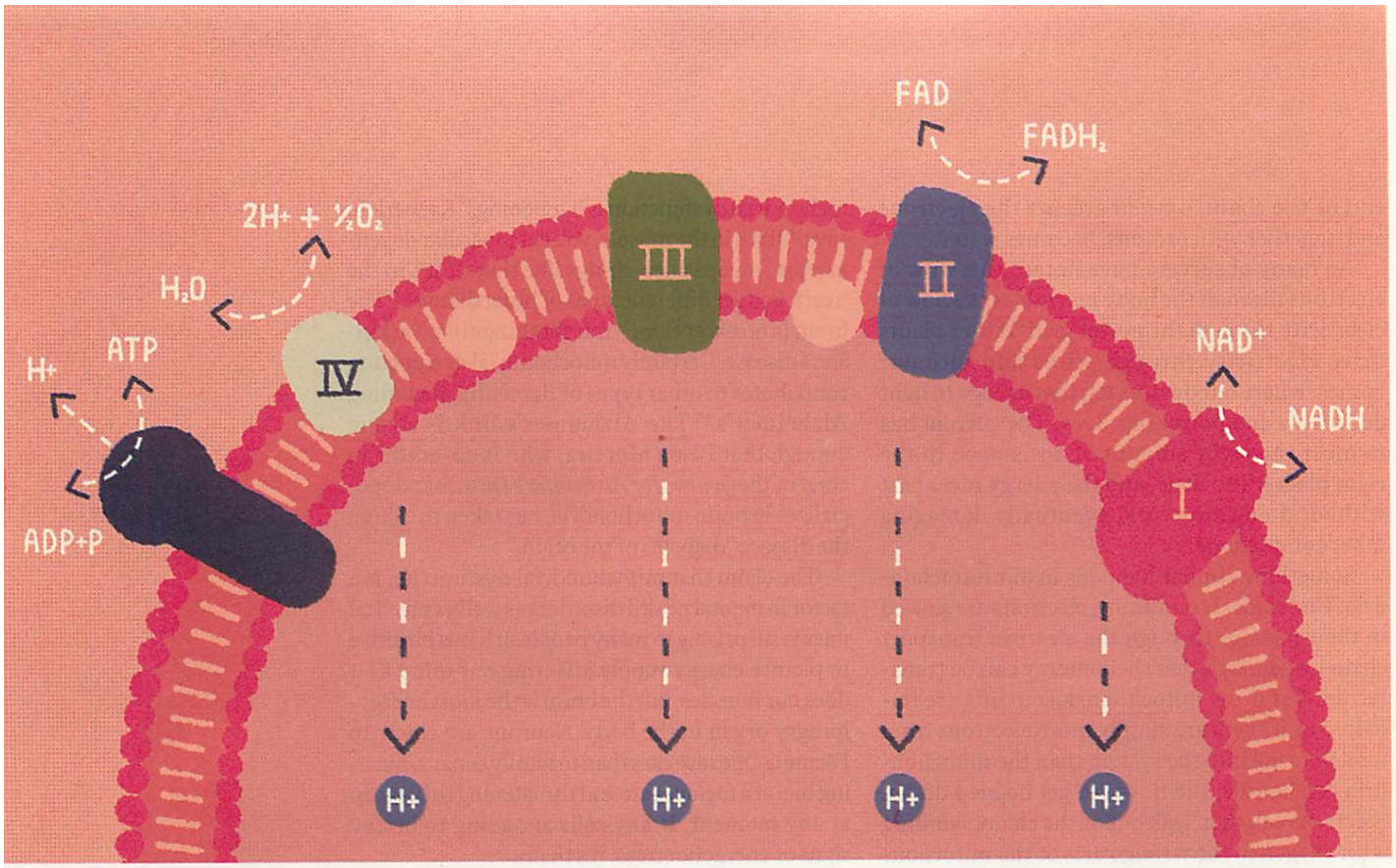
These disruptions in cellular energy can have very different consequences throughout the body. "The specific pathology depends on where the mitochondrial dysfunction is happening," Kaeberlein says. "If it's in the muscle, you get muscular degeneration, myopathies, things like that. If it's in the heart, you get different types of heart disease." The brain is no exception. "You get things like Parkinson's disease. Certainly mitochondrial dysfunction contributes to other types of dementia, including Alzheimer's." The Alzheimer's link is strong enough that Paula Moreira, who is co-editor in chief of the *Journal of Alzheimer's Disease* and specializes in brain mitochondria, has taken to calling the disease "diabetes of the brain."

The claim that mitochondrial dysfunction is a factor in mental health disorders as well as physical ones is surprising to many people. It's less intuitive to picture energy supply affecting our mind as it does our muscles, but the brain is the most energy-hungry organ in the body. Neurons are closer to Formula One race cars than to family sedans, burning fuel at a furious rate and threatening to blow up at any moment. If any cells are going to betray signs of energetic stress, it's them.

> "Mitochondrial dysfunction may contribute to the vast majority of common diseases."
>
> —MATT KAEBERLEIN *UNIVERSITY OF WASHINGTON*

AS MITOCHONDRIAL DYSFUNCTION has become a familiar suspect in disease and aging, efforts to tinker with it now range from a cottage industry of supplements, such as coenzyme Q10, that promise happier, healthier mitochondria, to experimental interventions involving gold nanoparticles. That worries Jonathan Jarry, a science communicator at McGill University's Office for Science and Society in Montreal. "My concern is that people start to believe that this has been successfully translated into the clinic when it hasn't," he says. "So it's one thing to say, 'Hey, here's what we know about this thing that's in our cells. It's really cool. People are studying this.' And it's another to say, 'Hey, we know the problems that this causes, and we know how to fix this, and we can sell you solutions.'"

Kaeberlein agrees that the hacks have thus far disappointed. "None of the data so far looks all that compelling," he says. Of all the supplements suspected to have mito-boosting powers, he says only one is convincing. "The one I would point to is creatine. There's a clear mitochondrial connection, and the biology is very plausible. I think it's a very



In mitochondria, the electron transport chain helps to convert energy from food into ATP, the molecule that powers our cells.

good supplement. It works in the context of also doing exercise, but there's emerging evidence on creatine and brain function, at least in situations like sleep deprivation or severe cognitive stress. You can buffer the ATP supply of the brain and muscle with creatine."

For now the boring advice has better evidence than the hacks: sleep, exercise and diet.

Sleep is extraordinarily important to mitochondrial health. That may be a big part of what drives our need for it. Neuroscientists at the University of Oxford have recently found direct links between oxidative stress in the brain and the need to sleep. As neurons fire furiously over the course of the day, ROS can accumulate. Specialized neurons track that buildup, and when a certain threshold is reached, they send a sleep signal to the brain at large. During sleep, neurons go quiet, ROS are cleared, and damaged mitochondria are repaired or recycled.

Exercise also improves the capacity of mitochondria to process energy, in part by stress-testing the system. Any kind of workout is a temporary emergency for the cells involved. Energy demand might rise to 100 times resting levels, which pushes mitochondria and their support systems to the limit, producing a burst of ROS and other stress signals. During recovery, though, the body responds to this challenge so it will be better prepared for the next one, fixing damaged tissue and building more blood vessels and mitochondria. The payoff is a system that can handle more energy without straining the rest of the time. The leg muscles of a marathoner can have twice as many mitochondria per cell as those of a couch potato, spreading the energetic load across much more capacity.

The system also gets better at repair, which may turn out to be a more important part of healthy aging than we've realized. Exercise triggers a process known as autophagy, the cell's salvage system for worn-out parts, including mitochondria. Damaged material gets dismantled; useful components go back into circulation.

Recycling also seems to help explain another old standby: calorie restriction. "Autophagy is an adaptive response to nutrient deprivation," Kaeberlein says. "When you're in nutrient shortage, you don't have the energy to produce a bunch of new complex machinery, so you break down the damaged machinery, and then you can reuse those components. And the most important time to recycle is when you don't have sufficient nutrients to build new machinery."

That efficient scavenging can also clear damaged components before they become a liability. At the same time, reducing the amount of energy entering the system eases the load on mitochondria and reduces oxidative stress. Calorie reduction reliably improves health and lifespan in many organisms, including yeast, worms, flies and rodents. In primates, the results aren't as clear, although long-running studies point to health benefits.

Diet-based interventions have shown promise for the brain as well as the body, a connection physicians made long ago when they noted that fasting

could often prevent seizures in people with epilepsy. "Hippocrates knew about it 2,000 years ago," says Christopher Palmer, a Harvard Medical School psychiatrist and author of the 2022 book *Brain Energy*. "In the 1920s physicians put it to the test. And to their shock, it actually worked."

We now know a lot about the mechanisms of action, Palmer says, including "changes in neurotransmitter function, changes in hormone signaling, changes in epigenetics, reduced brain inflammation and changes in mitochondrial function." Those changes seem to be linked to metabolic shifts, among them reductions in the load of glucose, the body's standard fuel, which is produced mostly from carbohydrates. A ketogenic diet can reproduce fasting's metabolic effects by strictly limiting carbohydrates and relying more on fat. When carb intake falls sharply, the liver turns fat into ketones, an alternative fuel for the brain and other tissues that may cause less metabolic stress. Whether this broader metabolic shift can improve psychiatric symptoms is now being put to the test.

In July a team led by researchers at the San Francisco VA Medical Center published the first randomized controlled trial of a ketogenic diet in people with bipolar I disorder and schizophrenia-spectrum disorders. After a month, the ketogenic group showed clear metabolic improvements; the more striking psychiatric and cognitive gains turned up at four months—by which point the diet had been offered to everyone, eliminating the control-group comparison. The clinical signal remains intriguing but preliminary.

"We've known for decades that a ketogenic diet is effective for antiseizure," Kaeberlein says. "It definitely has effects on brain metabolism that are potent. That's going to affect mitochondrial dysfunction. So it's reasonable to think a ketogenic diet will have broader-reaching effects on brain biology that could affect emotion, psychological state, cognitive abilities, all of those things."

Kaeberlein cautions that it is too early to assume that we understand how these incredibly complex systems work. "The arrows all point in the direction that repairing and preserving mitochondrial function during aging is important for the lifespan and health span benefits we see from these interventions. But because all of these things are multifactorial, it's hard to know how much is because of their effects on mitochondria versus other things that these interventions are doing." The wrinkle is that mitochondria live inside the cell and depend on it, so anything that improves their function will improve the cell, but anything that improves the cell will also improve them.

ON THEIR FACE, none of these interventions are revolutionary. The appeal of the energy-centric perspective is that it gives familiar advice—eat lightly, sleep well, get exercise—a common language. "The disease-centric point of view looks at a singular snapshot and then looks backward to see how that applies to health. The energy-resistance framework flips that," Murugan says. "It reframes health as a dynamic process, and it allows us to look at how different interventions can influence that process. It puts them into context."

A good example is type 2 diabetes. "From a molecular perspective," Picard says, "diabetes is excess blood sugar and insulin resistance. So you fix it with drugs. You give insulin to override the resistance." He reads insulin resistance differently. In some cases, he argues, cells may begin to resist glucose because their mitochondria are already struggling to process the fuel coming in. In that telling, they need a break, Picard says, not an override.

An energy-centric perspective may also offer early warning signs. Cells under stress release a signaling protein known as GDF15. "It's the way cells tell other cells, 'I'm not doing well,'" Picard says. High levels of GDF15, which also rise in pregnancy and illness, trigger feelings of malaise and nausea—a built-in brake on energetically costly activities such as movement and digestion. He thinks the body is then able to conserve energy while confronting the internal challenges. High levels are also among the best predictors of future disease and mortality, which he takes as strong evidence that energetic dysfunction within cells precedes later problems—and may offer us an early opportunity to head them off.

These disruptions in cellular energy can cause very different consequences throughout the body.

But beyond such practical applications, the biggest appeal of seeing health through the lens of energy may be the new light it shines on the very concept of disease. "Once we see ourselves energetically, it's going to change how we teach and practice medicine," Picard says. Rather than fixing parts piecemeal after they break down, we can ask what keeps us all happily humming along in the first place. In a sense, we are all energy benders, channeling an endless flow of what was once sunlight through the labyrinth of our molecules and gracefully shaping it into this thing we call life. ●

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27,286 results

Did you mean ***mitochondria and healthy*** (6,174 results)?

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Liu Y, Yao C, Sheng B, Zhi S, Chen X, Ding P, Zhang J, Tao Z, Li W, Zhuang Z, Mao J, Peng Z, Yan H, Jin W.
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Mitochondrial DNA In Aging and Disease
Scientific American
August 1997

Douglas Wallace
Director of the Center for Mitochondrial and Epigenomic Medicine at the Children's Hospital of Philadelphia Research Institute

Mitochondrial DNA (mtDNA) codes for 13 proteins and 24 RNA molecules required for the mitochondria to produce ATP energy.

"Every cell in the body contains hundreds of mitochondria, the power plant of cells."

"A single mitochondrion contains several loops of DNA [mtDNA], each of which contain 37 genes involved in energy generation."

"Injury to genes in mitochondria play a role in the aging process and in chronic, degenerative illnesses that become common late in life, such as Alzheimer's disease and various motor disturbances."

"Mitochondria provide about 90% of the energy that cells, and thus tissues, organs and the body as a whole, need to function."

"Anything able to compromise ATP production in mitochondria could harm or even kill cells and so cause tissues to malfunction and symptoms to develop."

"The tissues and organs most readily affected by cellular energy declines are the central nervous system, followed, in descending order of sensitivity, by heart and skeletal muscle, the kidneys and hormone-producing tissues."

Mitochondrial DNA mutations disrupt mitochondrial proteins, disturbing the energy-producing capacity of mitochondria and producing disease.

The inner membrane of the mitochondria contains 4 protein complexes called the respiratory chain. Electrons from food pass through these protein complexes with the help of Coenzyme Q10, interacting with oxygen and hydrogen to produce water and ATP energy.

"As the respiratory chain participates in energy production, toxic by-products known as oxygen free radicals are given off. These oxygen derivatives, which carry an unpaired electron and so are highly reactive, can attack all components of cells, including respiratory chain proteins and mitochondrial DNA. Anything that impedes the flow of electrons through the respiratory chain can increase their transfer to oxygen molecules and promote the generation of free radicals. A single mutation, then, can presumably initiate a recurring cycle of inhibited electron transport, leading to increased free-radical production and more mitochondrial DNA mutations."

"Progressive reductions in mitochondrial energy (ATP) production in nerve, muscle of other tissues could be an important contributor to aging and to various age-related degenerative diseases."

Exposure to environmental toxins cause mitochondrial energy production to decline. "Many of the most potent toxins work their mischief by inhibiting mitochondria."

"The mitochondrial theory of aging holds that as we live and produce ATP, our mitochondria generate oxygen free radicals that inexorably attack our mitochondria and mutate our mitochondrial DNA. This random accumulation of mitochondrial DNA mutations in people who began life with healthy mitochondrial genes would ultimately reduce energy output below needed levels in one or more tissues if the individual lived long enough. In so doing, the mutations and mitochondrial inhibition could contribute to common signs of normal aging, such as loss of memory, hearing, vision, and stamina."

"In people whose energy output was already compromised (by toxins of other factors), the resulting mitochondrial DNA injury would push energy output below desirable levels more quickly. These individuals would then display symptoms earlier and would progress to full-blown disease more rapidly than would people who initially had no deficits in their energy production capacity."

Mitochondrial DNA mutations increase with age, "especially in the brain (most notably in regions controlling memory and motion)," and also in the "mitochondrial DNA of skeletal muscle, heart muscle, skin and other tissues."

"If free-radical damage does indeed drive the accumulation of mitochondrial DNA mutations and thus influence the speed of aging, then treatments that block mitochondrial productions of such radicals and thereby protect mitochondrial DNA could slow aging and delay the onset of age-related diseases. Such approaches could consist of lifelong treatments with antioxidants (for example, coenzyme Q or vitamins C or E)."

Also, "long-lived, diet restricted animals, who produce fewer oxygen free radicals, accumulate less mitochondrial DNA damage than do their well-fed littermates." **[Intermittent Fasting]**

Neuroimmune Biology
The Neuroendrocrine immune Network In Ageing

Elsevier, 2004

Rainer Straub and Eugenio Mocchegiani, Editors

"One of the most accepted theories of ageing is the free radical theory of ageing." p. 66

"The overproduction of free radicals can induce cell death. Ageing, as stated in free radical theory of ageing is characterized by an increased production of free radicals in several tissues or a decreased antioxidant defense leading to chronic oxidative stress." p. 63

"One important source of free radicals is mitochondria." The mitochondria are the major source for the production of free radicals. p. 63

Mitochondria

"Mitochondria contain their own DNA."

"Each cell has hundreds to thousands of mitochondria and there are up to 100 mitochondrial DNA copies in each mitochondrion."

From Daniel Farkas, DNA from A – Z, 2000, pg. 73.

•••••

"The mitochondria are the source of most free radical substances produced in the body." P. 92

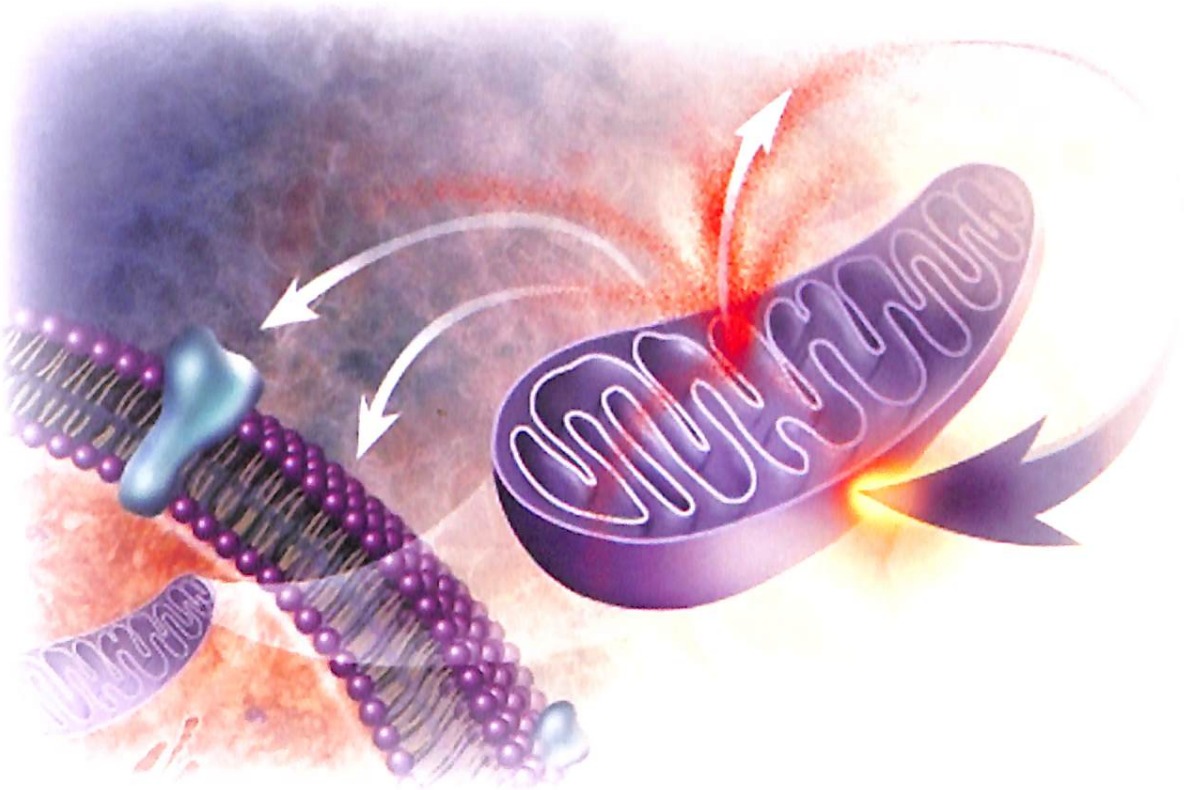
"The human aging process is tied to the function of the mitochondria throughout life." P. 94

Mitochondrial DNA "can readily sustain damage by free radicals."

"Mitochondrial DNA is about 15 times more susceptible than nuclear DNA to free radical oxidative injury." P.98

From Jeffery Bland, Nutrition Genetic Nutritioneering, How You Can Modify Inherited Traits and Live a Longer, Healthier Life, Keats, 1998

Oxidative Stress, Disease and Cancer



Editor Keshav K. Singh

2006

Imperial College Press

From the Preface

"The ability of cells to reduce oxygen to produce energy is fundamental to aerobic life.

Unfortunately, production of energy by reduction of dioxygen leads to the generation of reactive oxygen species that cause oxidative stress.

It is now well established that oxidative stress causes extensive damage to cellular components, which can lead to a number of diseases, including cancer."

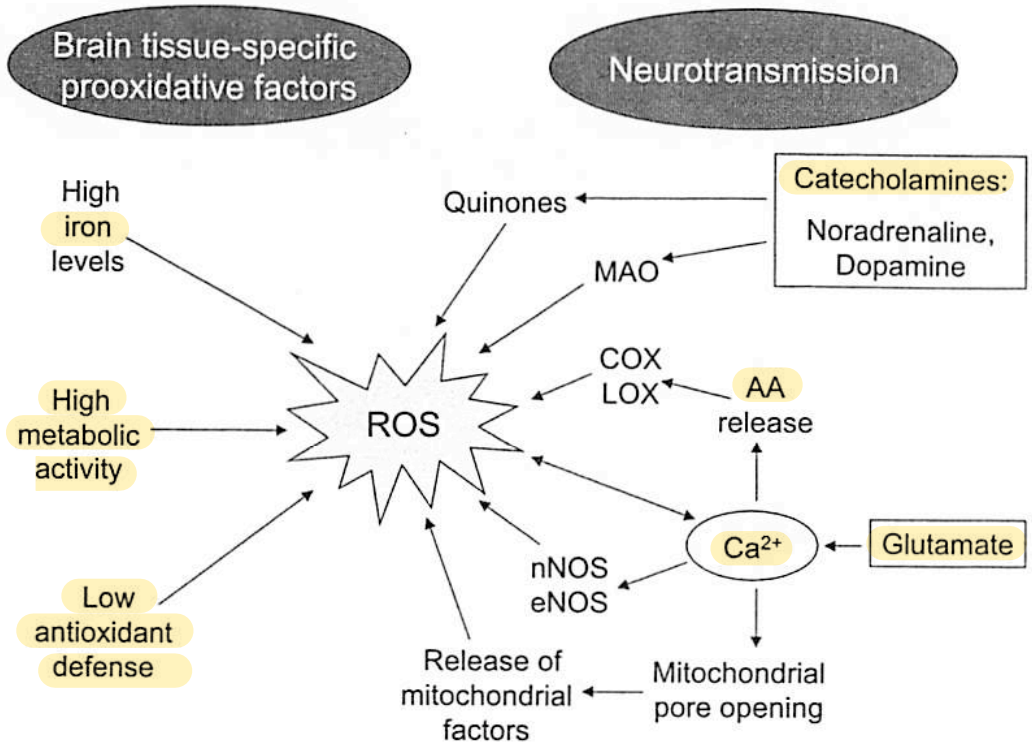
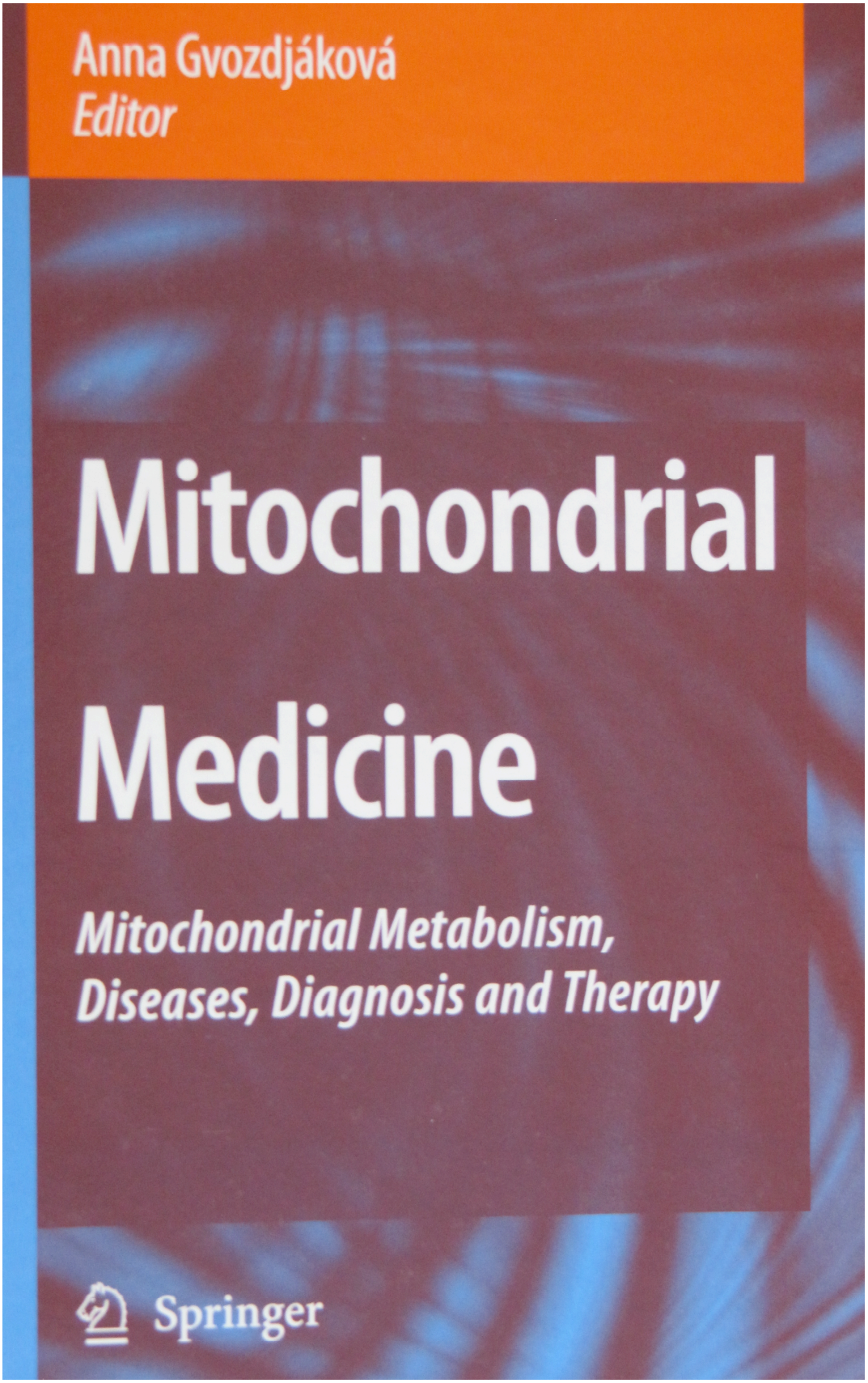
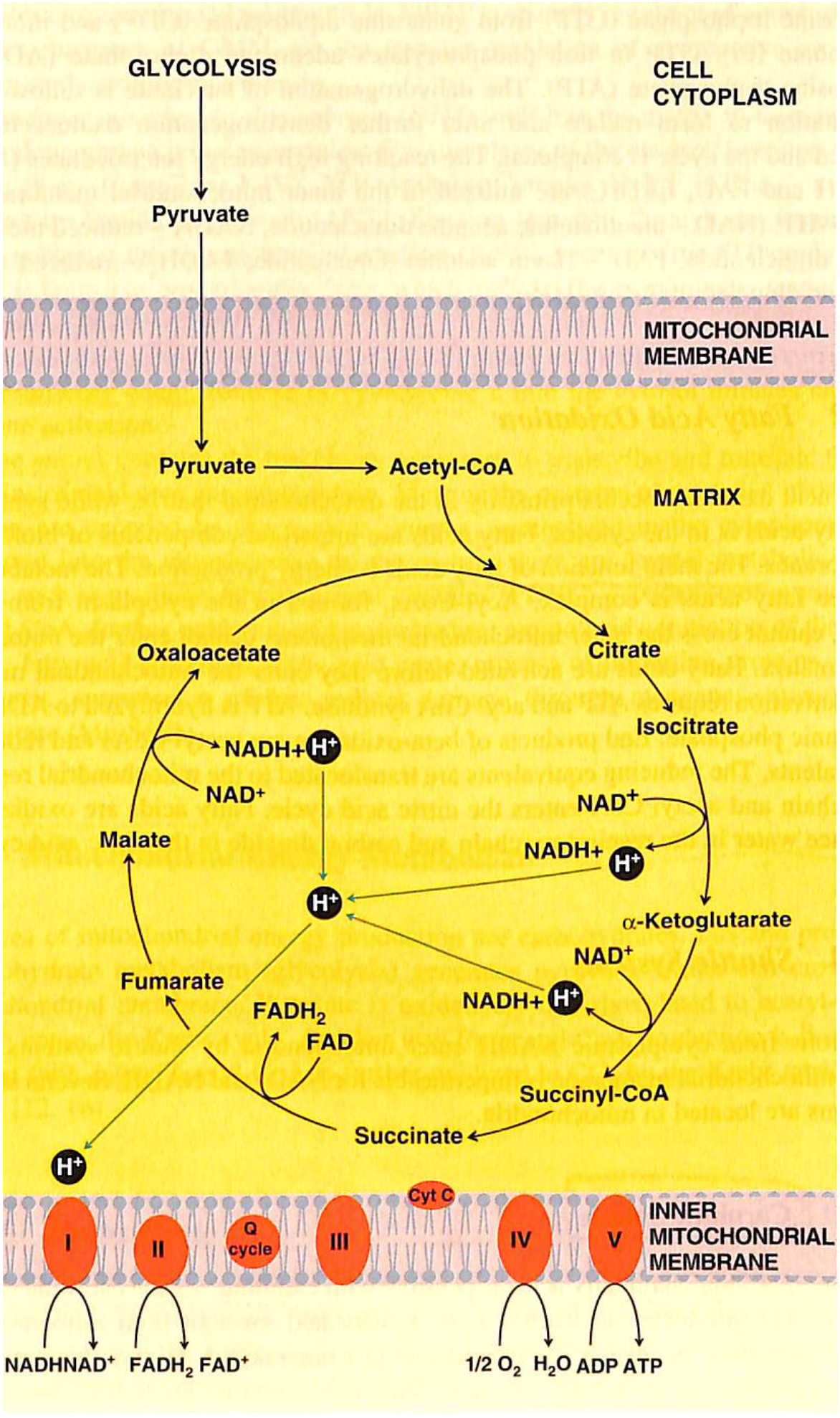


Fig. 1. Factors contributing to accumulation of reactive oxygen species (ROS) in brain tissue. See text for details. MAO, monoamine oxidase; COX, cyclooxygenase; LOX, lipoxygenase; AA, arachidonic acid; eNOS/nNOS, endothelial/neuronal nitric oxide synthase.


Anna Gvozdjáková
Editor
Mitochondrial
Medicine
Mitochondrial Metabolism,
Diseases, Diagnosis and Therapy
Springer


GLYCOLYSIS
CELL
CYTOPLASM
Pyruvate
MITOCHONDRIAL
MEMBRANE
Pyruvate
Acetyl-CoA
MATRIX
Oxaloacetate
Citrate
Isocitrate
NADH+ H+
NAD+
NAD+
Malate
NADH+ H+
H+
α-Ketoglutarate
NAD+
Fumarate
NADH+ H+
FADH2
FAD
Succinyl-CoA
Succinate
H+
Cyt C
I
II
Q
cycle
III
IV
V
INNER
MITOCHONDRIAL
MEMBRANE
NADHNAD+
FADH2 FAD+
1/2 O2
H2O
ADP
ATP

Mitochondria Gone Bad

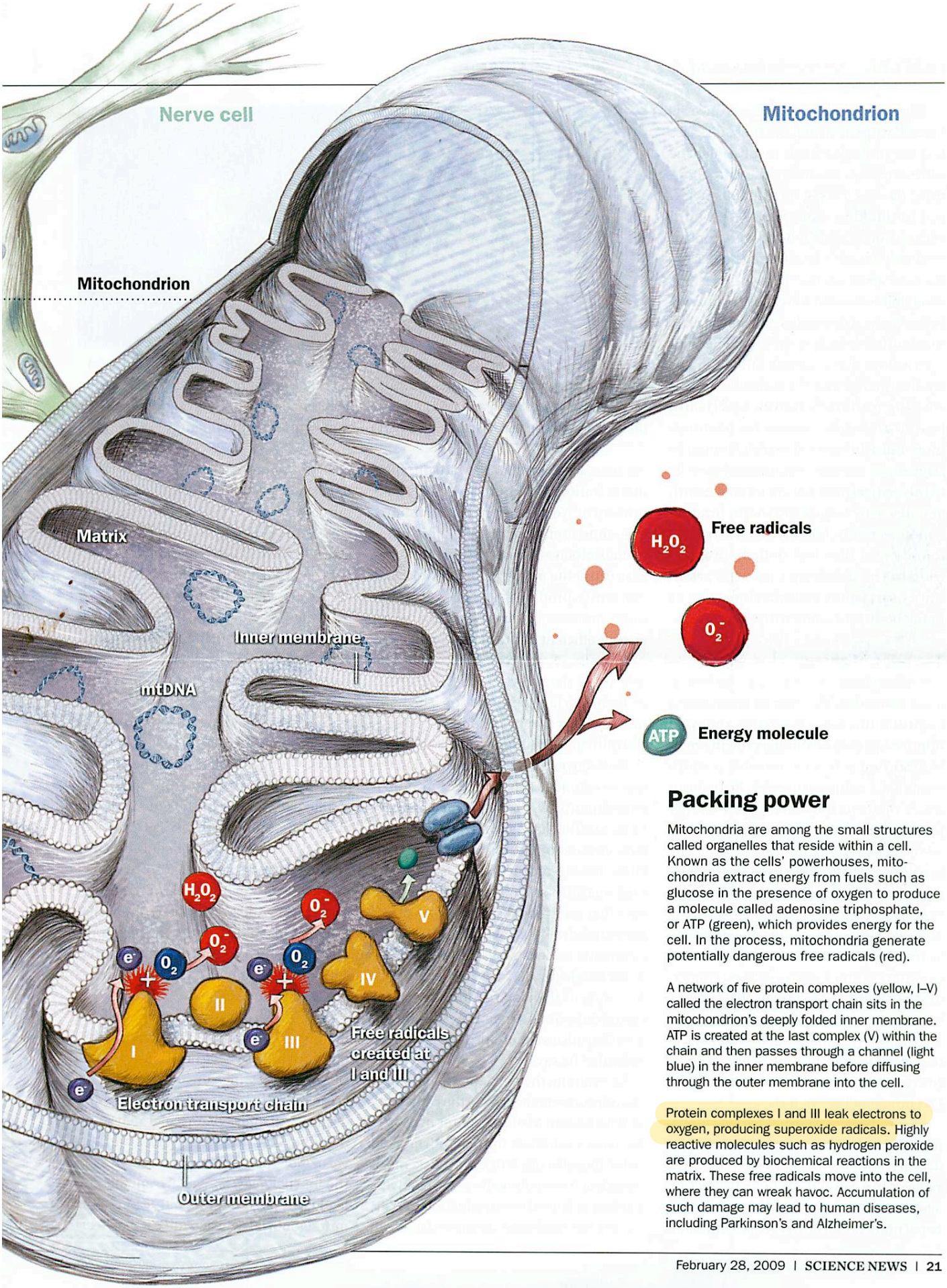
Problems in the cell's energy factories power new ideas on disease and aging

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."



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.

Includes Over 100 Recipes for a Healthy Brain



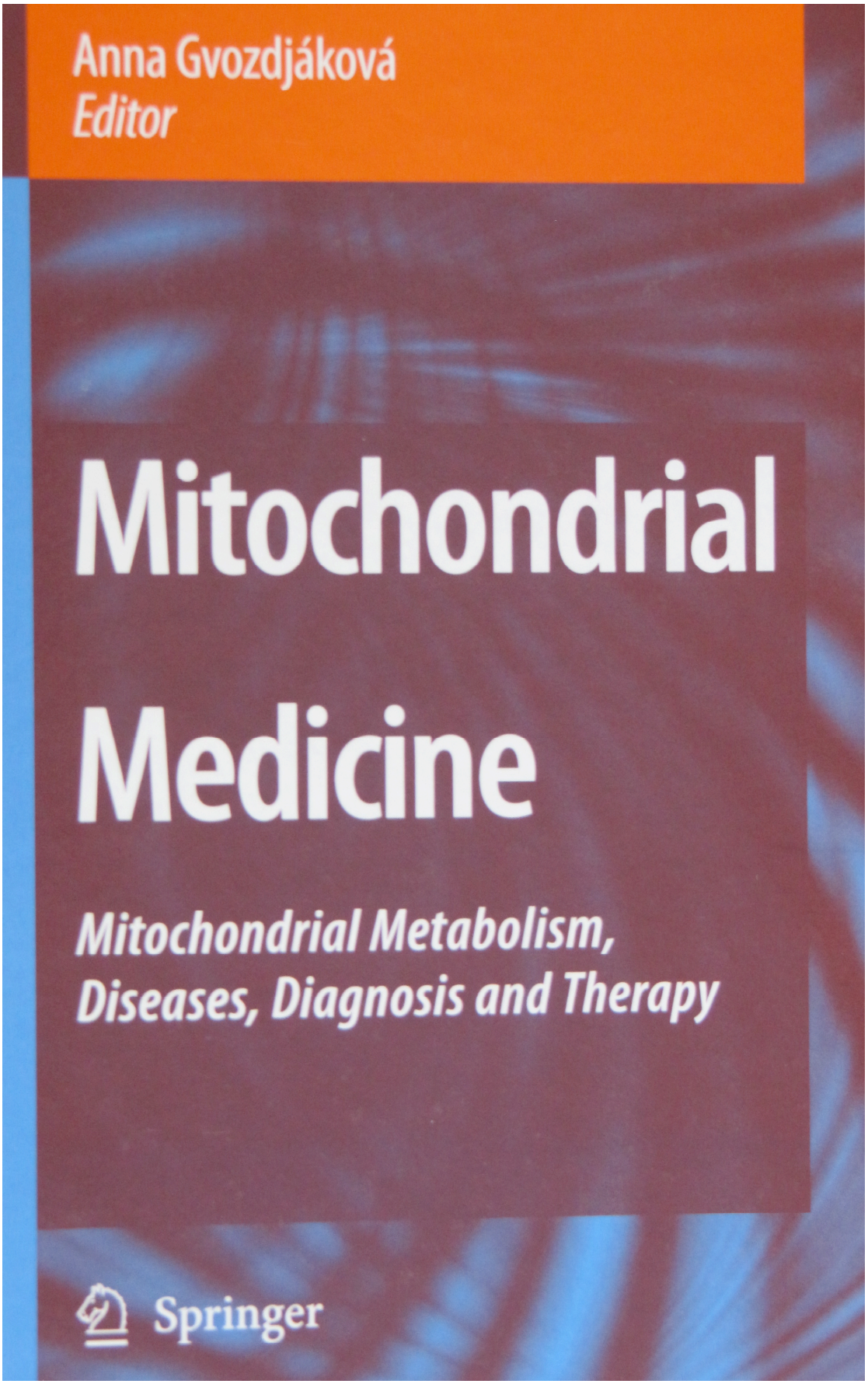
Minding My Mitochondria

2nd edition

2010

Terry L. Wahls, M.D.

How I overcame secondary progressive
multiple sclerosis (MS) and got out of my wheelchair.


Anna Gvozdjáková
Editor
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LEE KNOW, ND

MITOCHONDRIA AND THE FUTURE OF MEDICINE

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



2018

CHAPTER ONE

The Force

The Origins and Evolution of Mitochondria in Human Physiology

> *Without the midi-chlorians, life could not exist, and we would have no knowledge of the Force. They continually speak to us, telling us the will of the Force. When you learn to quiet your mind, you'll hear them speaking to you.*
>
> —*Star Wars: Episode I—The Phantom Menace*,
> Qui-Gon Jinn to Anakin Skywalker

A long time ago, in a galaxy far, far away, there were intelligent microscopic life forms called *midi-chlorians* that lived symbiotically inside the cells of all living things. When present in sufficient numbers, they allowed their symbiotic host to detect the pervasive energy field known as the Force. Midi-chlorian counts were linked to one's potential in the Force, ranging from normal human levels of 2,500 per cell to the much higher levels in a Jedi. The highest known midi-chlorian count (over 20,000 per cell) belonged to Jedi Anakin Skywalker.

Present in all life, midi-chlorians are the same on every world that supports life—in fact, midi-chlorians are necessary for life to exist. In sufficient numbers, midi-chlorians will allow their host organism to detect the Force, and this connection can be strengthened by quieting

Nick Lane

POWER, SEX, SUICIDE

Mitochondria and the meaning of life

NOW WITH A NEW PREFACE

2018

OXFORD LANDMARK SCIENCE

INTRODUCTION

MITOCHONDRIA

Clandestine Rulers of the World



A mitochondrion—one of many tiny power-houses within cells that control our lives in surprising ways

Mitochondria are tiny organelles inside cells that generate almost all our energy in the form of ATP. On average there are 300–400 in every cell, giving ten million billion in the human body. Essentially all complex cells contain mitochondria. They look like bacteria, and appearances are not deceptive: they were once free-living bacteria, which adapted to life inside larger cells some two billion years ago. They retain a fragment of a genome as a badge of former independence. Their tortuous relations with their host cells have shaped the whole fabric of life, from energy, sex, and fertility, to cell suicide, ageing, and death.

These considerations were enough for Mitchell to put forward a radical new hypothesis in *Nature* in 1961, while still at Edinburgh. He proposed that respiration in cells worked by *chemiosmotic coupling*, by which term he meant a chemical reaction that could drive an osmotic gradient, or vice versa. *Osmosis* is a familiar term from schooldays, even if we can't quite remember what it means. It usually means the flow of water across a membrane from a less concentrated to a more concentrated solution, but Mitchell, characteristically, didn't mean it in that sense at all. By 'chemiosmosis' we might imagine that he was referring to a flow of chemicals other than water across a membrane, but this was not what he meant either. He actually used the word 'osmotic' in the original Greek sense, meaning 'push'. Chemiosmosis, for Mitchell, was the pushing of molecules across a membrane *against* a concentration gradient—it is therefore, in a sense, the exact opposite of osmosis, which follows the concentration gradient. The purpose of the respiratory chain, said Mitchell, is no more nor less than to push protons over the membrane, creating a reservoir of protons on the other side. The membrane is little more than a dam. The pent-up force of protons, trapped behind this dam, can be released a little at a time to drive the formation of ATP.

It works like this. Recall from the previous chapter that the complexes of the respiratory chain are plugged through the membrane. The hydrogen atoms that enter the respiratory chain are split into protons and electrons. The electrons pass down the chain like the current in a wire, via a succession of redox reactions (Figure 7). The energy released, said Mitchell, doesn't form a high-energy chemical intermediate at all; the squiggle is elusive because it does not exist. Rather, the energy released by electron flow is used to pump protons across the membrane. Three of the four respiratory complexes use the energy released by electron flow to thrust protons across the membrane.

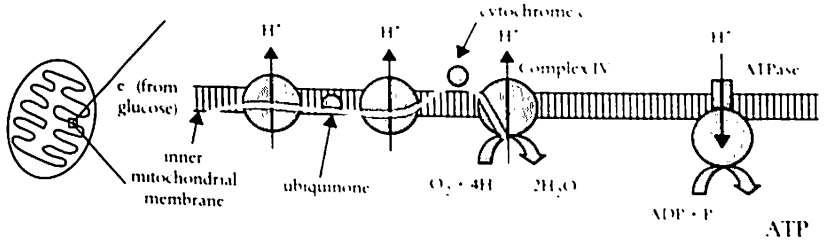
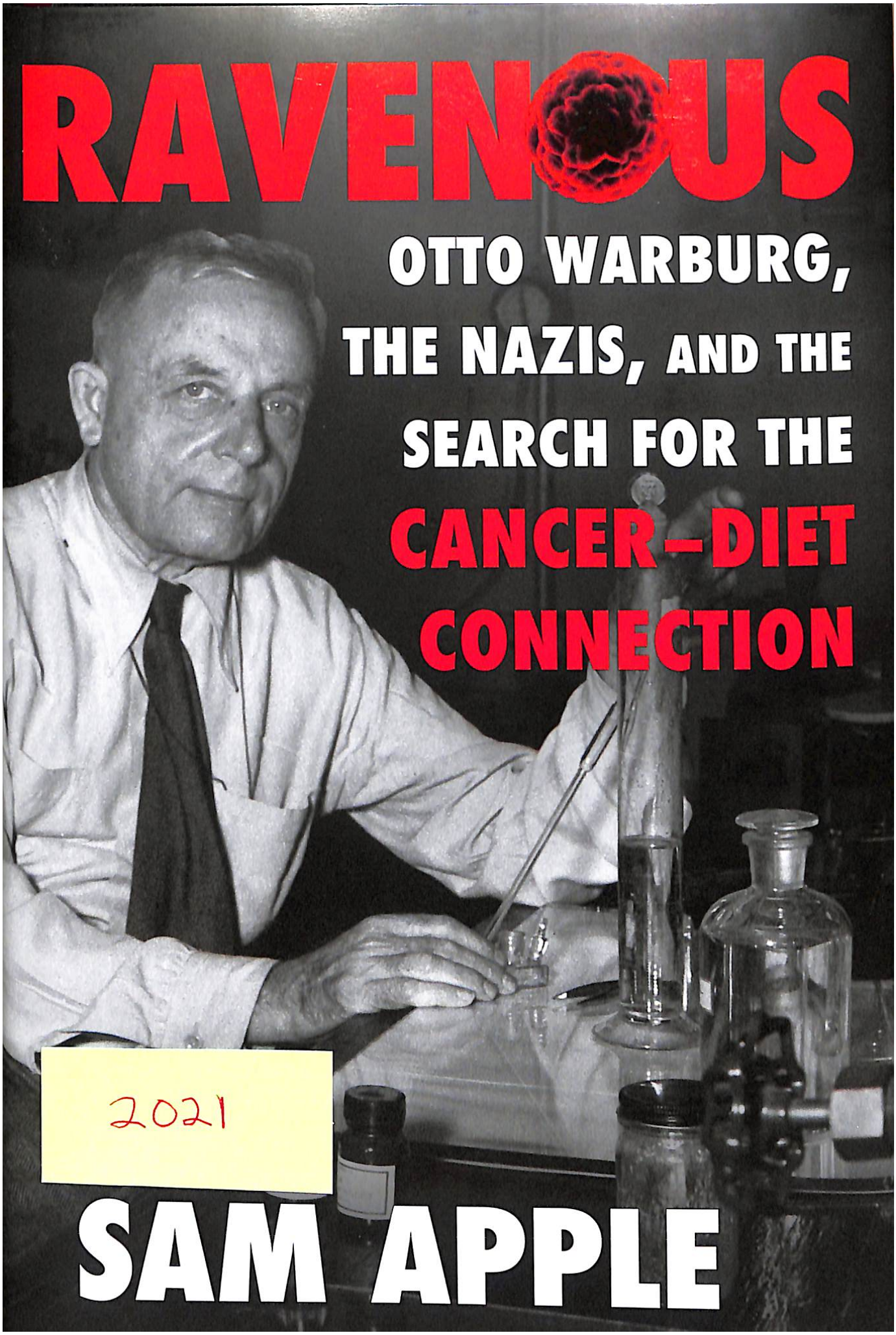


Figure 7. Simplified representation of the respiratory chain, as in Figure 5, but now showing the nature of the intermediate—the proton. Electrons (e⁻) pass down the chain from complex I to complex IV, and the energy released at each step is coupled to the expulsion of a proton across the membrane. This leads to a difference in proton concentration across the membrane, which can be measured as a difference in acidity (pH, or acidity, is defined as the proton concentration) and as an electrical potential difference, as protons carry a single positive charge. The reservoir of protons acts as a reservoir of potential energy, just as a reservoir of water on top of a hill acts as a reservoir of potential energy that can be used to generate hydroelectric power. Likewise, the flow of protons down the concentration gradient can be used to power mechanical tasks, in this case ATP synthesis. The flow of protons through the ATPase is called the 'proton-motive force' and it turns the tiny molecular motor of the ATPase, to generate ATP from ADP and phosphate.

The membrane is otherwise impermeable to protons, so any backflow is restricted, and a reservoir develops. Protons carry a positive charge, which means that the proton gradient has both an electrical and a concentration component. The electrical component generates a potential difference across the membrane, while the concentration component generates a difference in pH, or acidity (acidity is defined as proton concentration) with the outside more acid than the inside. The combination of pH and potential difference across the membrane constitutes what Mitchell called the 'proton-motive force'. It is this force that drives the synthesis of ATP. Because ATP is synthesized by the ATPase, Mitchell predicted that the ATPase would need to be powered by the proton-motive force—a current of protons flowing down the proton gradient

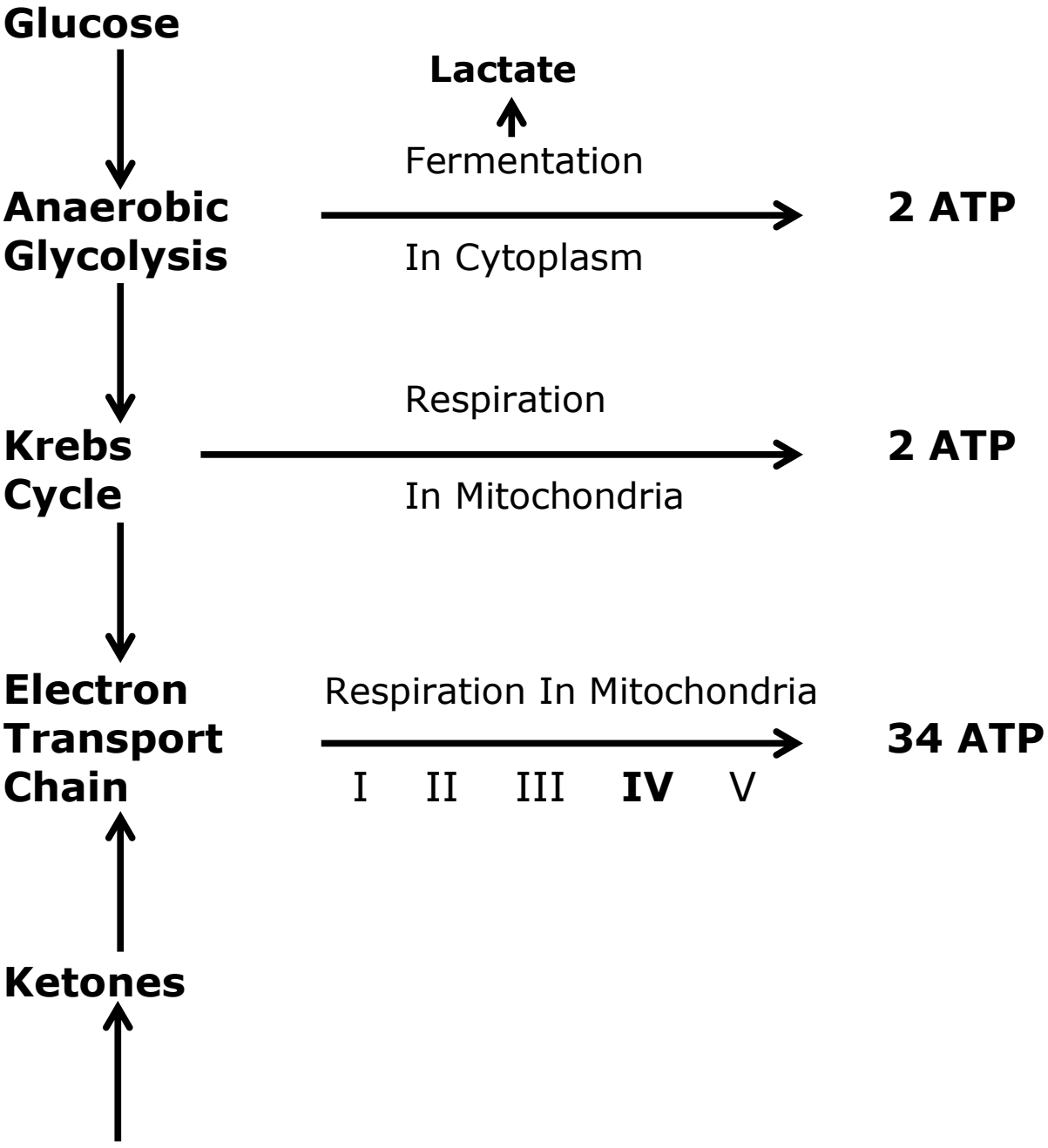
RAVENOUS

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



2021

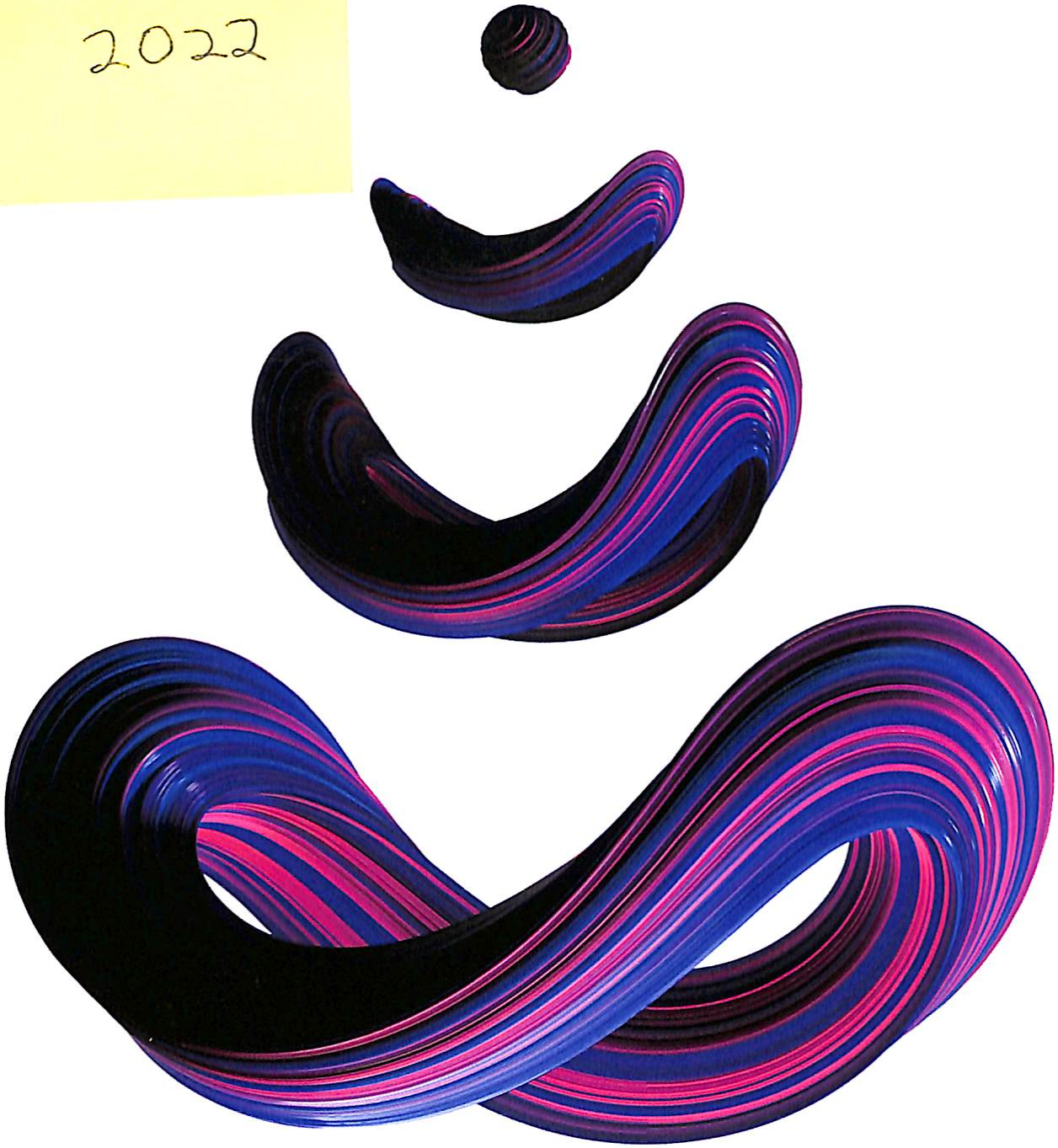
SAM APPLE



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.

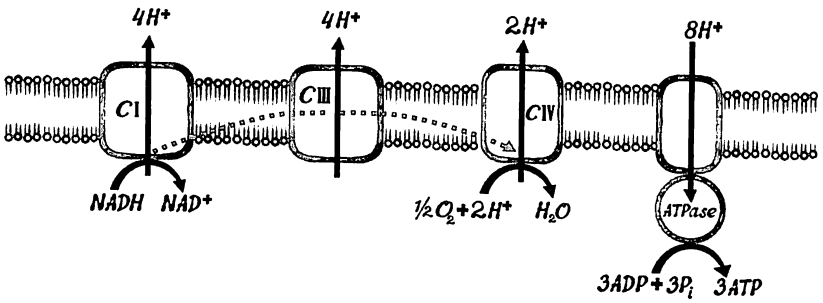
Here's the clever bit. CO can be detached from the catalyst through the absorption of light. That kick-starts respiration and oxygen consumption over again.

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

Good Energy

The Surprising Connection Between Metabolism and Limitless Health

Casey Means, MD
2024

"Nearly every heath problem we face can be explained by how well the cells in our body create and use energy."

"The next revolution in heath will come from the understanding how the root of almost every disease relates to energy..." "And when we shift our framework to this energy-centric paradigm, we will rapidly heal our system and our bodies."

"Imagine a powerful life force from within that allows you to take on each day with pleasure, energy gratitude and joy."

"An *underpowered* cell—metabolically dysfunctional, struggling to make energy, and sputtering along through its daily work—is a cell that is threatened and at risk. This failing cell will send out chemical alarm signals and recruit the immune system to help it. In their efforts to help,

the immune cells cause immense collateral damage—creating a literal war within the body to protect itself from itself—that results in worse symptoms. This is a key reason why chronic inflammation typically goes in lockstep with metabolic dysfunction and widespread symptoms."

"There's one simple measure that can powerfully reframe how we understand health can disease: how well or poorly the mitochondria in the cell are making energy."

"Given that mitochondria are the coordinators of cell immunity and cell survival, mitochondria function was implicated as early as 2020 as a key factor in the likelihood of getting COVID, dying from COVID, and experiencing long COVID."

"Researchers made recommendations to 'urgently' pursue preventive avenues to 'strengthen the mitochondria' for best COVID outcomes..."

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.

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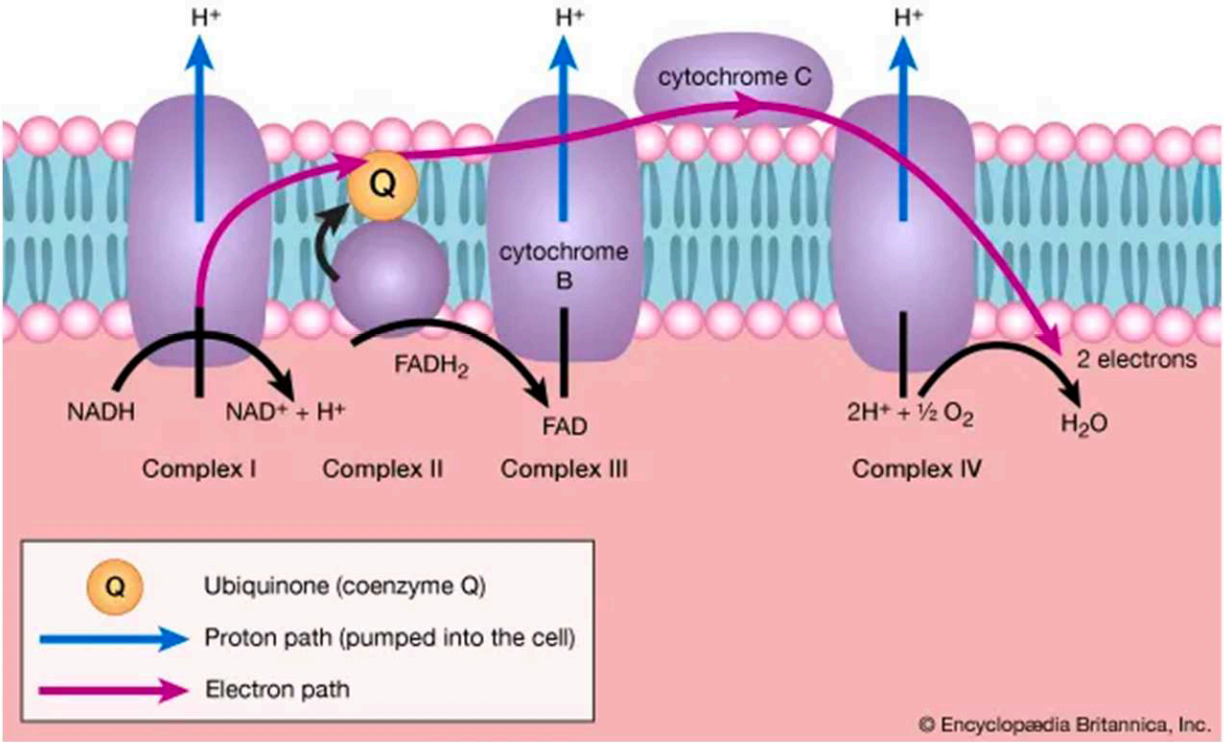
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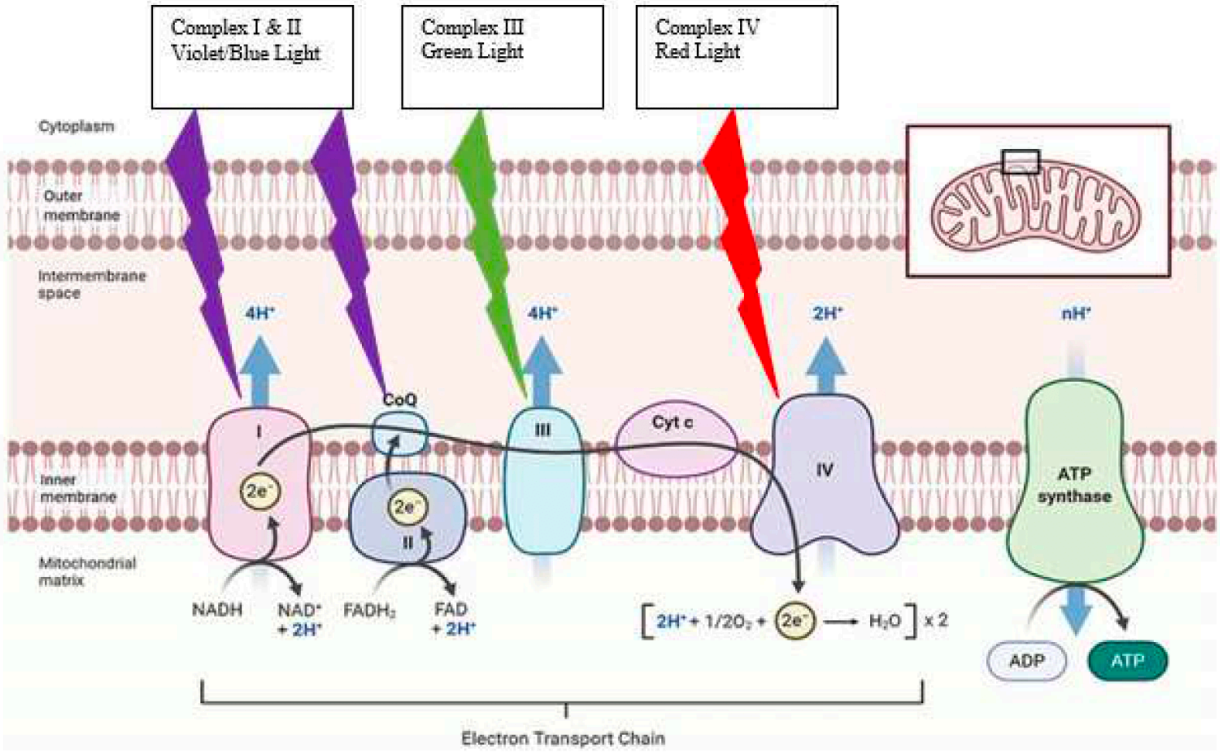
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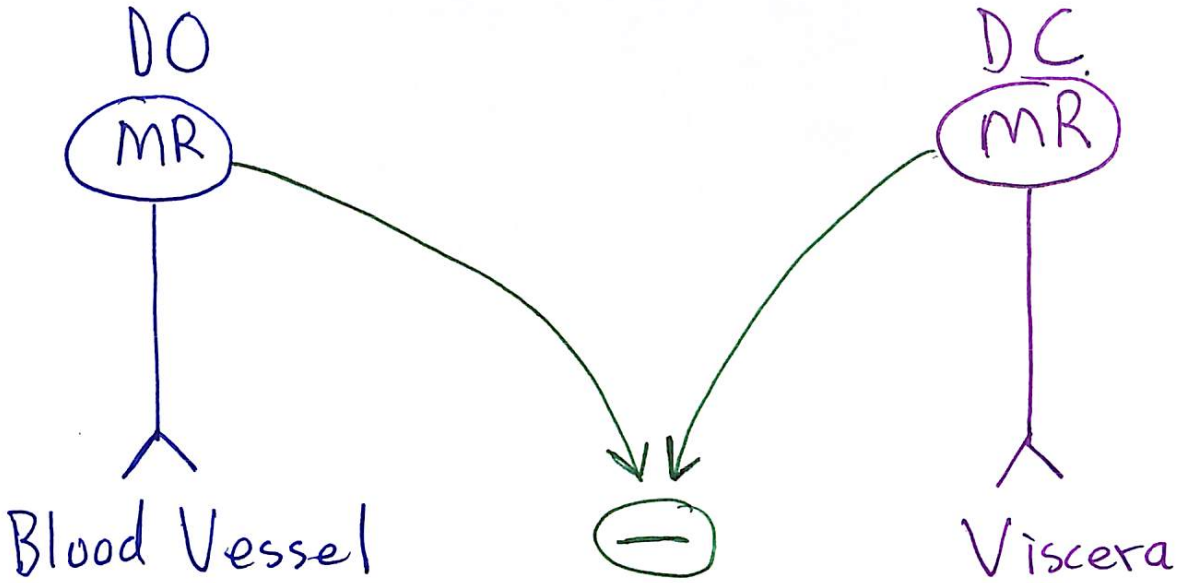
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MedlinePlus Health Information

Electron transport chain







Sympathetic Nervous System

↓

Blood Vessel Diameter

↓

O_2 ↓ Glucose – RA

↓

Mitochondria

↓

ATP

↓

DNA

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

Erchonia National Laser Expo 2026

Dan Murphy, DC

5 Hours

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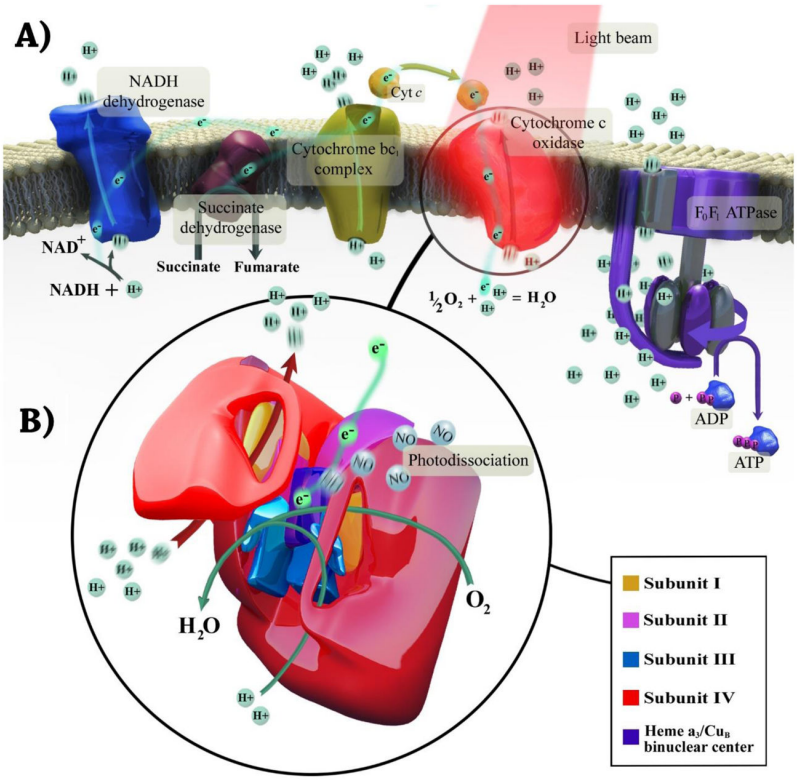


Fig. 1. Mechanism of photobiomodulation therapy in mitochondria

(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.

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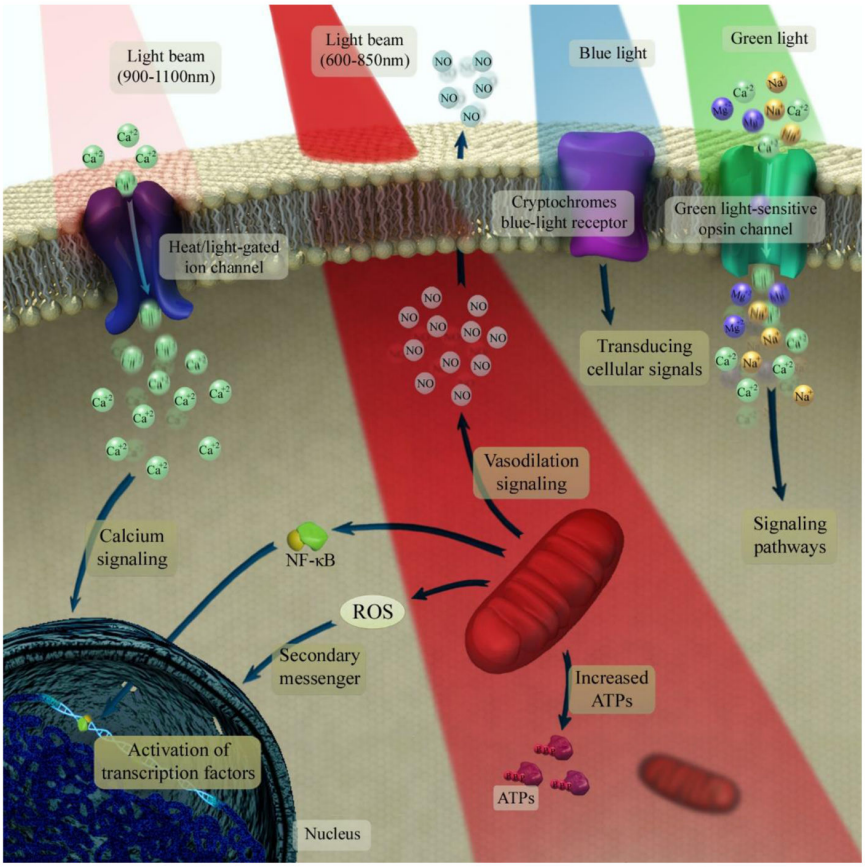


Fig. 2. Photobiomodulation underlying mechanisms at the cellular and molecular levels

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.

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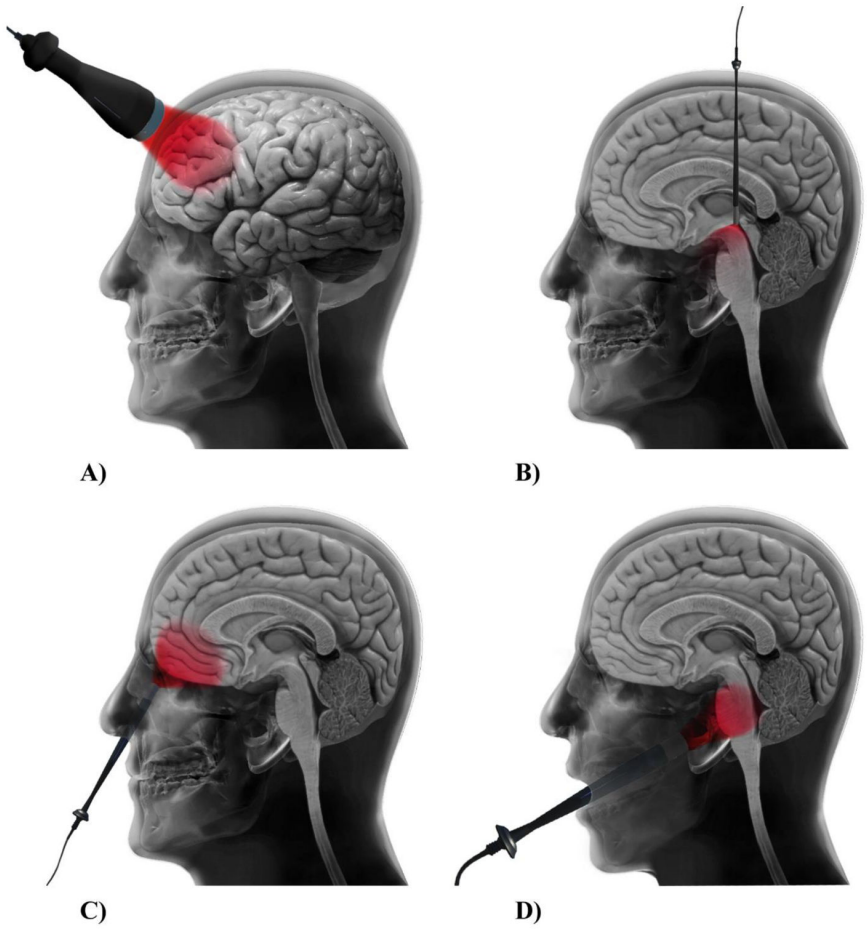


Fig. 3. Different approaches for light delivery to achieve brain photobiomodulation therapy
(A) Transcranial, (B) intracranial, (C) intranasal photobiomodulation therapy, (D) brain photobiomodulation via oral cavity.

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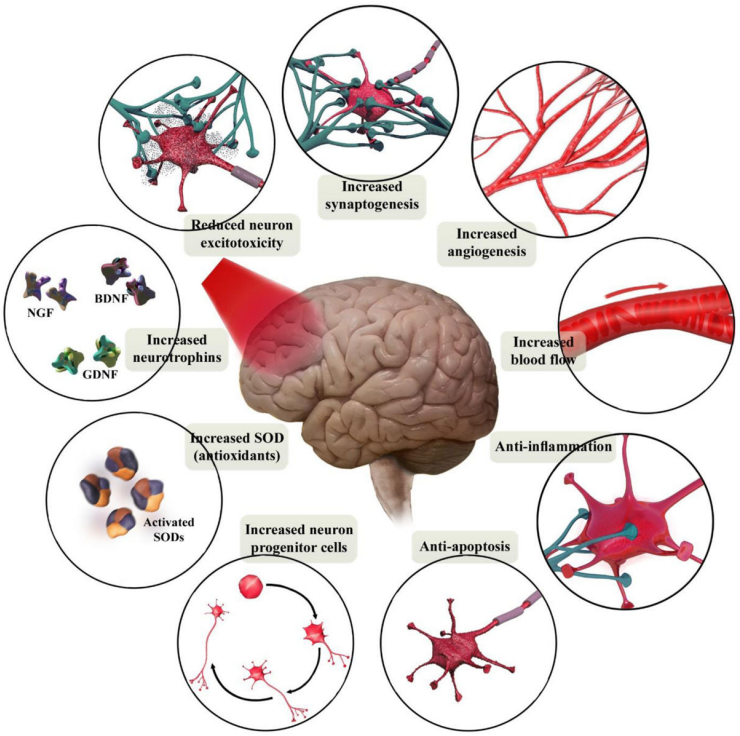


Fig. 4. Brain tissue-specific functional processes that occur after brain photobiomodulation therapy

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.

cells

Review

Photobiomodulation Therapy on Brain: Pioneering an Innovative Approach to Revolutionize Cognitive Dynamics

Tahsin Nairuz, Sangwoo-Cho and Jong-Ha Lee *

Department of Biomedical Engineering, Keimyung University, Daegu 42601, Republic of Korea;

June 3, 2024; Vol. 13; No. 11; Article 966

Photobiomodulation (PBM) therapy on the brain employs red to near-infrared (NIR) light to treat various neurological and psychological disorders.

The mechanism involves the activation of cytochrome c oxidase in the mitochondrial respiratory chain, thereby enhancing ATP synthesis.

This cascade of events not only augments neuronal metabolic capacity but also orchestrates anti-oxidant, anti-inflammatory, and anti-apoptotic responses, fostering neurogenesis and synaptogenesis.

It shows promise for treating conditions like dementia, stroke, brain trauma, Parkinson's disease, and depression, even enhancing cognitive functions in healthy individuals.

However, delivering sufficient light to the brain through transcranial approaches poses a significant challenge due to its limited penetration into tissue.

Photobiomodulation (PBM) constitutes a sophisticated approach rooted in utilizing visible and near-infrared light at minimal power densities, and represents a captivating frontier in medical treatment.

This application necessitates precise control over the administered fluence to ensure the avoidance of thermal consequences.

Cytochrome c oxidase (CCO), an integral player in the electron transport chain (complex IV) of mitochondria, exhibits absorbance within the wavelength range of approximately 600 to 900 nm.

Beyond this range, longer wavelengths are theorized to engage with water molecules and light-gated ion channels.

PBM demonstrates the remarkable capability to mitigate oxidative stress through dislodging inhibitory nitric oxide (NO) from the CCO complex, thus orchestrating a cascade of intricate cellular responses conducive to therapeutic outcomes.

In 1967, PBM was serendipitously stumbled upon by Endre Mester of Hungary,

Despite Mester's ruby laser being significantly less powerful than the one used by McGuff, it yielded unforeseen results.

Instead of eradicating tumors, Mester observed remarkable outcomes: a stimulation of hair regrowth and accelerated wound healing at the tumor sites.

Mester termed "laser biostimulation", subsequently recognized as "low-level laser therapy" (LLLT).

PBM holds substantial promise as a therapeutic avenue for a diverse array of neurological disorders, spanning from stroke and traumatic brain injury (TBI) to Parkinson's disease (PD), Alzheimer's disease (AD), and depression, as well as potentially offering cognitive augmentation among healthy individuals.

... significant improvements in memory, executive function, and mood disorders, as well as promising therapeutic avenues for stroke, TBI, and neurodegenerative diseases.

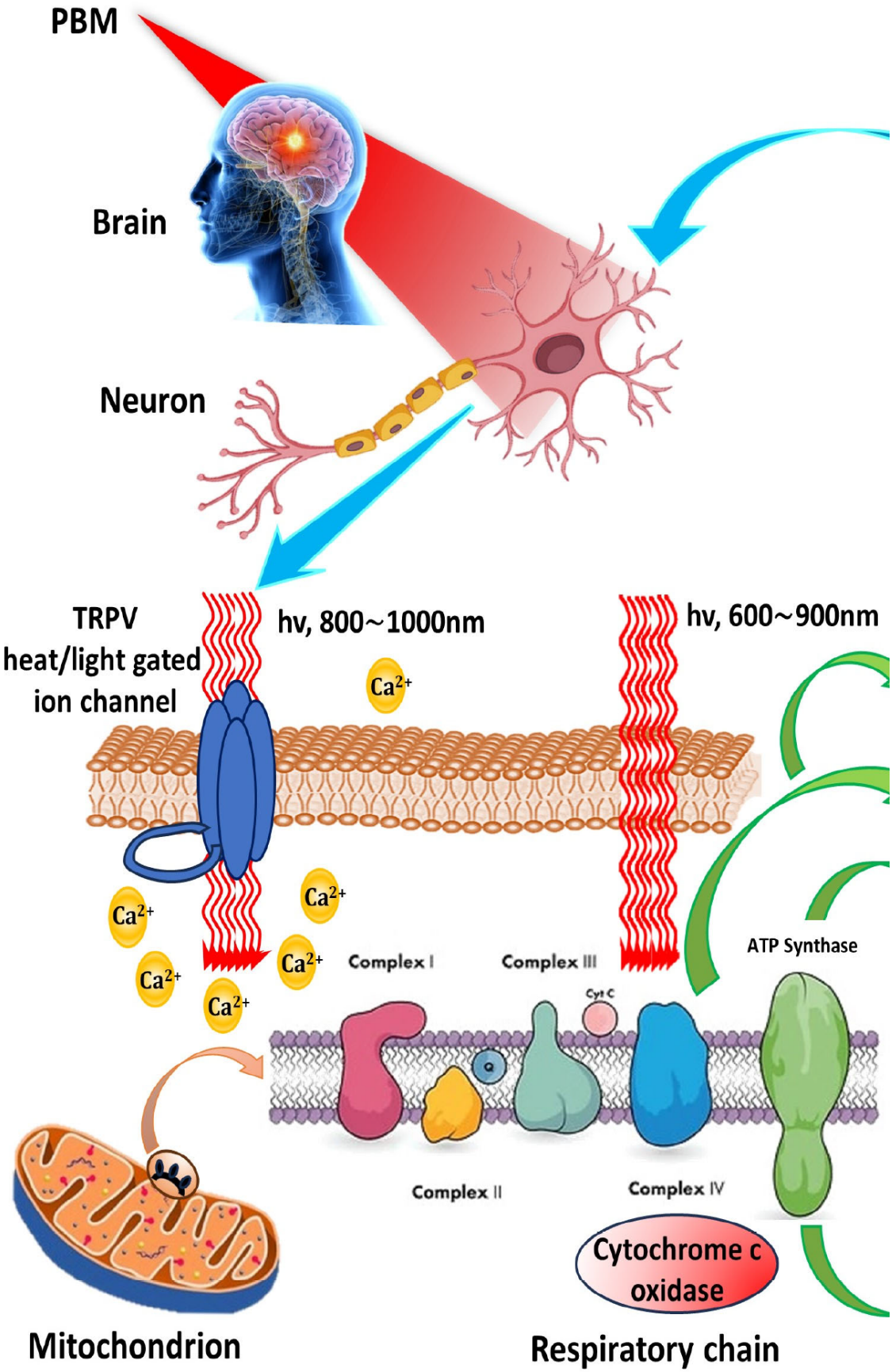
The predominant mechanism underlying PBM revolves around cytochrome c oxidase (CCO), an essential component in the respiratory chain of mitochondria.

... the final enzyme of complex IV of the mitochondrial electron transport chain.

In circumstances marked by hypoxia or cellular damage, nitric oxide (NO) can impede CCO enzyme activity.

Photons absorbed by CCO, especially within the red (600–700 nm) and near-infrared (760–940 nm) spectral ranges, can dissociate inhibitory NO.

This dissociation event triggers a cascade of effects: a surge in mitochondrial membrane potential, enhanced oxygen consumption, and intensified glucose metabolism, culminating in an amplification of ATP production within the mitochondria.


PBM
Brain
Neuron
TRPV
heat/light gated
ion channel
hv, 800~1000nm
hv, 600~900nm
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Complex I
Complex III
Cyt C
ATP Synthase
Complex II
Complex IV
Cytochrome c
oxidase
Mitochondrion
Respiratory chain

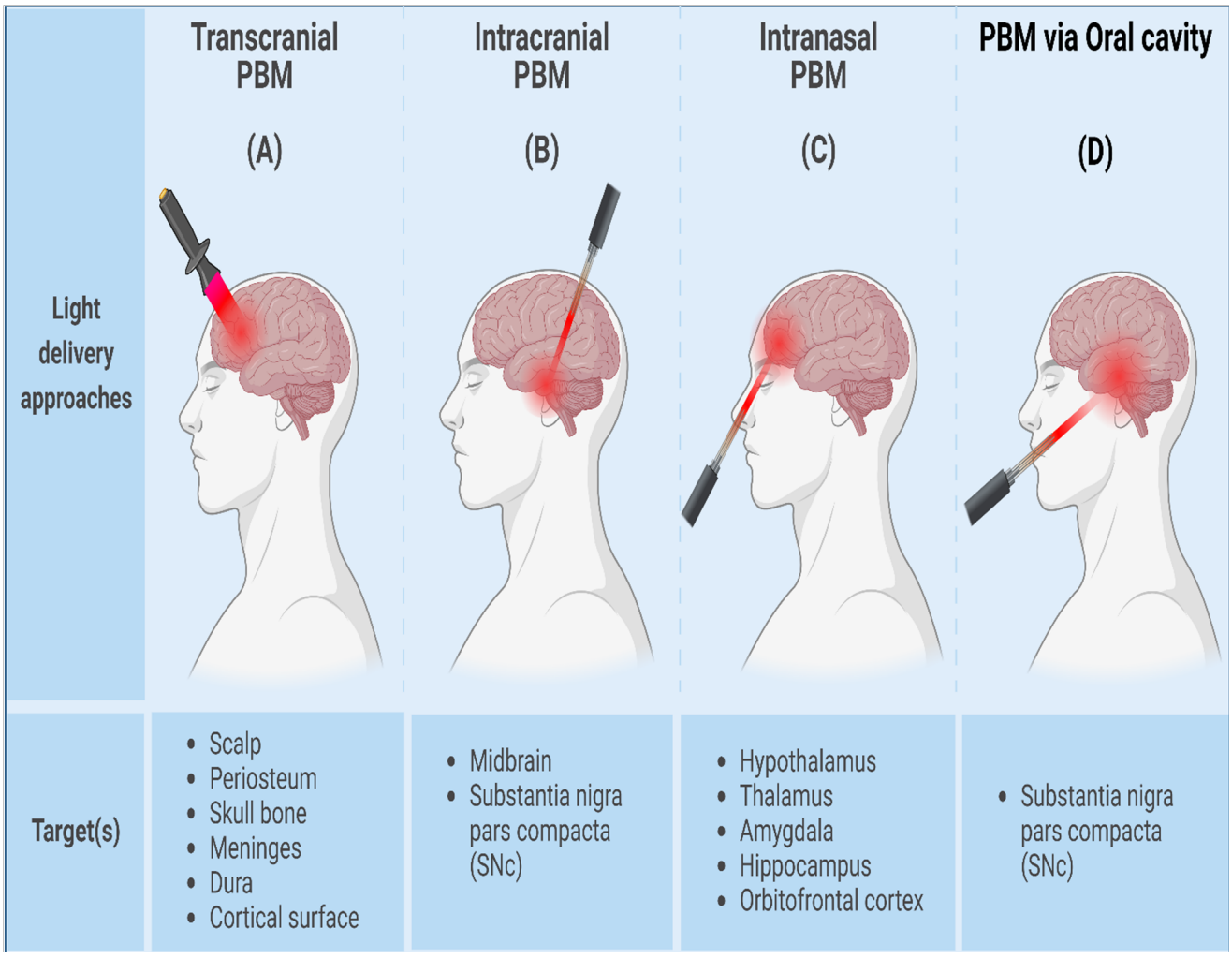
While green light has less practical clinical use due to its limited tissue penetration, infrared and near-infrared light are more promising.

As water predominantly absorbs infrared light ... [it] could conceivably induce alterations in protein conformation, potentially leading to the opening of ion channels.

PBM is thought to elicit retrograde mitochondrial signaling, an intriguing process where communication occurs between mitochondria and the cell nucleus, contrary to the typical flow of signals from the nucleus to other organelles.

Karu's insights suggest supplementary pathways, including directly increasing the expression of particular genes.

Transcranial photobiomodulation (tPBM) entails the non-invasive process of delivering light emitted by an external source, like a laser or LED, through several layers of the head, starting from the scalp, periosteum, skull bone, meninges, and dura, ultimately reaching the surface of the brain cortex.

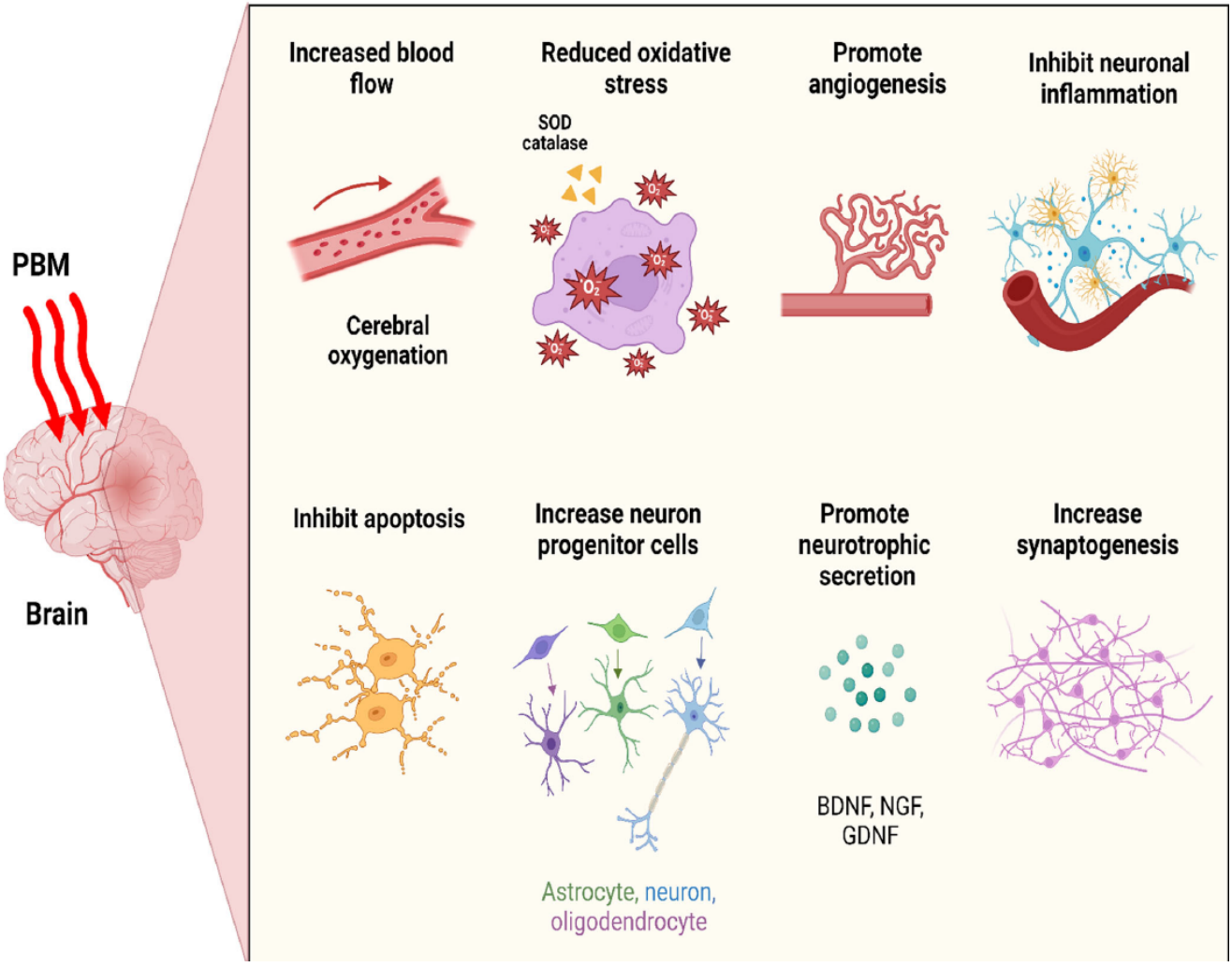


There is also promising evidence that light radiation via the nasal and oral cavities can improve symptoms of dementia and PD.

Combining light exposure through the sphenoid sinus and mouth cavity ... demonstrated cognitive and functional improvements in dementia patients.

A contentious issue yet to be definitively resolved is whether or not coherent monochromatic lasers outperform non-coherent LEDs.

At the pinnacle of brain photobiomodulation therapy, pivotal outcomes emerge: optimizing cerebral metabolic activity, enhancing blood flow and angiogenesis, mitigating apoptosis while bolstering antioxidant levels and diminishing inflammatory responses, promoting neurotrophins secretion, fostering the activation of neuroprogenitor cells, and facilitating synaptogenesis, thereby enabling the formation of novel neuronal connections.



BDNF = brain-derived neurotrophic factor; GDNF = glial-derived neurotrophic factor; NGF = nerve growth factor; SOD = superoxide dismutase

Mitochondria undergo significant alterations under pathological circumstances, including diminished activity for respiratory chain complexes and attenuated ATP synthesis, alongside excessive ROS production, mitochondrial membrane potential (MMP) disruption, a transition of permeability in the inner mitochondrial membrane, and the subsequent discharge of cytochrome c in the cytosol.

Therefore, mitochondrial malfunction plays a critical role in the progression of numerous neurological and psychological disorders.

Neural tissue is notably abundant in mitochondria, and is thus highly responsive to light interactions, particularly with CCO, a key player in neuronal energy metabolism.

Neural tissues exhibit profound reliance on ATP generated by mitochondria for energy demands.

Diminished blood flow within the cerebral vasculature often represents one of the initial indicators of various brain disorders.

Nitric oxide (NO), a potent vasodilator, has the potential to be released from its binding sites during PBM via photodissociation in the respiratory chain.

PBM can widen blood vessel diameter, elevate NO levels in the brain, and enhance CBF.

PBM therapy on specific brain regions may influence regional CBF.

PBM has emerged as a potent modulator of angiogenesis, thereby facilitating improved blood flow.

Mitochondria are significant contributors to oxidative stress as they generate reactive oxygen species (ROS) that detrimentally impact neurons by impairing their mitochondrial functionality. A burgeoning body of literature has revealed links between oxidative stress and neurological conditions like AD, TBI, stroke, and major depressive disorder (MDD).

The beneficial or adverse impact of PBM is intricately tied to mitochondrial ROS production. While low PBM doses induce mild mitochondrial ROS, affecting cellular signaling, higher doses, can prompt excessive ROS generation, potentially activating cellular apoptosis.

The prolonged and excessive release of NO can exert neurotoxic effects, potentially leading to tissue damage.

Brain PBM emerges as a crucial initial intervention for ameliorating mitochondrial dysfunction induced by oxidative stress.

Neuroinflammation, a hallmark of brain disorders, is primarily facilitated by activated microglial cells.

Following various neuronal injuries, microglia undergo a cascade of morphological and proliferative changes, culminating in the secretion of pro-inflammatory mediators such as cytokines, chemokines, NO, and ROS.

PBM intervenes in this inflammatory cascade by impeding NF-κB signaling pathways, thereby lowering the release of pro-inflammatory cytokines and mitigating inflammatory reactions.

PBM has been shown to reduce pro-inflammatory cytokines such as IL-1β, IL-6, TGFβ, and TNFα.

PBM exhibits a profound ability to downregulate the expression of ROS-generated inducible nitric oxide synthase (iNOS), further underscoring its anti-inflammatory potential.

There is abundant evidence indicating that PBM can be employed for neuroprotection, enhancing the survival and lifespan of neuronal cells by significantly ameliorating neuronal apoptosis through anti-apoptotic effects.

The potential of PBM to enhance both synaptogenesis and neurogenesis is one of its most remarkable and substantial effects on the brain.

PBM facilitates neuronal connectivity by intricately regulating the expression and function of different neurotrophic factors (neurotrophins) including brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and nerve growth factor (NGF).

PBM can also stimulate the generation of neuroprogenitor cells, similar to neural stem cells, which could positively impact neurogenesis.

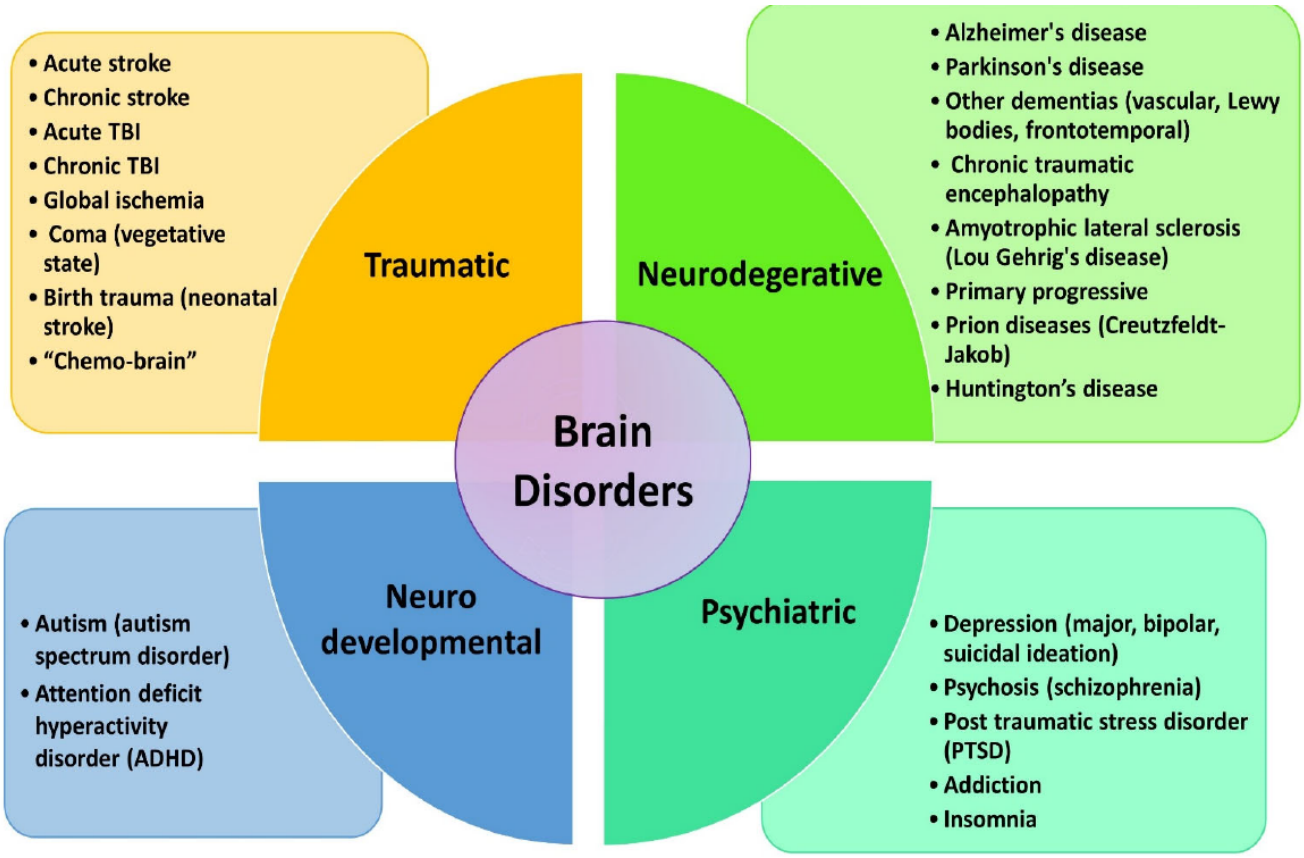
While direct brain PBM is considered the predominant therapeutic approach, there is a burgeoning understanding of neuroprotective effects stemming from irradiating specific non-brain regions. This implies that the light stimulation of certain organs may yield systemic benefits that indirectly influence the brain.

... enhanced immune cell activity, the modulation of cytokines, and increased mitochondrial ATP levels.

Mesenchymal stem cells may be mobilized via PBM of the bone marrow, allowing them to migrate to the brain and potentially restore cognitive function in AD patients as the disease progresses.

Particularly, noninvasive multisensory 40 Hz stimulation, comprising combined light and sound stimulation, reduces amyloid deposition across the cortex, notably the prefrontal cortex, thereby enhancing neural activity in an Alzheimer's disease.

A wide array of disorders afflicts the brain, and are broadly categorized into four groups: traumatic events, degenerative diseases, and neurodevelopmental and psychiatric disorders that could potentially benefit from various forms of transcranial photobiomodulation therapy.



As people age, there is often a decline in cognitive functions, making the enhancement or preservation of these abilities particularly important, especially for older adults who face increased susceptibility to dementia.

PBM therapy targeted towards the prefrontal region might enhance the brain's hemodynamics as well as oxygenation, which are critical to higher-level cognitive functions.

The future prospects of PBM in the field of neuroscience appear exceedingly promising, owing to its remarkably positive outcomes in animal models and the encouraging results from initial clinical trials.

Given the considerable challenges encountered in developing pharmaceutical interventions for conditions like stroke.

The favorable outcomes demonstrated by brain PBM therapy in mitigating symptoms of depression and anxiety may pave the way for novel trials targeting a broader range of psychiatric disorders including bipolar disorder, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), as well as schizophrenia and autism.

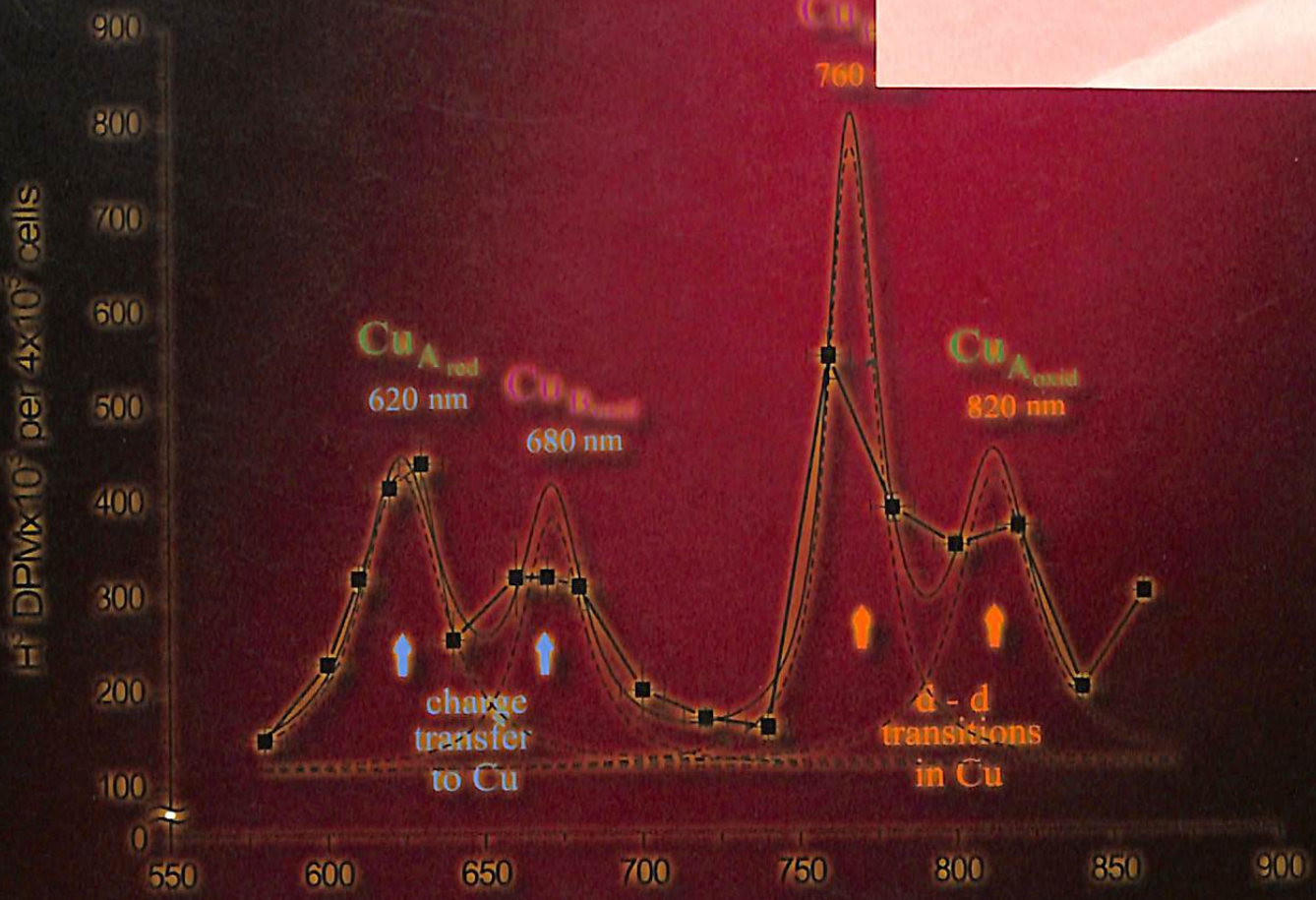
Considering PBM's well-documented safety profile and its notable absence of adverse effects, alongside its relative cost-effectiveness, there is a strong argument for initiating comprehensive clinical trials for these indications. Furthermore, the disappointingly low efficacy rates and often distressing side effects associated with conventional psychiatric medications, such as antidepressants, highlight the need for novel therapeutic modalities like PBM.

This study cites 172 references.

Ten Lectures on Basic Science of Laser Phototherapy

Tiina Karu

2007



Ten Lectures on Basic Science of Laser Phototherapy

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Prima Books
2007

"One of the most important biological mechanisms based on activation/upgrading of the terminal enzyme of the mitochondrial respiratory chain, **cytochrome *c* oxidase**, is shown to be a universal mechanism controlling many aspects of the metabolism in different types of irradiated cells." Back Cover

"Monochromatic light in the visible-to-near region can be a subtle instrument to regulate cellular metabolism." (1)

Laser radiation can modulate cell metabolism through the mediation of a universal photoreceptor. **Cytochrome *c* oxidase** is an enzyme that catalyzes the final step in the mitochondrial respiratory chain. (2)

"**Cytochrome *c* oxidase** plays a central role in the bioenergetics of the cell." (120)

Laser irradiation may cause a shift in the cellular redox state. (4) Cells respond to the light stimulus in stronger or weaker manner depending on their redox potential at the moment of the irradiation. (113)

"Upgrading of **cytochrome *c* oxidase** may prove a protective influence against the detrimental effects of environmental pollutants like chemicals and ionizing radiation." (5)

Laser irradiation can reduce the formation of scar tissue. (6)

Laser phototherapy may be useful in reducing the severity of chemotherapy or radiation therapy. (9)

Laser irradiation can enhance bone repair about two-fold. (10)

632.8 nm laser irradiation can modulate immune responses. (12)

"Laser phototherapy is used by physiotherapists (to treat a wide variety of acute and chronic musculoskeletal aches and pains), by dentists (to treat inflamed oral tissues and to heal diverse ulceration), by dermatologists (to treat edema, indolent ulcers, burns, and dermatitis), by rheumatologists (to relieve pain and treat chronic inflammation and autoimmune diseases), and by other specialists, as well as by general practitioners. Laser phototherapy is also widely used in veterinary medicine (especially in racehorse-training centers) and in sports medicine and rehabilitation clinics (to reduce acute swelling and hematoma, relieve pain, improve mobility, and treat acute soft-tissue injuries." (21-22)

Clinical treatment laser dose intervals are generally administered on a daily or every other day basis. Multiple laser treatments enhanced the collagen growth in the repairing ligaments, superior to a single treatment with a similar dosage. (76-77)

Mitochondria are sensitive to irradiation with monochromatic visible and near IR light. (116)

Cytochrome *c* oxidase "plays a central role in the bioenergetics of the cell." (120)

Cytochrome *c* oxidase "is the photoacceptor responsible for various cellular responses connected with light therapy in the red-to-near IR region." (124)

"It is well known that it is only in the ideal case where the supply of electrons from **cytochrome *c* oxidase** is unlimited that electrons are always present to reduce oxygen," thus maximizing production of ATP and minimizing production of oxygen free radicals. (134)

Monochromatic visible and near IR radiation in initially absorbed by the mitochondria and eventually causes stimulation of DNA synthesis. (197)

"It is known that even small changes in the ATP level can significantly alter cellular metabolism. However, in many cases the regulative role of the redox homeostasis has proved to be more important that that of ATP." (198) This is because the redox-based regulation of gene expression appears to represent a fundamental mechanism in cell biology. (200)

In a laser irradiated muscle, the density of mitochondria increases. (205)

With laser irradiation, there is a "significant upregulation of gene expression involved in mitochondrial energy production and antioxidant cellular protection." (205)

Irradiation with monochromatic bands of visible light can change the redox properties of some respiratory chain components and therefore increase electron flow in the respiratory chain." (212)

Mitochondrial DNA plays a role in the processes of ageing and carcinogenesis. (222)

"Irradiation at 630-760 nm cannot cause mutations through direct action upon DNA. The energy of these photons is too low to cause ruptures of covalent bonds in a molecule." (248)

Laser irradiation can generate an electrical impulse in neurons, the action potential. "The action potential depended on the wavelength: the effect was strong at 540 and 632.8 nm, but radiation at 904, 660, 830, 880, and 950 nm had no effect." (277)

"The activation of cells via the mitochondria is suggested to be a universal photobiological mechanism." (305)

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

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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

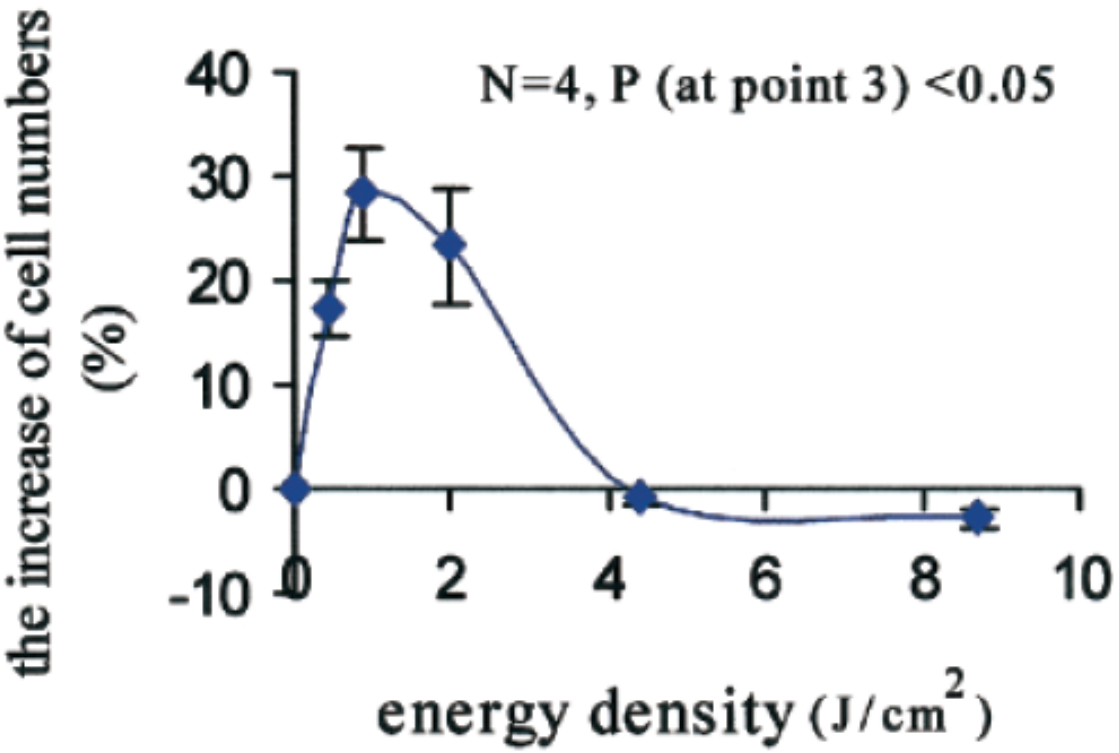
et al, 2001). Previous studies showed that low-intensity red laser light was capable of affecting cellular processes in the absence of significant thermal effects (Karu, 1989). Fibroblasts are an important cellular component of wound healing, and it has been re-

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;

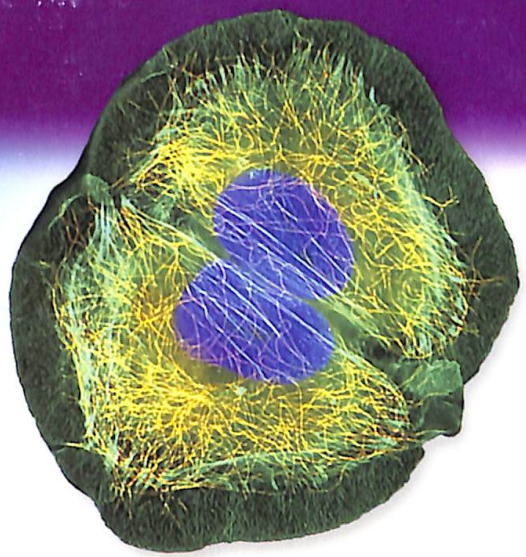
of the tissue culture plates at the irradiation distance of 0.75 cm. Samples were irradiated for various time periods to yield final energy doses of 0, 0.44, 0.88, 2.00, 4.40, and 8.68 J per cm^2. The temperature was monitored

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

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)

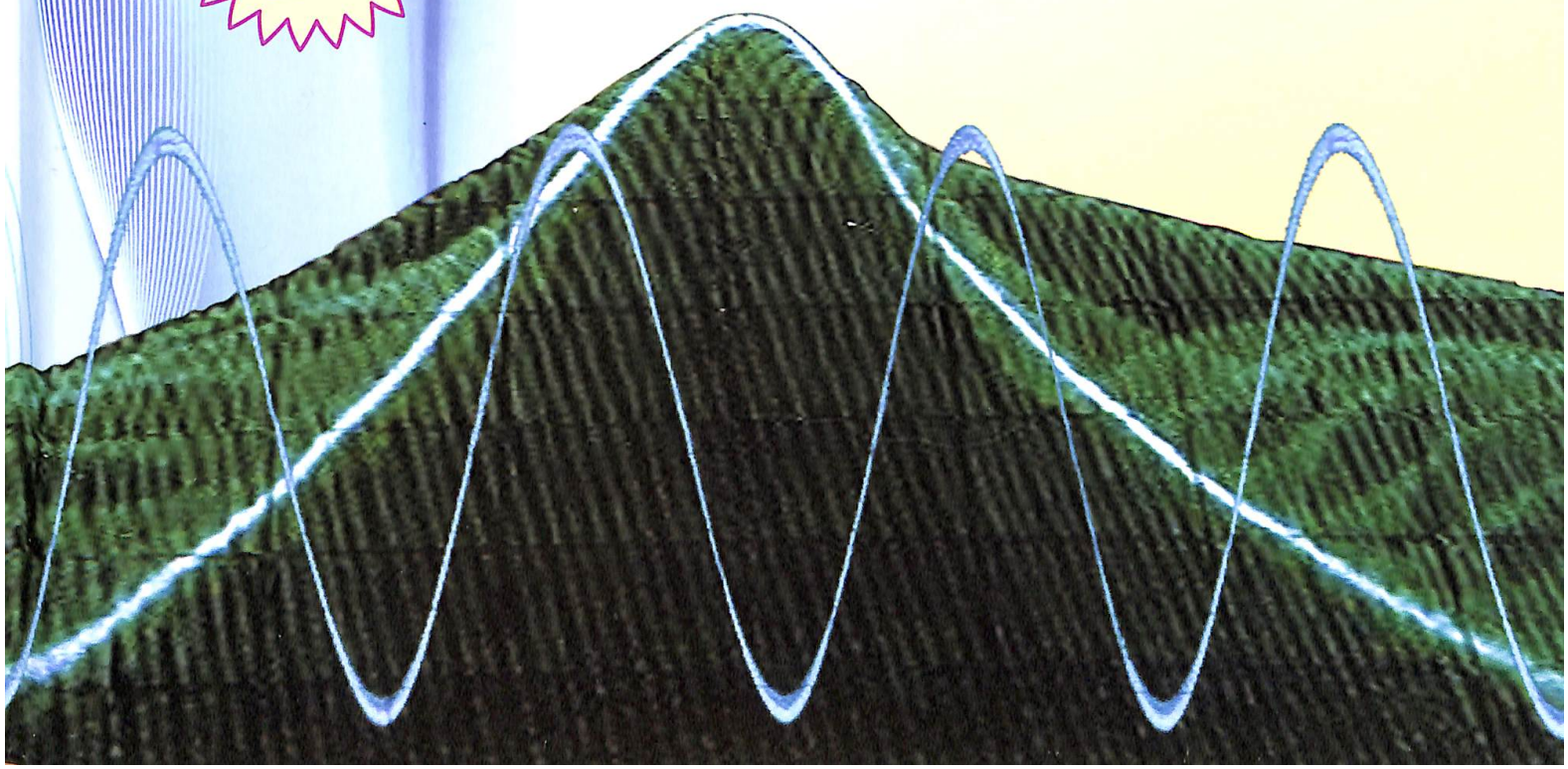
Nenah Sylver, PhD



The Rife Handbook

of Frequency Therapy and Holistic Health

REVISED 2011 EDITION



Nenah Sylver, PhD

The Rife Handbook of Frequency Therapy and Holistic Health

Royal Rife's Universal Microscope weighed 200 pounds, had 5,682 parts, and stood between 2 and 3 feet high. It was completed in 1933.

Rife used pulsed *radio* waves to find a pathogenic microbe's Mortal Oscillatory Rate.

"[It is] now known that selected [pulses] can regenerate tissues." 675

"Pulsing a wave means that the signal is 'on' for a brief period, then off, then on, then off, etc. Pulsing is independent of the frequency." 670 **[Key Point]**

[in light, frequency (wavelength) is a single color; in sound, frequency (wavelength) is a single note][pulsing is the rhythm]

"Any frequency can be pulsed." 670 **[Key Point]**

[In electromagnetic devices, pulsing will] "induce movement into the body. The movement of the EM radiation in the body translates into ion transport, increases in blood and lymph flow, and more." 670

"Pulsed electromagnetic radiation induces therapeutic results, which is why it is used." 671

"[Pulsing] means there is an 'off' period to the signal, it ensures that the human or animal receiving the signal does not become resistant to its effects. That is one of the secrets of electromedicine devices that are effective." 673 **[Key Point]**

"Correctly employed [pulsing] can increase cell energy, normalize membrane conductivity, lessen oxidative stress, reduce amounts of inflammatory chemicals in the blood, improve protein synthesis, boost feel-good endorphins, restore depleted adrenal function, and enhance immune function. The restoration of these metabolic processes leads to the regeneration of tissues as well as resistance to disease." 673

"Pulsing light stimulates healing." 680

"'Bigger is better' and 'More is better' figure prominently in the Western mindset."

"'Less is more'—reflects what the body usually needs. The exquisite sensitivity of cells to electromagnetic fields of all kinds explains why electromedical devices work—and why more gentle ones work the best. Low power energies might not be easily perceived subjectively, but they are the most compatible with living systems precisely because they are of lower power." 673

"Lasers and LEDs (short for *Light Emitting Diodes)* can be made to produce any color wavelength. The emission of the light (whether it's a red, green, blue, or other color) is due not to glass, paint, or pigment—it is solely the wavelength of the light itself that gives the beam its characteristic color. Since the wavelength is always a single frequency, the color is known as *monochromatic.*" 679

"Laser and LED therapies differ in some important ways, but they also share similarities. Both light technologies are based on the energetic behavior of electrons. Normally, electrons occupy a fixed place in one or more orbital rings that sequentially surround the atom's nucleus. When they become excited, electrons move faster and jump to higher orbits. When they relax and return to their original position, electrons release energy in the form of light, or photon units. The wavelength of a photon—in other words, its color—is determined by the amount of energy released when the electron drops to a lower orbit. *It is this emitted light that is harnessed in visible light laser and LED technology.*" 679

"The frequency being used is almost always identified by the length of the wave, rather than the actual frequency itself as described in hertz. In the band of visible light, wavelengths are measured in nanometers (nm). One nanometer, the length of one complete wave, is one billionth of a meter and roughly about the size of a human cell."

"Research published in the *Journal of Clinical Laser Medicine Surgery* stating that a 630-nm wavelength appears "to be most commonly associated with bacterial inhibition. The findings of this study might be useful as a basis for selecting LLLT (low level laser therapy] for infected wounds." [ATTACH ABSTRACT Nussbaum] 680

"In this case, 'bacterial inhibition' consists of the retardation of the growth and functioning of pathogens. What is good for the body is usually bad for pathogens..." "635 nm is the worst wavelength for most pathogens but is beneficial for human tissue." 680

"Monochromatic red light stimulates blood circulation, increases lymphatic drainage, and promotes cell metabolism by stimulating photoreceptors in the mitochondria living within the cell. (Mitochondria are tiny living organelles with their own DNA and reproduction cycles, which live in symbiotic harmony with the cell, and control many important cellular processes including energy production.)" 680

"Except on the eyes in the case of a laser, the light can be applied to every part of the body: skin, soft tissue, muscle, bone, brain, organs, lymphatic fluid, glands, and blood. Used over an artery, the light can improve the condition of immune cells—leukocytes, T-cells, and B-cells within the bloodstream so they can more efficiently disable pathogens." 680

"There are photoreceptors at the molecular-cellular level which, when triggered, activate a number of biological reactions: DNA/RNA synthesis, increased cAMP levels [cyclic adenosine monophosphate, a molecule involved in many biological processes], protein and collagen synthesis, and cellular proliferation. The result is rapid regeneration, normalization, and healing of damaged cellular tissue. In essence, light is a trigger for the rearrangement of cellular metabolism." 680

"Single-wavelength light maintains its integrity while radiating. Its ability to travel along the meridians of the body without being dispersed into the surrounding tissues." 680

In low-level laser therapy, "the energy output is low enough so that the treated tissue does not rise above . . . normal body temperature." 681

"*Pulse* refers to the number of times the beam of light is turned on and off in one second." "Even though the eye cannot detect movement above 45 Hz or so...," the body's tissue can clearly detect and recognize these pulse rates." 681

"Laser therapy works on all manner of conditions. These include injuries to ligaments, tendons, nerves, and other tissue; skin conditions; bone problems such as osteoarthritis); first, second, and third-degree burns; dental problems; infections including herpes; and, of course, chronic pain." 681

"The laser beam can be applied without risk to almost any part of the body (including trigger points and fascia). However, due to the precision of the beam, care must be taken to avoid shining the device directly into the eyes or even on the closed eyelid, because this can cause tissue damage and even blindness." 681

"LED is an acronym for *Light Emitting Diode*. It is sometimes erroneously called a soft laser or laser, but it is not—the monochromatic light emitted by *LEDs is incoherent.* This means, from a physics standpoint, that the waves are emitted at random intervals because the peaks and valleys of the waves do not line up. In practical terms, this means that the light is multi-directional and diffuse, *not* directional and focused (collimated)." 681

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



Short Wavelengths

High Frequency

High Energy

Cause Mutations (genetic damage)

Does Not Penetrate Well

405
Violet

520
Green

635
Red

Long Wavelengths

Low Frequency

Low Energy

Does Not Cause Mutations

Better Penetration

Opens Ca++ Channel (VGCIC)
(Free Radicals; Genetic Damage; Cell Death)

Alters Shape of Vitamin D Receptor
(Immunology; Autoimmunity)

Havana Syndrome?

5G
1-10 mm
Millimeter W
1000 ft range

4G
150-450 mm
Centimeter Wave
10 mile range

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

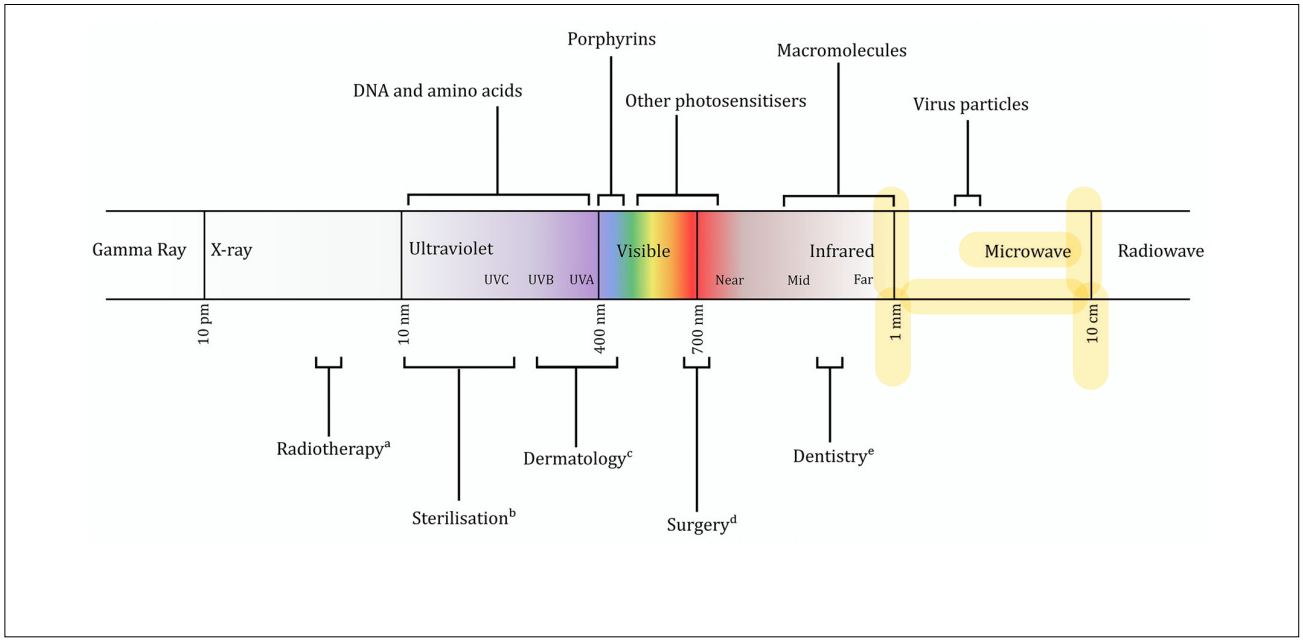


TABLE 1 | Optical properties of selected wavelengths in skin.

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).

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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

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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.

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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

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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

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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

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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.

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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

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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

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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.

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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.

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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

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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

What is Light Coherence?

Light coherence is important for deep-tissue photomedicine because it forms microscopic intensity patterns called laser *speckles* that increase the probability of photon absorption.

Coherence means order or synchronicity. It describes light waves that maintain a steady phase relationship with each other over distance and time. While standard light sources like LEDs emit chaotic, uncoordinated waves (incoherent light), lasers emit highly organized and coherent light.

Why Coherence Matters for Deep Tissues

Laser Speckles:
When coherent light enters tissue, it creates a pattern of tiny spots called *speckles* that have higher light intensity.

Overcoming Low Flux:
In deep tissue, most light gets scattered or absorbed before reaching deep targets. The high-intensity peaks inside individual *speckles* help the light cross the threshold needed to trigger a biological response.

Better Penetration:
Coherent laser light often penetrates deeper through structures like bone or thick tissue compared to non-coherent LEDs of similar power.

When Coherence Matters Less

Superficial Treatments:
For shallow wounds, skin surface issues, or hair growth stimulation, non-coherent polarized light and LEDs often perform just as well as coherent lasers.

Basic Absorption:
The primary chemical trigger in light therapy is photon absorption by the mitochondria, which depends on the wavelength and dose. Research reviewed by the National Institutes of Health shows that coherence acts as an optimizer for specific deep targets.

The importance of coherence in phototherapy

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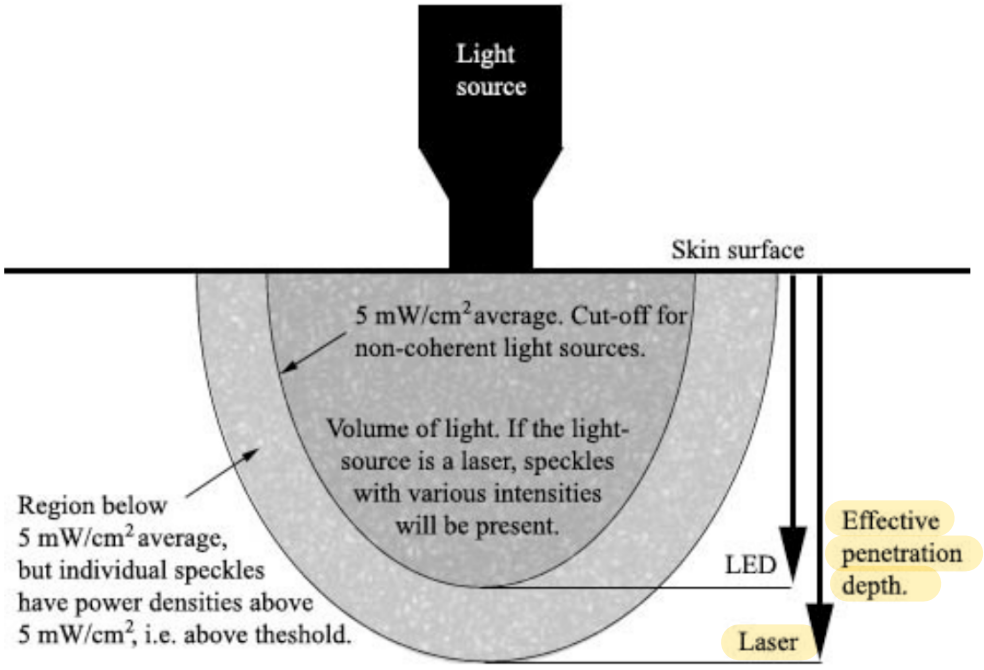
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... account for the effects of laser speckle *in vivo*. Laser speckles intensity is higher than the surrounding environment. This is important because the probability for a photon absorption event to occur largely depends on intensity and the photon absorption of the molecule.

In deep tissue where the photon flux is extremely low, the increased probability of photon absorption from individual laser speckles increases the probability of reaching the necessary power density thresholds.

Because of the non-coherent nature of radiation from light/IR emitting diodes speckle does not occur in the tissue with LED therapy, which may explain why head-to-head comparisons between lasers and LEDs in deep tissue seem to be in favor of lasers.

Several comparative studies have shown that laser phototherapy appears to be more effective than LED phototherapy in the treatment of deeper indications, as well as in in vitro and wound healing studies.



Before any speckle-effects in tissue can be discussed it is important to clarify that coherence is not lost in a scattering media (such as tissue), only reduced.

In the case of coherent light (where a speckle field is present), there will be individual speckles with intensities of up to 5X the average intensity, which means that tissue situated deeper than the average power density threshold cut-off will be exposed to power densities above the phototherapeutic threshold.

In other words, the effective penetration depth of coherent light-sources (i.e. lasers) is greater than for non-coherent light-sources (e.g. LED's).

The speckle intensity distribution shows intensities of up to five times the mean intensity will randomly occur in the speckle field.

The coherence is not lost when tissue is illuminated with a laser, which means that a 3-dimensional speckle pattern will appear in the tissue during laser phototherapy, but not when non-coherent light sources are used.

The speckle pattern has a significant impact on the effective penetration depth of in vivo laser phototherapy since it becomes easier to reach the required intensity thresholds.

In a clinical setting, this increased effective depth of penetration can make the difference between having to rely on systemic effects vs. getting direct effects in the target tissue.

Our simulations suggest that intensities of up to five times the mean intensity occur in a speckle field.

These observations could also explain why LED phototherapy in many cases appears to be comparable to laser phototherapy for superficial indications such as wound healing, but not as effective as laser phototherapy in cases of deeper-seated indications.

Photomedicine and Laser Surgery
Volume 33, Number 4, 2015
© Mary Ann Liebert, Inc.
Pp. 183–184
DOI: 10.1089/pho.2015.9848

Editorial

Low-Level Light/Laser Therapy Versus Photobiomodulation Therapy

Juanita J. Anders, PhD,[1] Raymond J. Lanzafame, MD, MBA,[2] and Praveen R. Arany, DDS, PhD[3]

Niels Ryberg Finsen pioneered the use of red and blue light to treat various human ailments, especially Lupus vulgaris.

He was awarded the Nobel Prize in medicine and physiology in 1903 for his pioneering demonstration that concentrated chemical rays from sunlight could be bactericidal as well as stimulating surrounding tissue.

Mester et al. noted that laser light at low doses demonstrated increased hair growth at an accelerated rate, and promoted excisional wound healing. This observation was termed "laser biostimulation."

In addition to biostimulation, a few of the other names previously used for this therapy have included low-level laser (or light) therapy (LLLT), low-intensity laser therapy, low-power laser therapy, cold laser, soft laser, photobiostimulation, and photobiomodulation.

There is clearly a dismal lack of consistency and consensus on terminology. The most frequently used term is low-level laser therapy (LLLT).

LLLT, utilizes endogenous chromophores with low-dose illumination delivered at the target site.

... it distinguishes photobiomodulation therapy, which is nonthermal, from the popular use of light-based devices for simple heating of tissues as can be accomplished using near-infrared (NIR) lamps, or other applications of light energy that rely on thermal effects for all or part of their mechanism of action.

It is a nonthermal process involving endogenous chromophores eliciting photophysical and photochemical events at various biological scales.

This process results in beneficial therapeutic outcomes including but not limited to the alleviation of pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration.

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J Appl Biomater Funct Mater. 2019 Jan-Mar;17(1):2280800018816013.
doi: 10.1177/2280800018816013.

Laser versus LED polymerization: Comparison of in vitro preventive sealing procedures

Filiberto Mastrangelo [1], Isabella Perraro [2], Sabrina Mattia [2], Giuseppe Troiano [1], Khrystyna Zhurakivska [1], Elisabetta Polizzi [2], Roberto Chiesa [3], Enrico Gherlone [2], Lorenzo Lo Muzio [1]

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PMID: 30803291 DOI: 10.1177/2280800018816013
Free article

Abstract

Introduction:: The technique of sealing is a widely accepted procedure for prevention of caries. The aim of our in vitro study was to compare the effect of two different curing units (traditional LED source and innovative laser diode lamp) on the integrity of fissure sealant material and its interface with tooth enamel.

Materials and methods:: Sixty healthy third molars were randomly assigned to two groups. In group A were teeth intended for polymerization by LED B lamp, and group B comprised teeth to be polymerized by an innovative laser diode. Both groups were treated with the traditional sealing technique, subjected to a metallization process, and analyzed by scanning electron microscope.

Results:: Micro-gaps between the sealant and the enamel were found in specimens in both A (43%) and B (40%) groups (p=0.793), and sealant shrinkage was seen. Significant differences between the groups emerged in the percentage of perimetric micro-erosion sites (80% vs. 100%, p=0.010) and the presence of holes and micro-bubbles on the sealant surface (21% vs. 63%, p=0.001).

Conclusions:: Although macroscopic clinical polymerization occurred with both instruments, the microscopic evaluation showed significant differences between the studied groups in terms of perimetric micro-erosion sites and micro-bubbles, which were higher in laser-cured samples.

Keywords: LED; Preventive sealing; laser polymerization; polymerization.

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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

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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.

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

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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

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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.

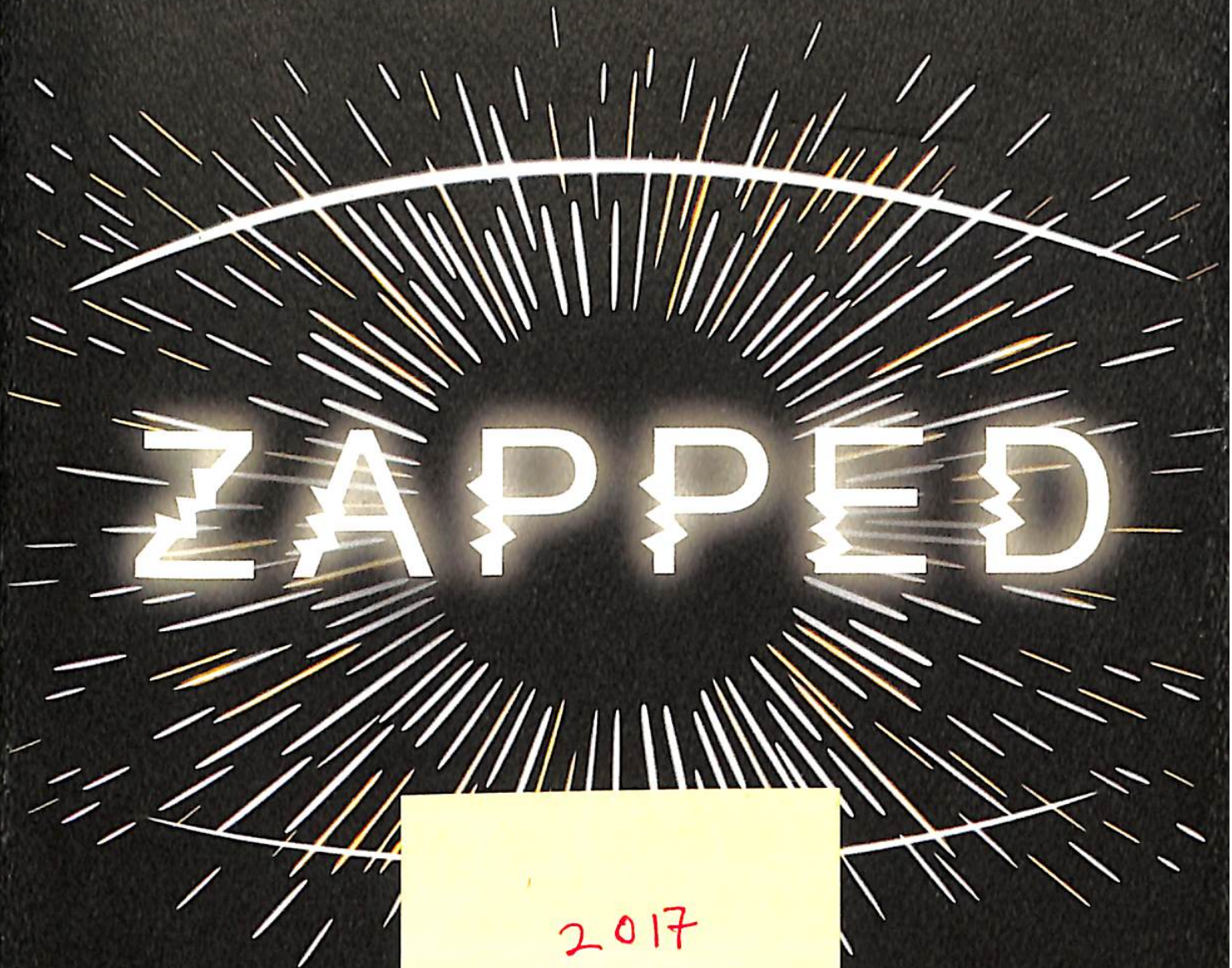
3.1 PBM parameters

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



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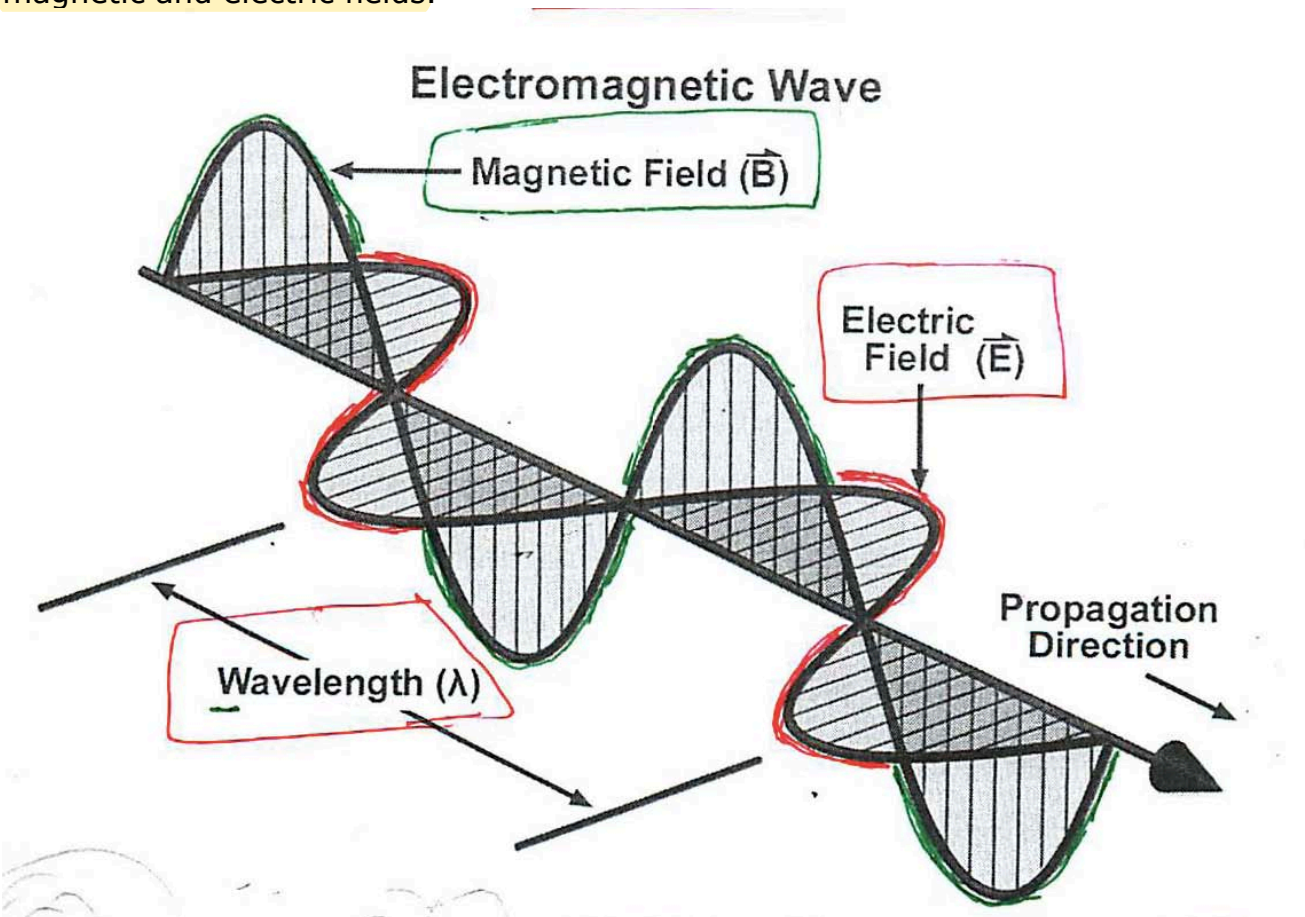
There is a "whole world of light outside our range of vision."

"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*

Light Numbers

Healing is linked to photonic energy (E).

The higher the photonic energy the greater the healing.

All light has a *wavelength*, distance from crest to crest. "*Wavelength* is the distance from one peak of a wave's electrical field to the next peak."

All light has a *frequency*, the period of time it takes the wave to pass you and to be replaced by the next wave. Frequency is the "number of wavelengths that pass you every second."

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

(WL) X (F) = 186,282 miles/second

$$F = \frac{186{,}282}{WL}$$

Plank's Constant (Nobel Prize Physics 1918, Max Plank) = PC

$$E = \frac{(PC) \times (186{,}282)}{WL}$$

E = (PC) X (F)

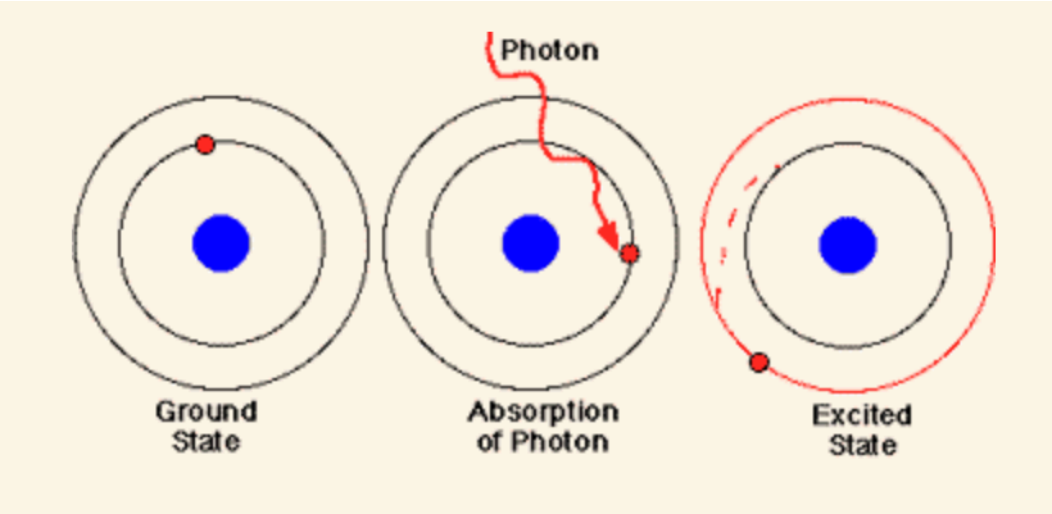
Color Wavelength Frequencies

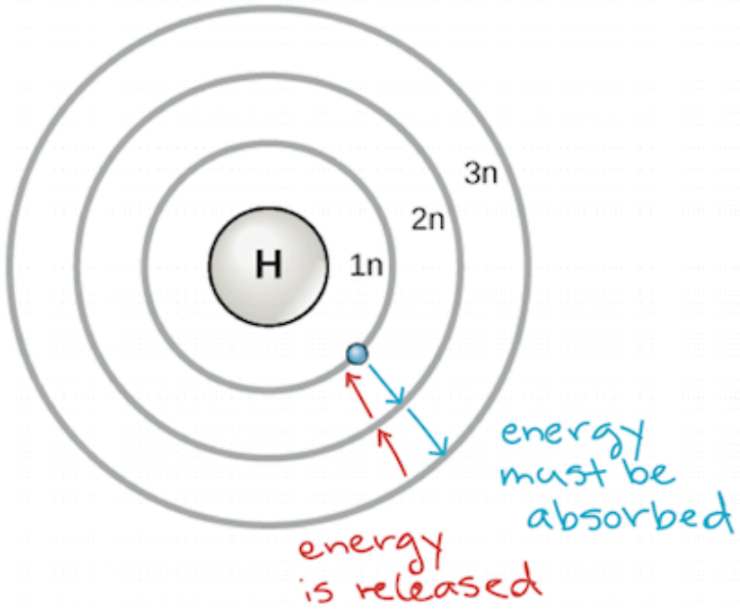
405 nm	535 nm	635 nm	800 nm	Micro	Radio
Violet	Green	Red	Infrared	In - Ft	Ft - Miles
Quadrillion	Trillions	Trillions	Billions	Millions VGCIC VDR	Thousands

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.

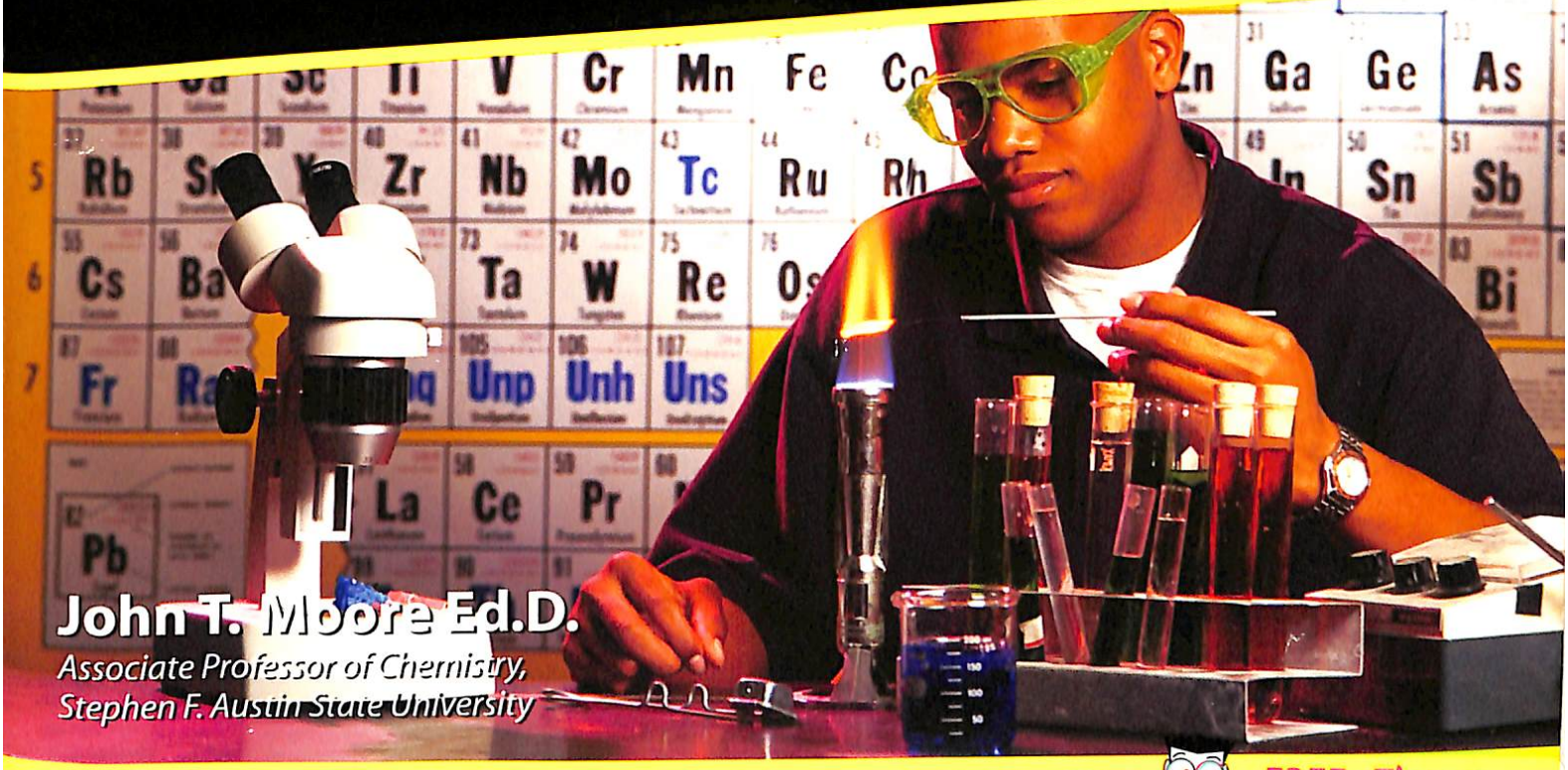




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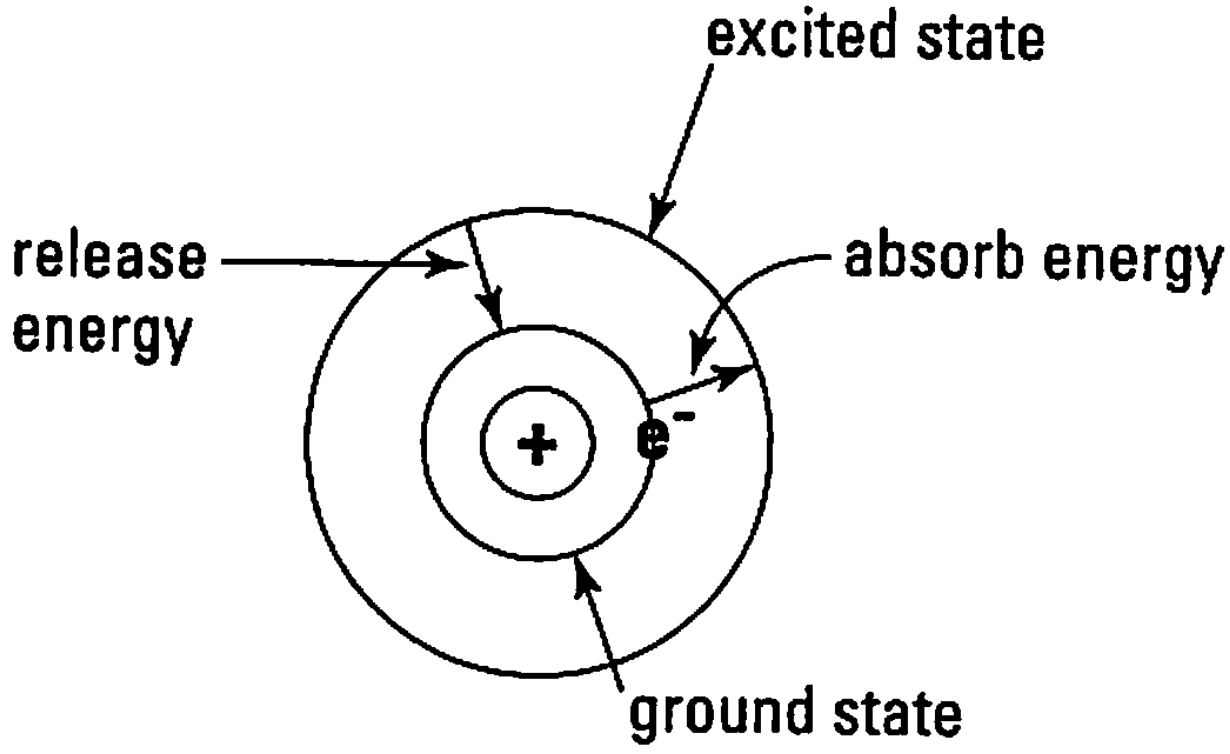


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Niels Bohr (1885-1962, Nobel Prize 1922), a Danish Physicists, showed that electrons in atoms orbit around the nucleus at different energy levels (shells).

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*.

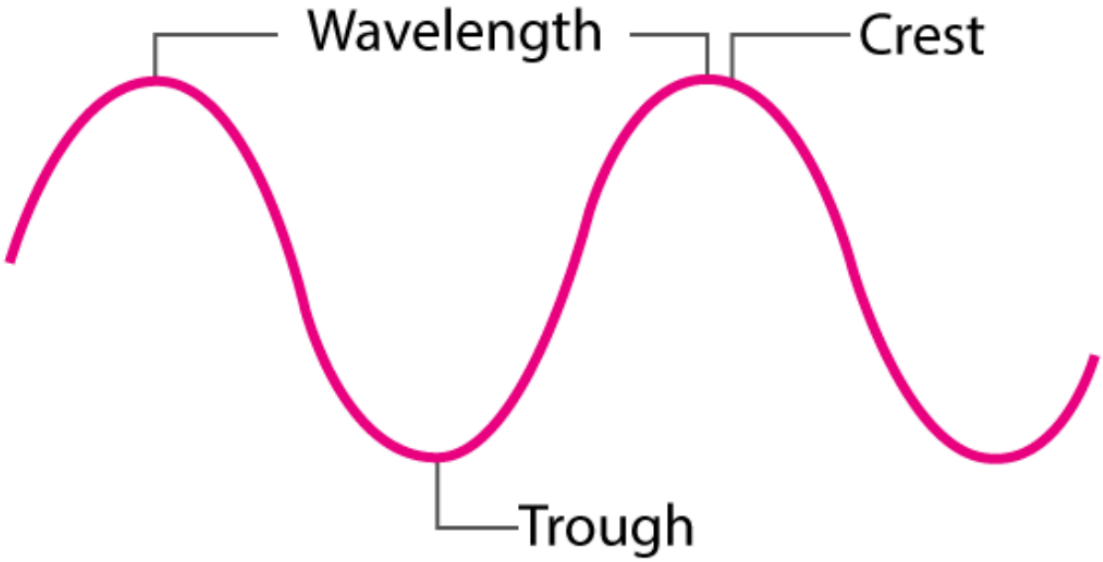
When an excited electron returns to its original ground state, energy is released, and this energy becomes the *electromagnetic spectrum*.



"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

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
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ISSN: 1559-3258
DOI: 10.2203/dose-response.09-027.Hamblin

International Dose-Response Society
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BIPHASIC DOSE RESPONSE IN LOW LEVEL LIGHT THERAPY

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□ 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

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(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

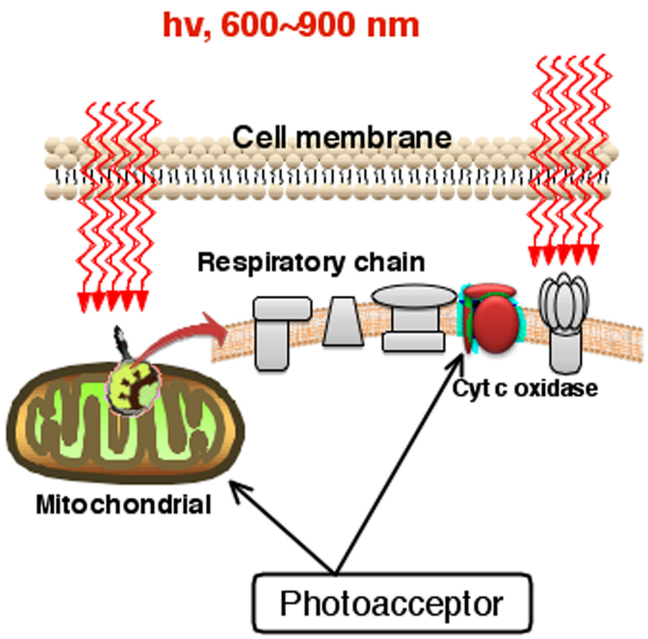


FIGURE 1. Schematic diagram showing the absorption of red and NIR light by specific cellular chromophores or photoacceptors localized in the mitochondrial respiratory chain

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

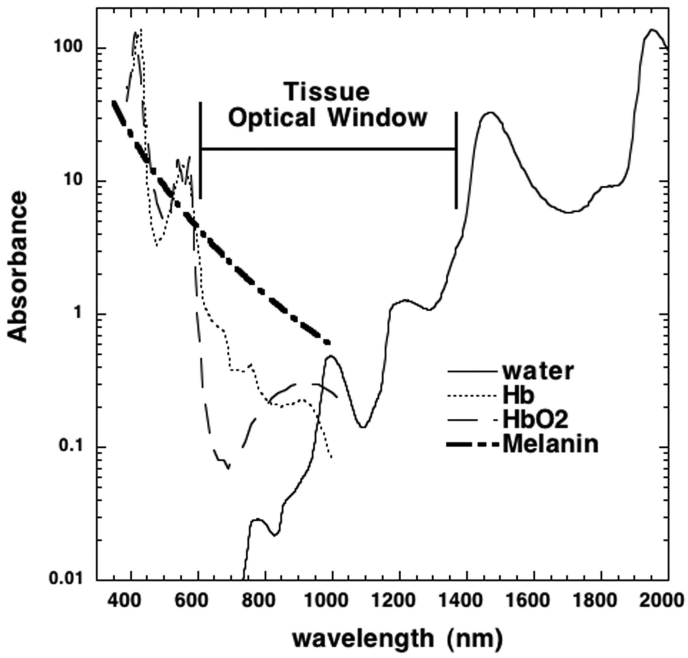


FIGURE 2. Absorption spectra of the main chromophores in living tissue on a log scale showing the optical window where visible and NIR light can penetrate deepest into tissue.

"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

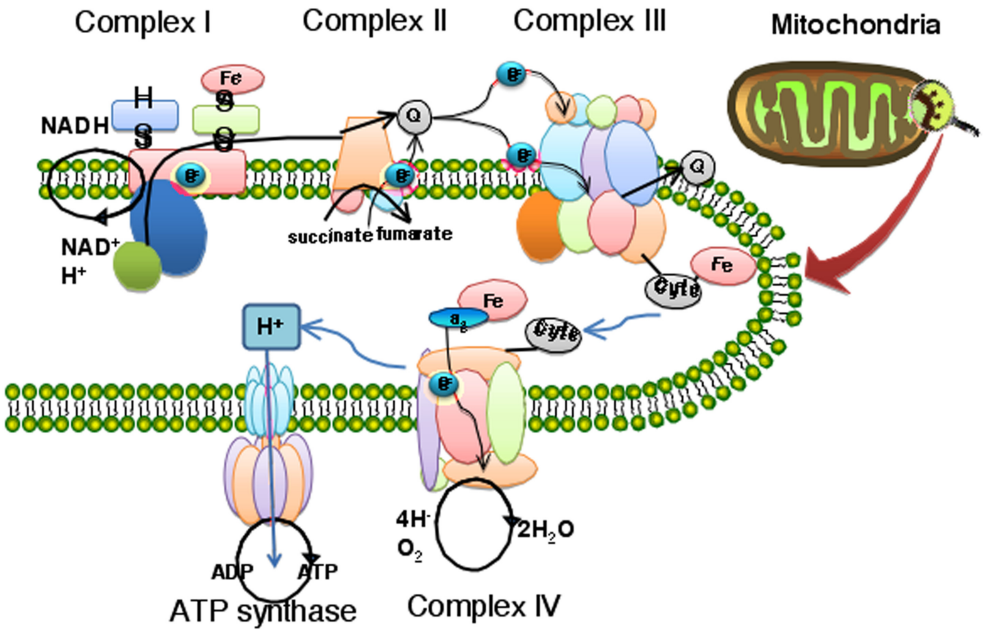


FIGURE 3. Mitochondrial respiratory chain consisting of contains five complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), cytochrome c oxidase (Complex IV), and ATP synthase (ComplexV).

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

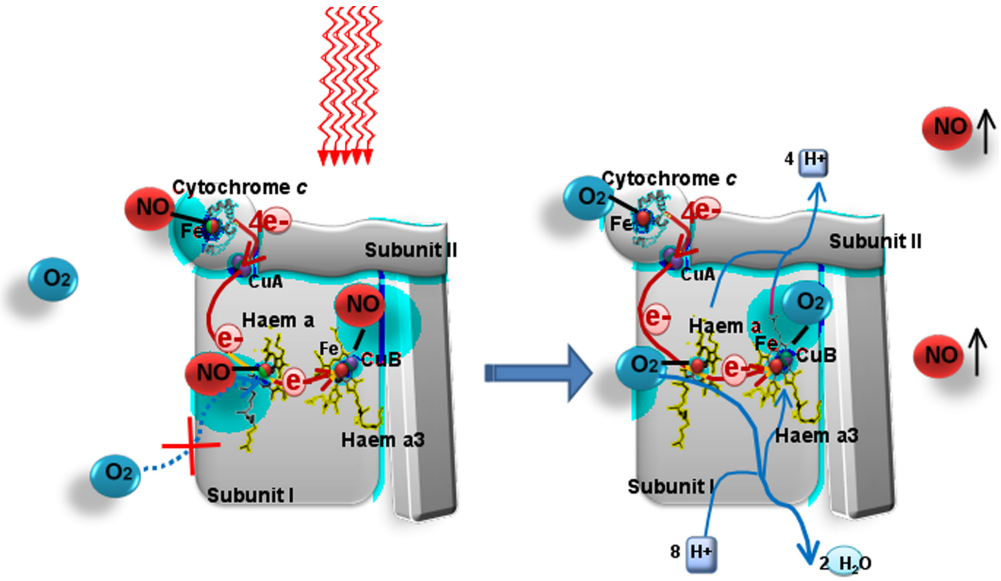


FIGURE 4. When NO is released from its binding to heme iron and copper centers in cytochrome c oxidase by the action of light, oxygen is allowed to rebind to these sites and respiration is restored to its former level leading to increased ATP synthesis.

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

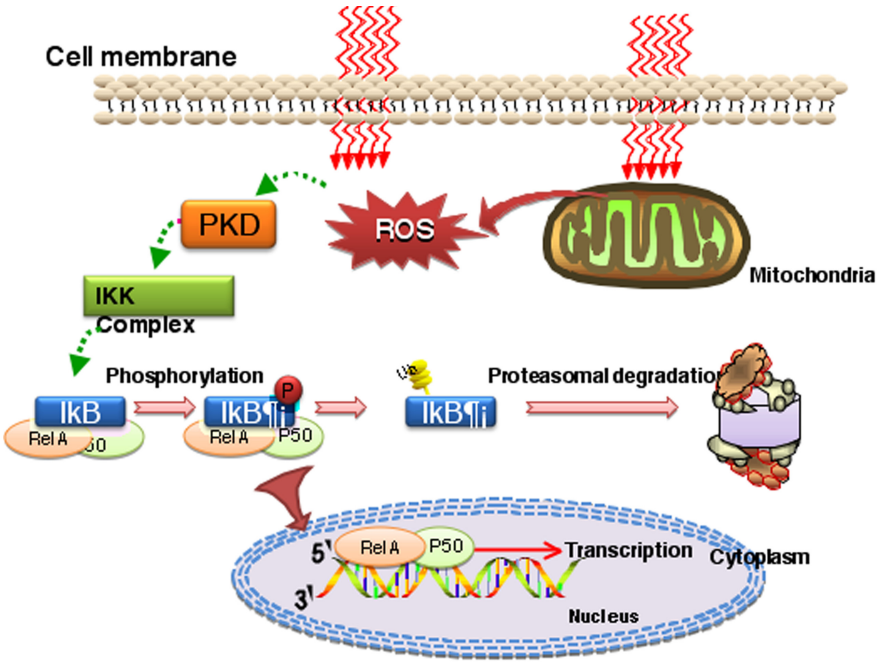


FIGURE 5. Reactive oxygen species (ROS) formed as a result of LLLT effects in mitochondria may activate the redox-sensitive transcription factor NF-κB (relA-p50) via protein kinase D (PKD).

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

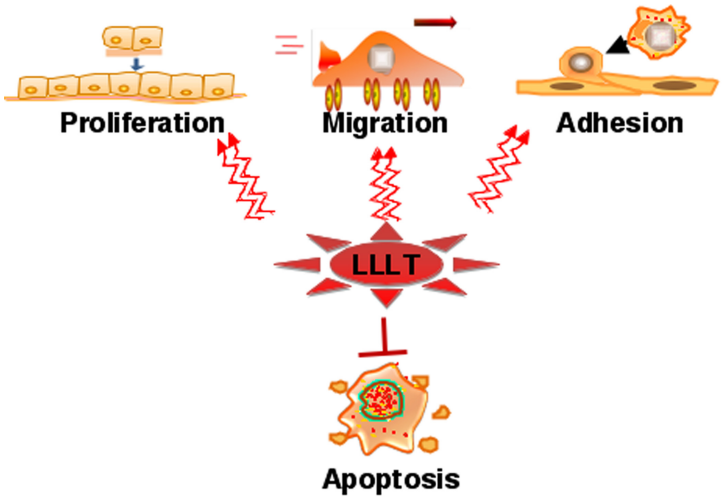


FIGURE 6. The downstream cellular effects of LLLT signaling include increases in cell proliferation, migration and adhesion molecules. Cell survival is increased and cell death reduced by expression of proteins that inhibit apoptosis.

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).

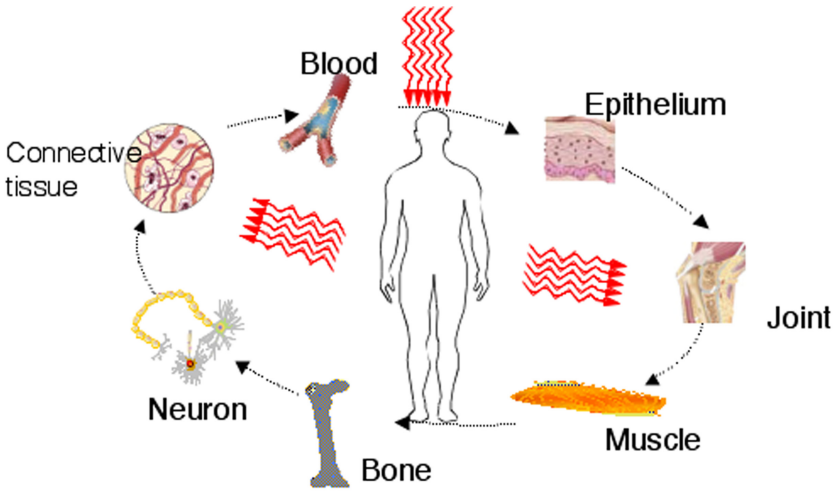


FIGURE 7. Beneficial tissue effects of LLLT can include almost all the tissues and organs of the body.

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).

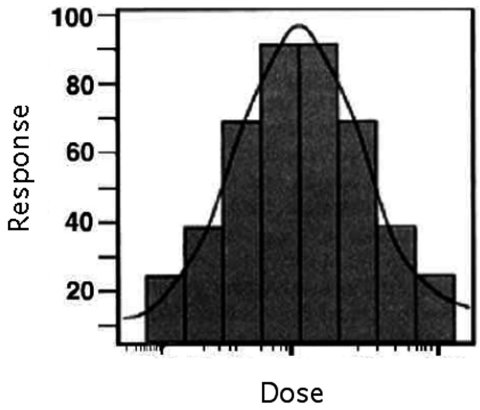


FIGURE 8. Idealized biphasic dose response curve (often termed Arndt-Schulz curve) typically reported in LLLT studies.

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.

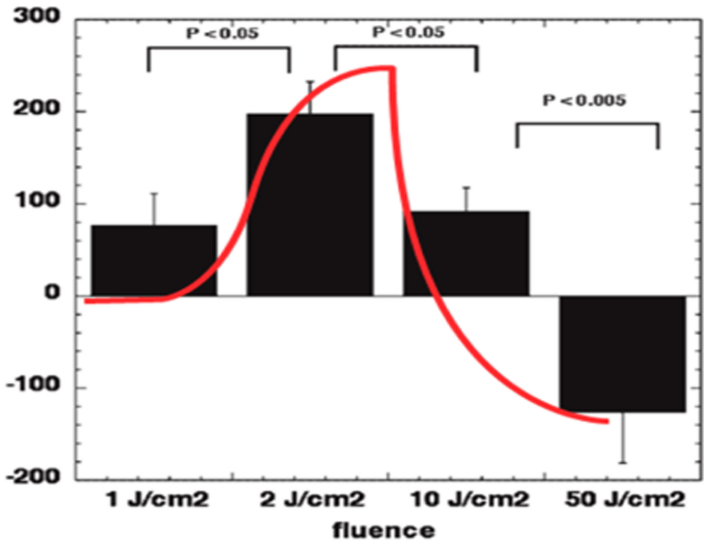


FIGURE 11. Biphasic dose response in measured difference in integrated area under the curve of time course of wound size compared to no treatment control, with a clear maximum seen at 2 J/cm^2, and the high dose of 50 J/cm^2 gave a worsening of the wound healing time curve.

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).

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Photomedicine and Laser Surgery
Volume 29, Number 7, 2011
© Mary Ann Liebert, Inc.
Pp. 443–446
DOI: 10.1089/pho.2011.9908

Editorial

Potential for Transcranial Laser or LED Therapy to Treat Stroke, Traumatic Brain Injury, and Neurodegenerative Disease

Margaret A. Naeser, Ph.D., L.Ac.,[1,2] and Michael R. Hamblin, Ph.D.[3,4,5]

Near-infrared (NIR) light passes readily through the scalp and skull and a small percentage of incident power density can arrive at the cortical surface in humans.[1] The primary photoreceptors for red and NIR light are mitochondria, and cortical neurons are exceptionally rich in mitochondria. It is likely that brain cells are ideally set up to respond to light therapy. The basic biochemical pathways activated by NIR light, e.g., increased adenosine-5′-triphosphate (ATP) production, and signaling pathways activated by reactive oxygen species, nitric oxide release, and increased cyclic adenosine monophosphate (AMP) all work together to produce beneficial effects in brains whose function has been compromised by ischemia, traumatic injury, or neurodegeneration. One of the main mechanisms of action of transcranial light therapy (TLT) is to prevent neurons from dying, when they have been subjected to some sort of hypoxic, traumatic, or toxic insult. This is probably because of light-mediated upregulation of cytoprotective gene products such as antioxidant enzymes, heat shock proteins, and anti-apoptotic proteins. Light therapy *in vitro* has been shown to protect neurons from death caused by methanol,[2] cyanide or tetrodotoxin,[3] and amyloid beta peptide.[4]

There is also probably a second mechanism operating in TLT; increased neurogenesis. Neurogenesis is the generation of neuronal precursors and birth of new neural cells.[5] Two key sites for adult neurogenesis include the subventricular zone (SVZ) of the lateral ventricles, and the subgranular layer (SGL) of the dentate gyrus in the hippocampus.[6] Neurogenesis can be stimulated by physiological factors, such as growth factors and environmental enrichment, and by pathological processes, including ischemia and neurodegeneration.[7] Adult neurogenesis (in the hippocampus particularly) is now recognized as a major determinant of brain function both in experimental animals and in humans. Neural progenitor cells in their niche in the SGL of the dentate gyrus give birth to newly formed neurons that are thought to play a role in brain function, particularly in olfaction and in hippocampal-dependent learning and memory.[8] In small animal models neurogenesis can be readily detected by incorporation of bromodeoxyuridine (BrdU), injected before euthanasia, into proliferating brain cells. Increased neurogenesis after TLT, has been demonstrated in a rat model of stroke,[9] and in the Hamblin laboratory after TLT for acute traumatic brain injury (TBI) in mice (W. Xuan, T. Ando, et al., unpublished data). These two mechanisms of action of TLT in ameliorating brain damage (prevention of neuronal death and increased neurogenesis) have motivated studies in both animals and humans for diverse brain disorders and diseases. TLT for acute stroke is the most developed,[10] but acute TBI has also been shown to benefit from TLT.[11] These areas are reviewed further.

Stroke

In an early study with TLT to treat acute stroke in rats, significant beneficial results were obtained whether TLT was applied in a bilateral, ipsilesional or contralesional manner.[12] TLT (808 nm) significantly improved recovery ($p < 0.01$) at 3 weeks following ischemic stroke when treated once, at 24 h post-stroke (contralesional; power density, 7.5 mW/cm^2 to brain tissue).[9] The number of newly formed neuronal cells, assessed by double immunoreactivity to BrdU and tubulin isotype III, as well as migrating cells (doublecortin immunoreactivity), was significantly elevated in the ipsilesional SVZ. There was no significant difference in the stroke lesion area between control and laser-irradiated rats. The authors suggested that an underlying mechanism for the functional benefit post-TLT was possible induction of neurogenesis. Other studies have also suggested that because improvement in neurologic outcome may not be evident for 2–4 weeks in the post-stroke rat model, delayed benefits may be caused, in part, by induction of neurogenesis and migration of neurons.[13,14]

A recent study with embolized rabbits showed a direct relationship between level of cortical fluence (energy density, J/cm^2) delivered, and cortical ATP content.[15] Five minutes following embolization (right carotid), rabbits were exposed

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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

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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

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"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]

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Foreword by Deepak Chopra, M.D.



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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

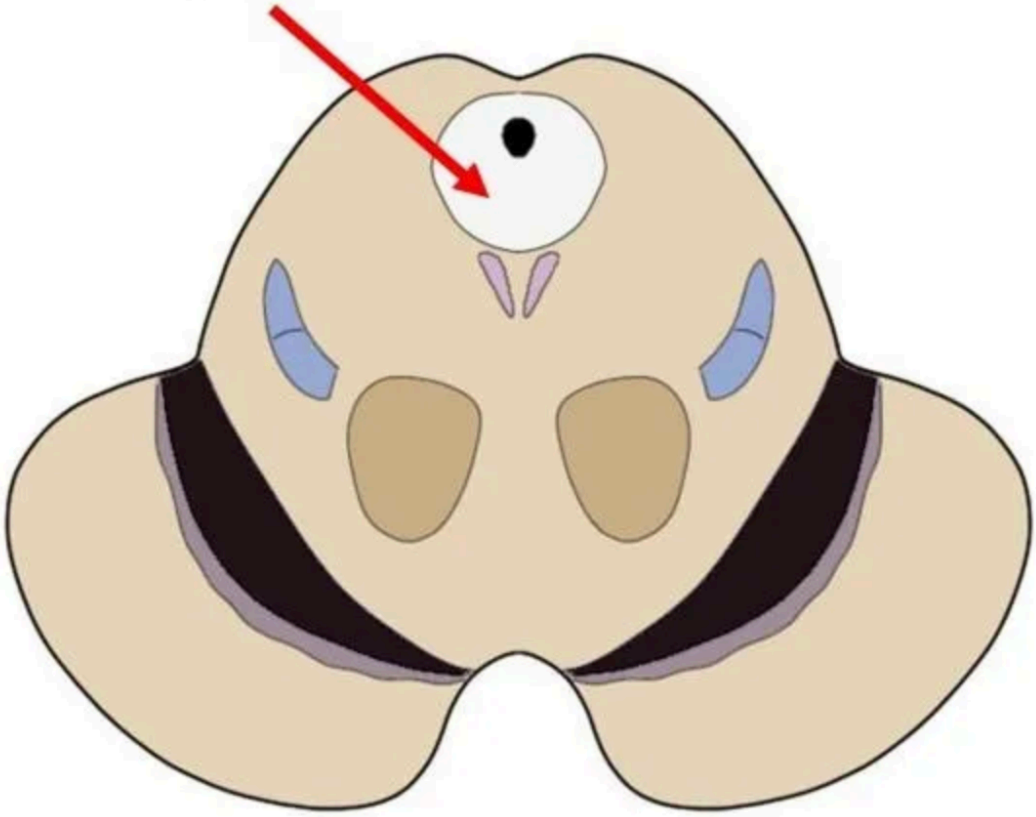
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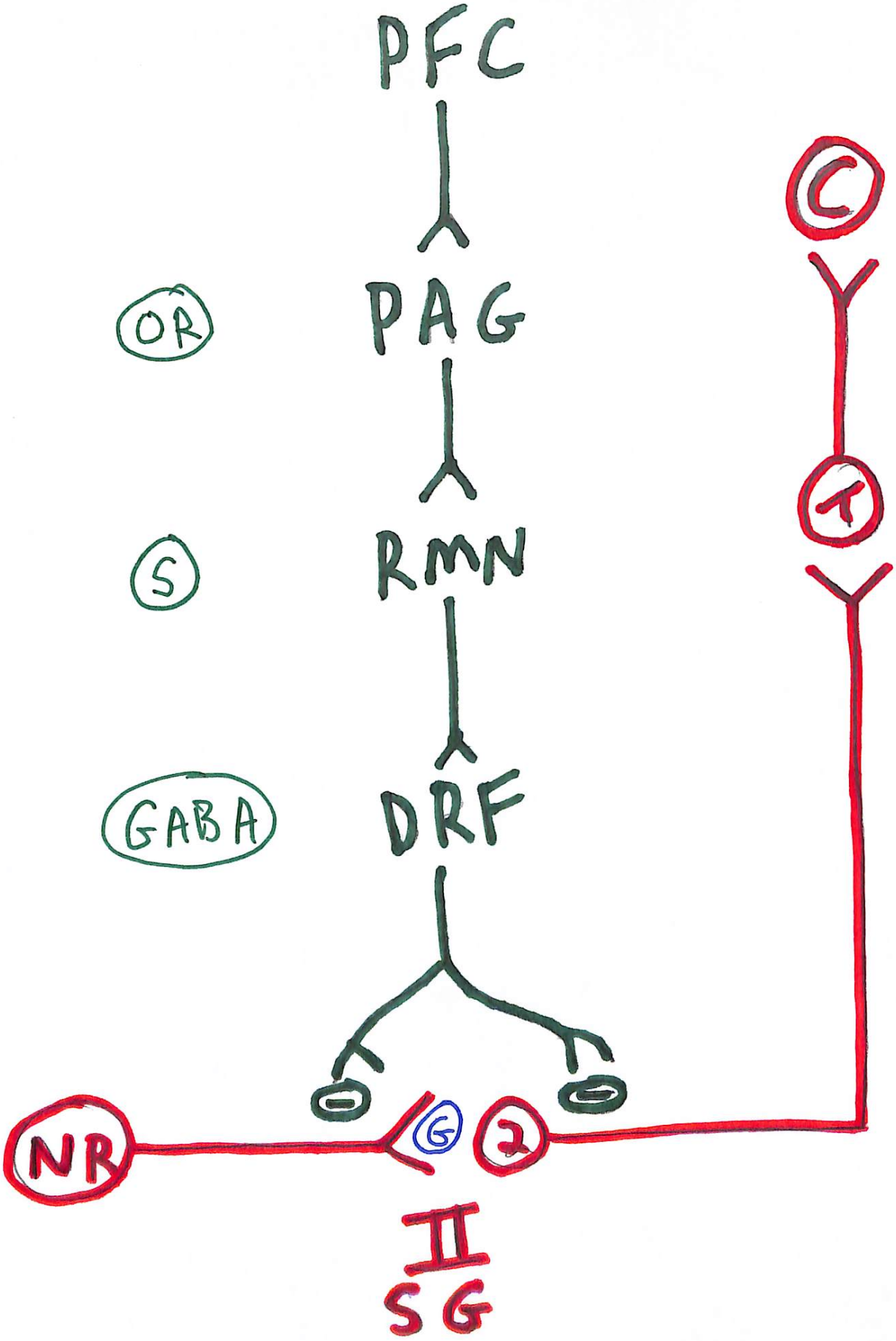


RICHARD AMBRON

Illustrated by Ahmet Sinav

PERIAQUEDUCTAL GRAY




PFC
PAG
OR
RMN
S
GABA
DRF
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."

••••••

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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

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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

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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.

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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

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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

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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.

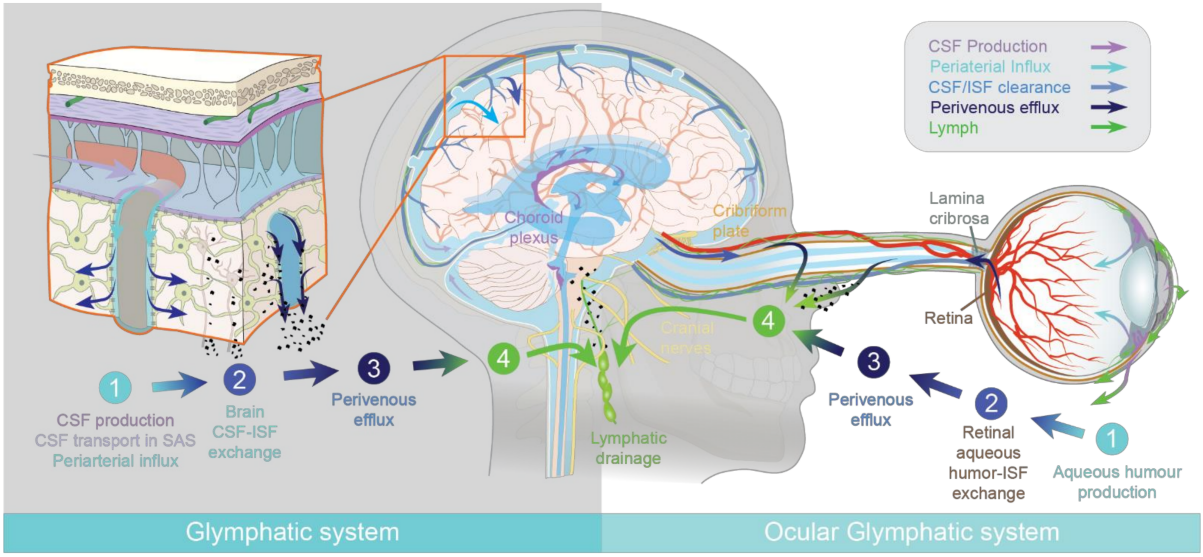


Figure 1. The glymphatic systems in the brain and the eye export fluid and solutes from metabolically active neural tissue. The organization of brain and ocular fluid flow can be divided into four distinct segments that share similarities, but differ in specific respects. (1) The first segment of the 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

New Scientist

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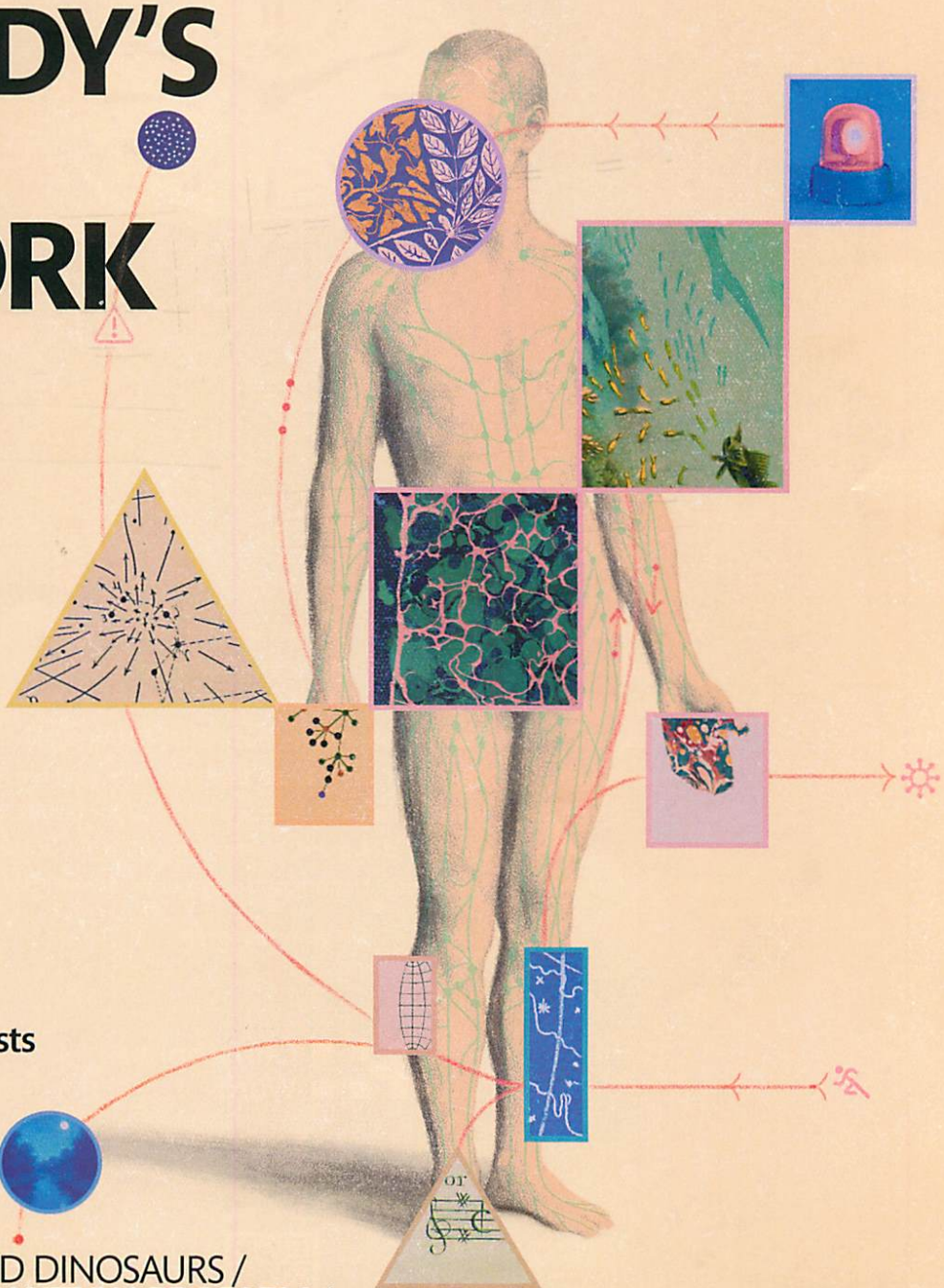
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Your hidden helper

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

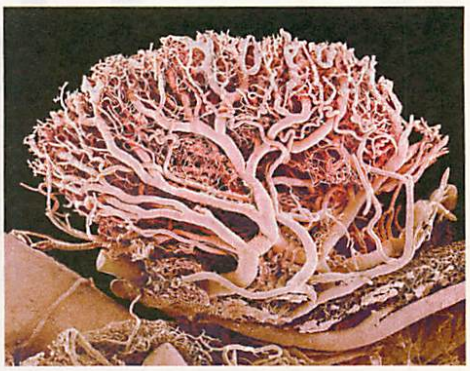
Such findings have prompted scientists to wonder whether lymphatic ageing also impairs cognition in people. There are very early hints that it does. In a study out earlier this year, Sarosh Irani at the Mayo Clinic, Da Mesquita and their colleagues analysed lymph extracted from the cervical lymph nodes 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?"

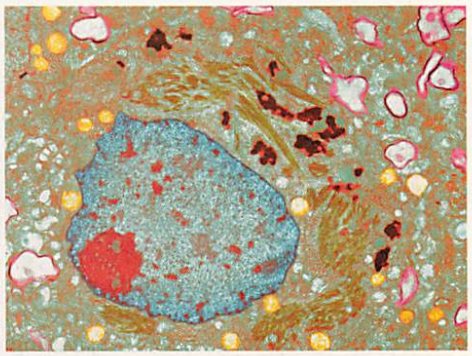
Indeed, some researchers are already pursuing this idea. In a study in May, Rong Hu at the Army Medical University in China and colleagues recruited 26 people with Alzheimer's disease to undergo surgery to their cervical lymphatic vessels that boosted the drainage of fluid from the brain. One month later, 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



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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



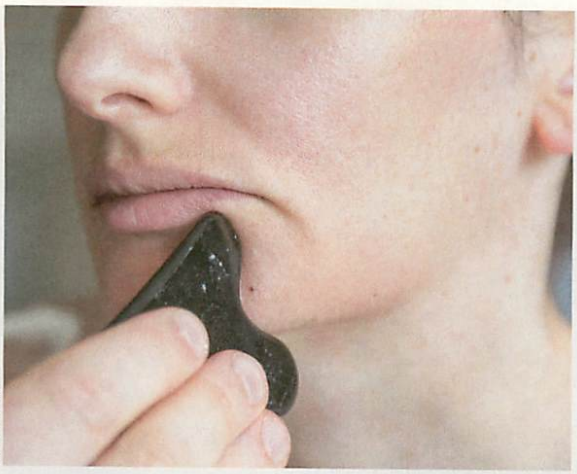
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doesn't affect the lymphatic system. Three months later, about 20 per cent of mice from the latter group had survived. In the former, the figure was 80 per cent – in some cases, their tumours had completely disappeared. "We were over the moon," says 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*

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

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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

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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).

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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.

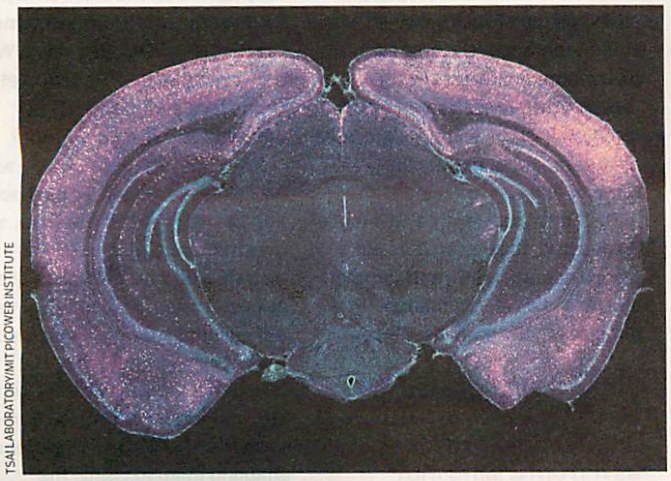
As it was known that visual or auditory stimulation at a certain frequency can boost brainwaves at that same frequency, in 2016, Tsai's team investigated if stimulation at 40 Hz might boost cognitive abilities in people with Alzheimer's.

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.

The Brain

Trauma

Neurodegenerative Diseases
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- Parkinson's
- Chronic Traumatic Encephalopathy
- Amyotrophic Lateral Sclerosis

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Anxiety

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Etc.

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JCBFM

Journal of Cerebral Blood Flow & Metabolism
2016, Vol. 36(5) 941–953
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Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity

Rahul Agrawal[1], Emily Noble[1], Laurent Vergnes[2], Zhe Ying[1], Karen Reue[2] and Fernando Gomez-Pinilla[1,3]

Abstract

Fructose consumption has been on the rise for the last two decades and is starting to be recognized as being responsible for metabolic diseases. Metabolic disorders pose a particular threat for brain conditions characterized by energy dysfunction, such as traumatic brain injury. Traumatic brain injury patients experience sudden abnormalities in the control of brain metabolism and cognitive function, which may worsen the prospect of brain plasticity and function. The mechanisms involved are poorly understood. Here we report that fructose consumption disrupts hippocampal energy homeostasis as evidenced by a decline in functional mitochondria bioenergetics (oxygen consumption rate and cytochrome C oxidase activity) and an aggravation of the effects of traumatic brain injury on molecular systems engaged in cell energy homeostasis (sirtuin 1, peroxisome proliferator-activated receptor gamma coactivator-1alpha) and synaptic plasticity (brain-derived neurotrophic factor, tropomyosin receptor kinase B, cyclic adenosine monophosphate response element binding, synaptophysin signaling). Fructose also worsened the effects of traumatic brain injury on spatial memory, which disruption was associated with a decrease in hippocampal insulin receptor signaling. Additionally, fructose consumption and traumatic brain injury promoted plasma membrane lipid peroxidation, measured by elevated protein and phenotypic expression of 4-hydroxynonenal. These data imply that high fructose consumption exacerbates the pathology of brain trauma by further disrupting energy metabolism and brain plasticity, highlighting the impact of diet on the resilience to neurological disorders.

Keywords

Cognition, energy homeostasis, metabolic syndrome, mitochondria, plasticity, traumatic brain injury

Received 8 April 2015; Revised 7 July 2015; Accepted 19 July 2015

Introduction

The rise in consumption of high caloric foods has triggered a metabolic epidemic such that the number of diabetic and prediabetic persons in the U.S. is now estimated at over 40% of the population.[1] A high fructose diet can induce several parameters of metabolic disease such as reduced sensitivity to insulin and increased risk factors for cardiometabolic disease in humans and rodents.[2] Furthermore, the deleterious effects of fructose extend to the brain where neuronal signaling, which is crucial for supporting brain plasticity and function, is compromised.[2] These data raise the question of whether fructose-induced metabolic dysfunction can reduce brain resilience against neurological disorders. Indeed, a new line of studies in humans indicates an association between metabolic disease and disturbances in cognition, emotional health, and reduced quality of life.[3]

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Format: Abstract

Full text links

Photomed Laser Surg. 2016 Dec;34(12):587-598. doi: 10.1089/pho.2015.4051.

Transcranial Low-Level Laser (Light) Therapy for Brain Injury.

Thunshelle C[1,2], Hamblin MR[2,3,4].

Author information

Abstract

BACKGROUND: Low-level laser therapy (LLLT) or photobiomodulation (PBM) is a possible treatment for brain injury, including traumatic brain injury (TBI).

METHODS: We review the fundamental mechanisms at the cellular and molecular level and the effects on the brain are discussed. There are several contributing processes that have been proposed to lead to the beneficial effects of PBM in treating TBI such as stimulation of neurogenesis, a decrease in inflammation, and neuroprotection. Both animal and clinical trials for ischemic stroke are outlined. A number of articles have shown how transcranial LLLT (tLLLT) is effective at increasing memory, learning, and the overall neurological performance in rodent models with TBI.

RESULTS: Our laboratory has conducted three different studies on the effects of tLLLT on mice with TBI. The first studied pulsed against continuous laser irradiation, finding that 10 Hz pulsed was the best. The second compared four different wavelengths, discovering only 660 and 810 nm to have any effectiveness, whereas 732 and 980 nm did not. The third looked at varying regimens of daily laser treatments (1, 3, and 14 days) and found that 14 laser applications was excessive. We also review several studies of the effects of tLLLT on neuroprogenitor cells, brain-derived neurotrophic factor and synaptogenesis, immediate early response knockout mice, and tLLLT in combination therapy with metabolic inhibitors.

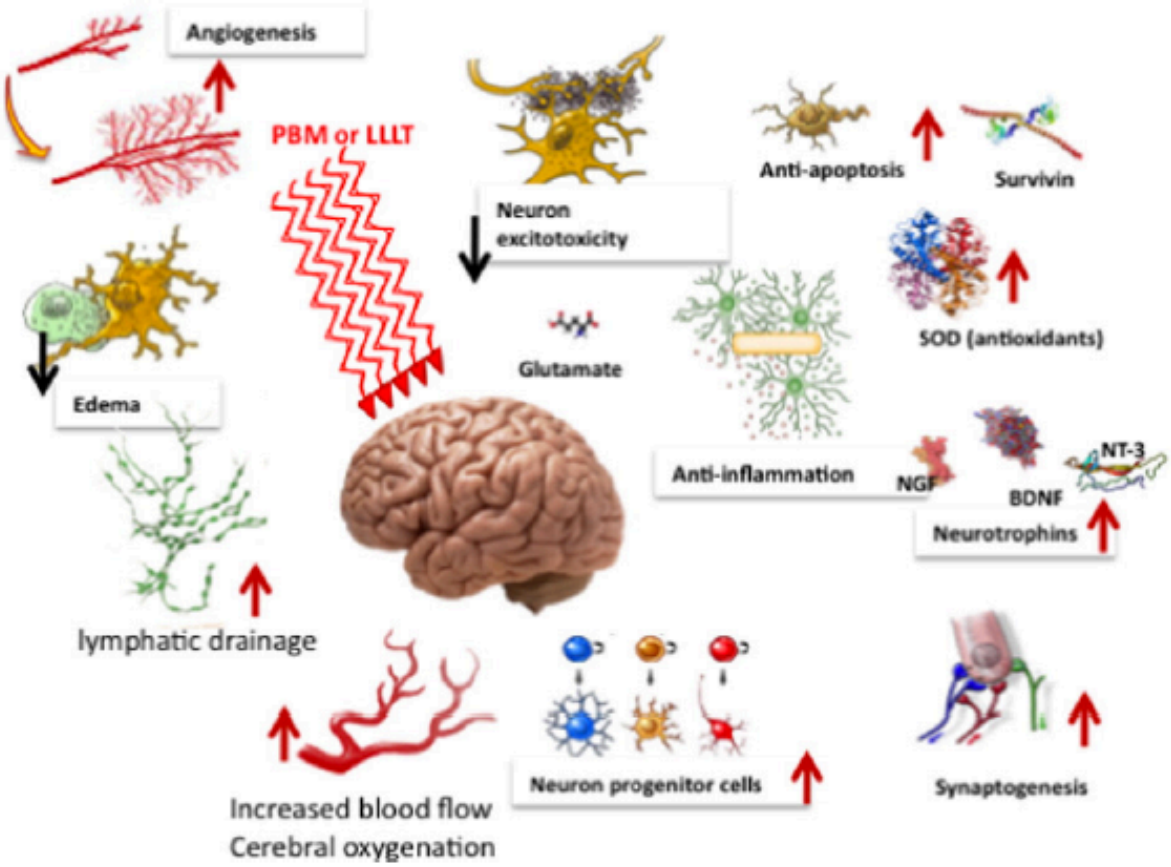
CONCLUSIONS: Finally, some clinical studies in TBI patients are covered.

KEYWORDS: brain disorders; low-level laser therapy; photobiomodulation; stroke; traumatic brain injury

PMID: 28001759 PMCID: PMC5180077 [Available on 2017-12-01] DOI: 10.1089/pho.2015.4051

Shining Light on the Head: Photobiomodulation for Brain Disorders
BBA Clinical (Biochimica et Biophysica Acta Journal)
2016; No. 6; pp. 113-124

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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

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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.

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Disclosure key can be found on the Table of contents and at www.pmrjournal.org

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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)

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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

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<< Prev Figure 1 Next >>

Figure 1

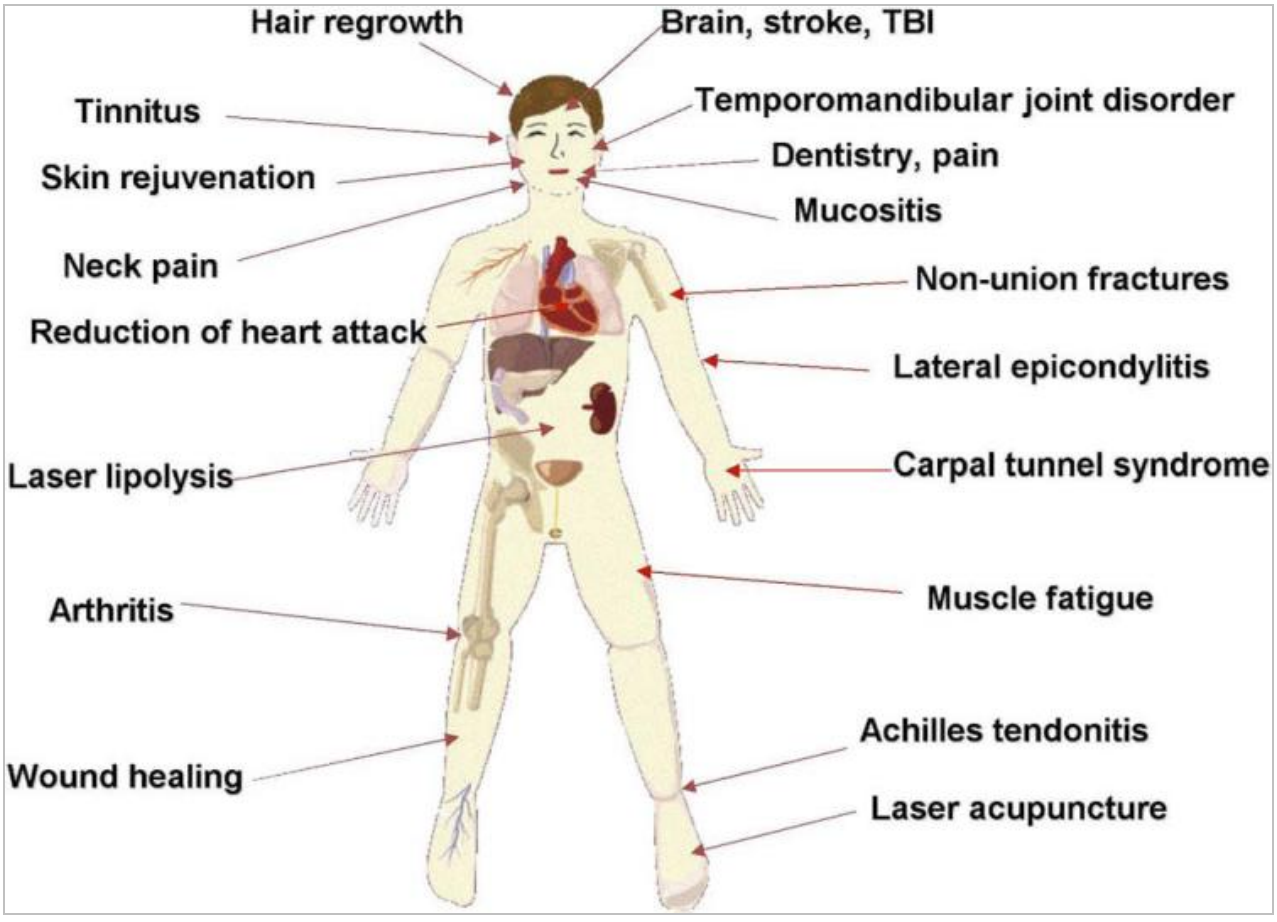


Diagram of the various medical applications of low-level light therapy.

Images in this article

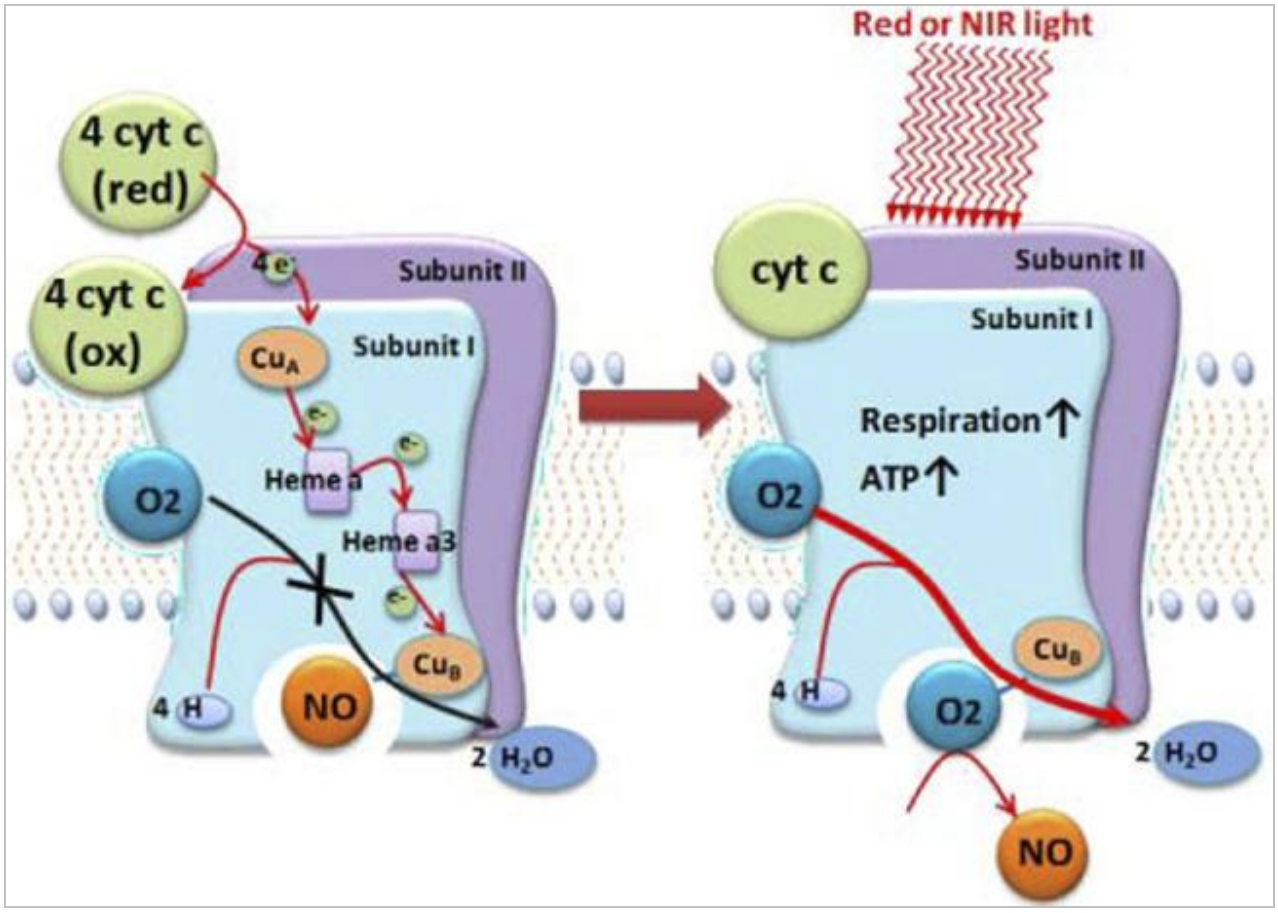
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From: PM R. Author manuscript; available in PMC 2011 December 1.
Published in final edited form as:
PM R. 2010 December; 2(12 Suppl 2): S292–S305.
doi: 10.1016/j.pmrj.2010.10.013

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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

Neurodegenerative Prevention Protocol; Cognitive Enhancement
Brain Trauma Rehabilitation Protocol

Stop consuming refined/glycating carbohydrates and ultra-processed foods

Balance omega-6/omega-3 ratio (1.5 – 3 /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 medial to SCM low neck: 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

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.

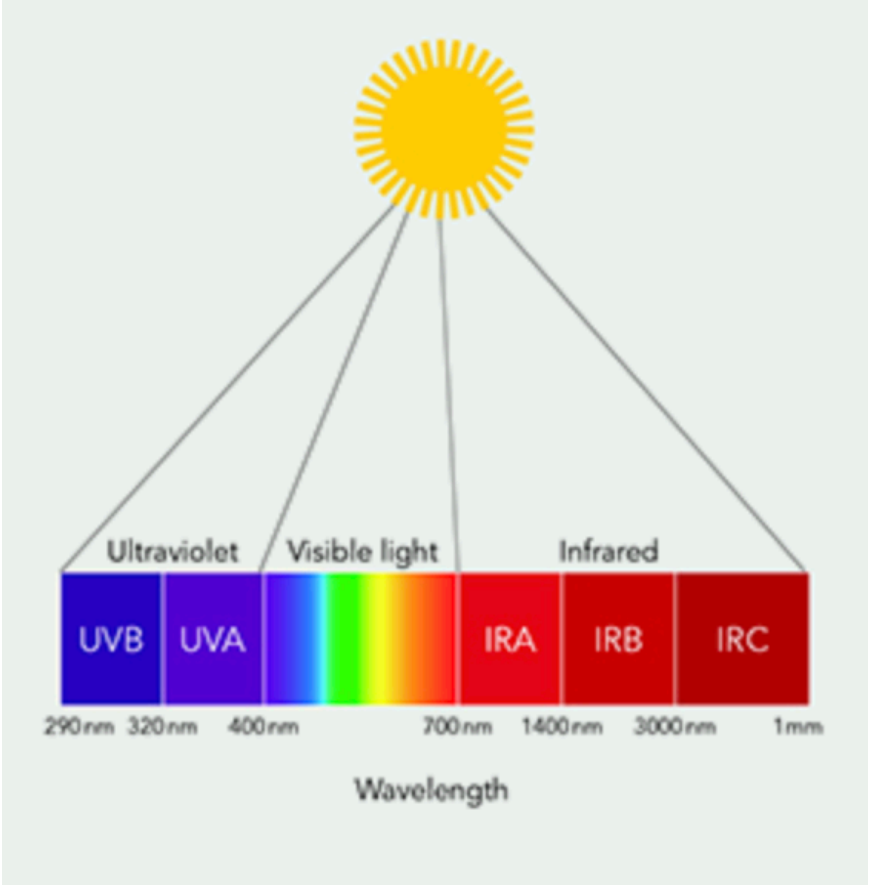
Wavelengths

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**



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.

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

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□ 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

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(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.

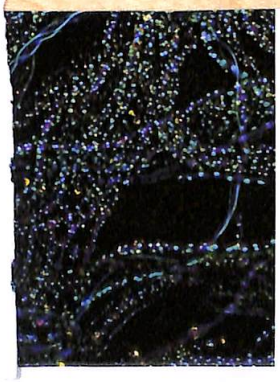
In the experiment, the solution contained no LH1, so LH2 emitted a photon instead of passing its energy on to LH1. The emitted photon had a different wavelength than the absorbed photon, a sign that energy had been transferred between LH2's two rings, a first step of photosynthesis. The team detected 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.

Received: 8 December 2023 | Revised: 15 January 2024 | Accepted: 21 January 2024

DOI: 10.1002/jbio.202300521

RESEARCH ARTICLE

JOURNAL OF BIOPHOTONICS

Light stimulation of mitochondria reduces blood glucose levels

Michael B. Powner[1] | **Glen Jeffery**[2]

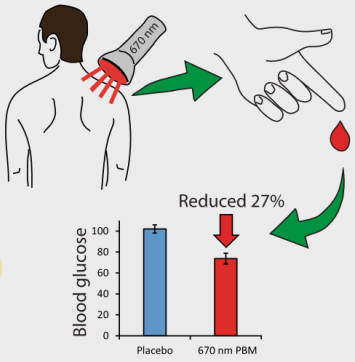
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Funding information
Sight Research UK

Abstract



Mitochondria regulate metabolism, but solar light influences its rate. Photobiomodulation (PBM) with red light (670 nm) increases mitochondrial membrane potentials and adenosine triphosphate production and may increase glucose demand. Here we show, with a glucose tolerance test, that PBM of normal subjects significantly reduces blood sugar levels. A 15 min exposure to 670 nm light reduced the degree of blood glucose elevation following glucose intake by 27.7%, integrated over 2 h after the glucose challenge. Maximum glucose spiking was reduced by 7.5%. Consequently, PBM with 670 nm light can be used to reduce blood glucose spikes following meals. This intervention may reduce damaging fluctuations of blood glucose on the body.

KEYWORDS

670 nm, glucose, human, mitochondria, oral glucose tolerance test, photobiomodulation, red light

current issues in molecular biology

MDI

Review

A Translational Review of Mechanisms of Effectiveness of Photobiomodulation on Somatosensory Neurons and the Peripheral Nervous System—From Molecular Mechanisms to Clinical Applications in Medicine and Dentistry

Roberta Chow * and Patricia Armati

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July 9, 2026; Vol. 48; No. 7; Article 695

This review aims to provide a translational link between clinical evidence in the application of photobiomodulation for treatment of painful conditions in medicine and dentistry and neurophysiological effects of photobiomodulation therapy (PBMt).

Central to the therapeutic effects of PBMt for pain is its interaction with neurons.

PBM influences cytoskeletal organization, mitochondrial structure and function, and intracellular signaling pathways, with downstream effects on neuronal excitability and nerve conduction.

Pain remains a problematic and universally important clinical challenge with treatments for acute and chronic pain varied as to their effectiveness.

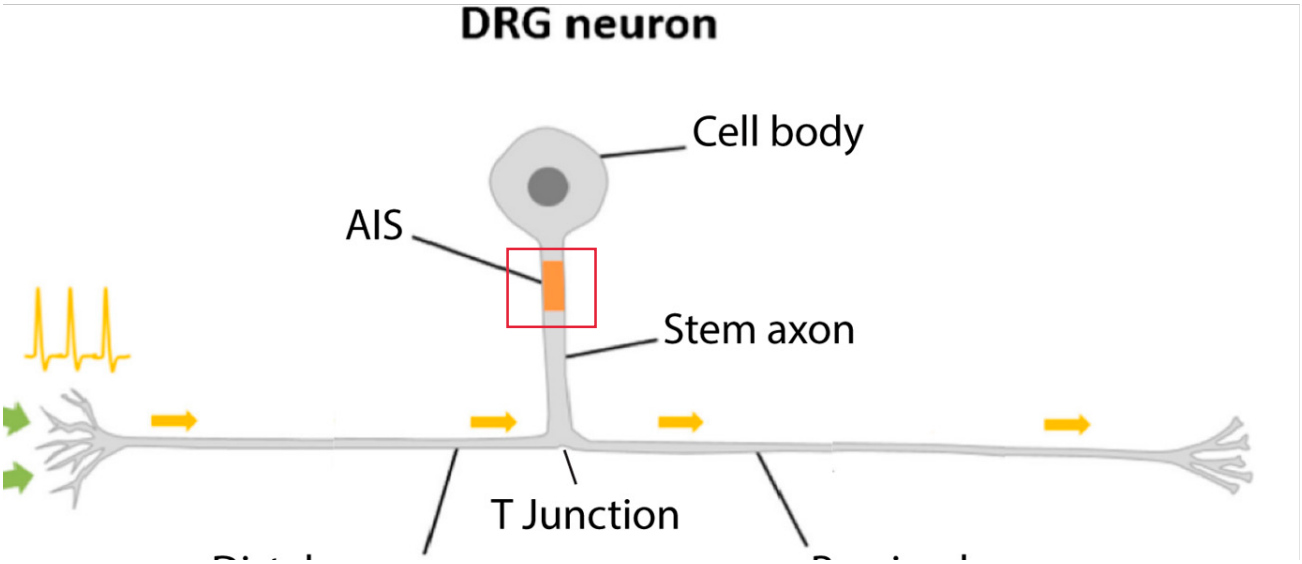
The idea of using light for pain remains outside mainstream medicine's accepted practice.

There are well-designed clinical trials showing PBMt's effectiveness for painful musculoskeletal conditions.

The Peripheral Nervous System (PNS) is made up of somatosensory first-order neurons however peripheral nerves include not only afferent axons transmitting sensory information to the Central Nervous System (CNS) but also motor axons arising from ventral horn cells of the spinal cord and sympathetic axons.

The sensory nerve cell bodies lie within the DRG- and PNS-related ganglia such as the trigeminal nerve ganglia in humans and are of particular interest in understanding how noxious and other PNS stimuli are transmitted and perceived as pain.

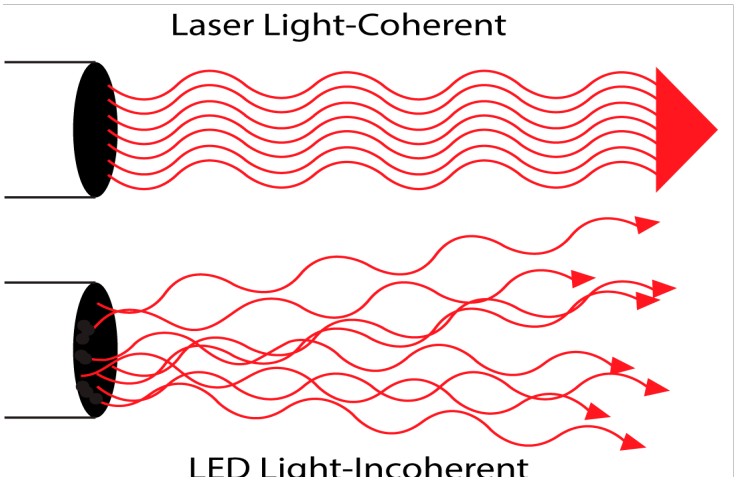
AIS axon initial segment is essential for propagation, integration and modulation of the action potential at the bifurcation of the axon into the proximal and distal branches.



The importance of the AIS within the DRG neuron, which plays a major role in the propagation, integration and modulation of the action potential, has been emphasized previously. It therefore presents as a potential target for PBMt as a logical research step.

Photobiomodulation Therapy (PBMt) describes the interaction between photons and cells at sub-ablative fluences to modulate cell physiology to achieve therapeutic effects and pain modulation.

There are significant differences between laser and light emitting diodes (LEDs) which can alter therapeutic outcomes.



Coherence is one of the unique properties of laser radiation.

Lasers diffuse and scatter very differently from LEDs within biological tissues.

Coherence may influence light distribution in tissue, and it can be demonstrated that lasers produce light speckles or pockets of intense light within tissues. Lasers therefore have the potential for a greater depth of penetration than LEDs.

From a clinical perspective, the use of LED can be effective in treating conditions such as diabetic neuropathy which involves damaged C neurons which lie only a few microns under the keratin in skin and does not require significant penetration.

Variables critical to "dose" and application include wavelength (λ), power output (W), time of exposure (seconds or minutes), "spot size" and mode (pulsed or continuous wave).

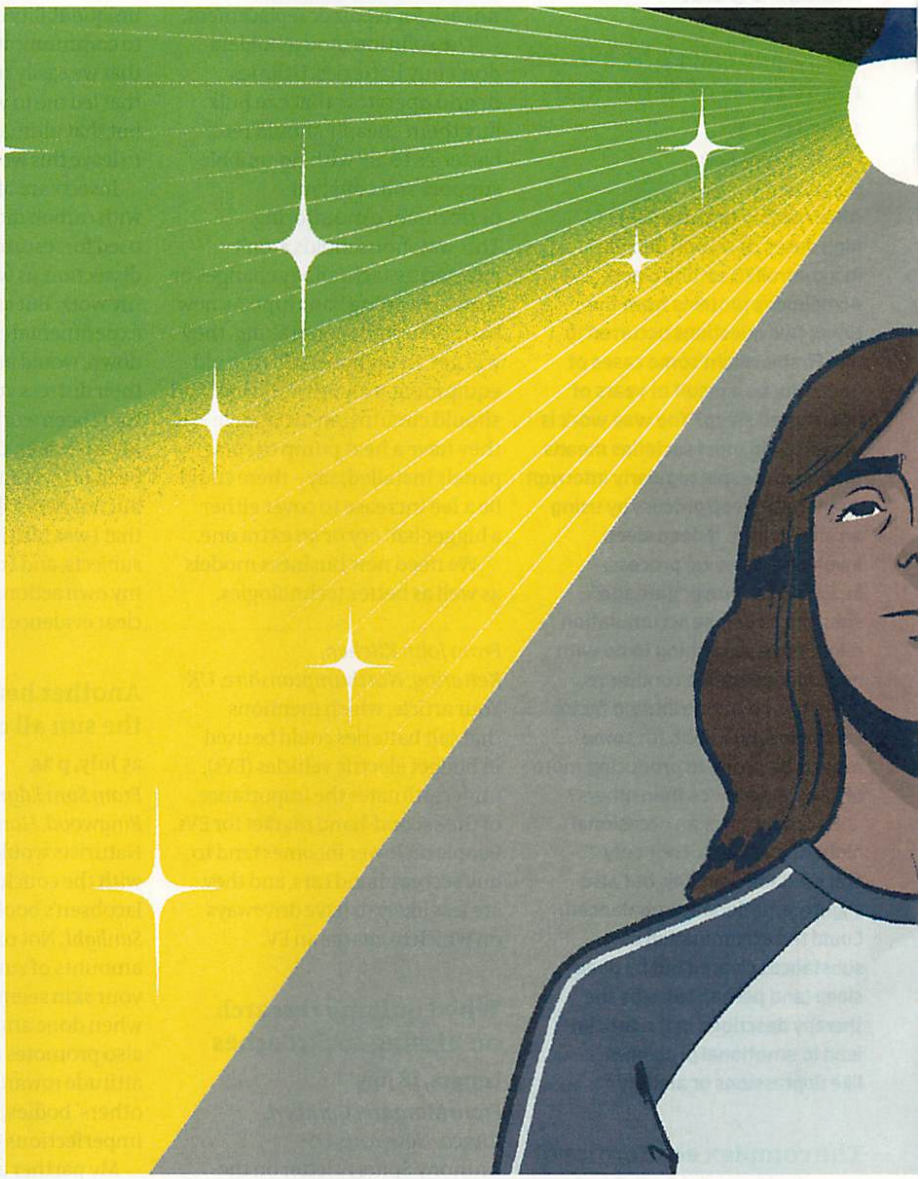
There are now several significant systematic reviews and randomized controlled trials of PBM for multiple painful medical conditions, including neck pain, knee osteoarthritis, diabetic peripheral neuropathy, shoulder tendinopathy, neuropathic pain, chemotherapy-related neuropathy and musculoskeletal pain.

Other clinical trials and reviews have reported favorable outcomes in PBM delivered transcutaneously in back pain, trigeminal neuralgia, post-herpetic neuralgia, fibromyalgia, and crystalline arthropathies.

The complex cascade of intra- and extracellular signaling initiated by photon absorption by cytochrome c oxidase in mitochondria in multiple compact cell types, such as fibroblasts, macrophages and neutrophils, has been well described and underpins many other diverse applications of PBMt such as wound healing and sports performance.

The collective body of evidence demonstrates biological plausibility and internal consistency across multiple levels of investigation. They reflect a systems-level neurophysiological basis for pain modulation and support the hypothesis that PBM modulates the somatosensory nervous system as an independent mechanism for pain modulation in medicine and dentistry and provide a platform for further research.

This study cites 134 references.



EMANUEL SANTOS

Red-light starvation

Since the 2000s, the spectrum of light we are exposed to has drastically shrunk. Now, we're learning how this can wreak havoc with our metabolism, finds **Graham Lawton**

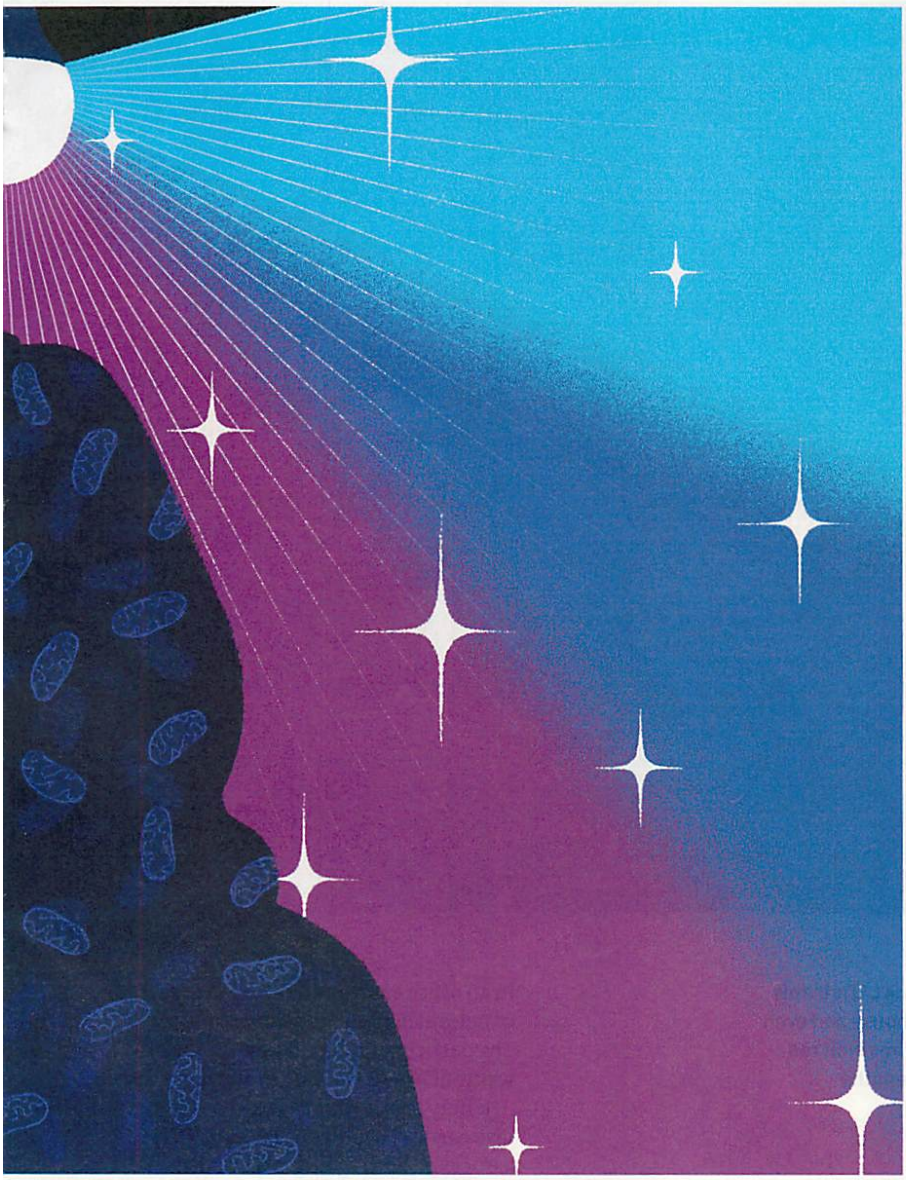
Take a flashlight – the one on your phone will do – turn it on and place the pad of your index finger over the bulb. See that red glow? You might think it's something to do with blood, but you'd be wrong. It's photons of red light bouncing around inside your finger, looking for somewhere to land.

This simple experiment is a doorway to one of the most profound and surprising biological discoveries of recent years. "Light is a nutrient," says Bob Fosbury, who was an astrophysicist at the European Southern Observatory before he turned his attention to the biology of light. That's obviously true for plants, which use light to make carbohydrates. But it turns out it's also true for animals and fungi, all of which exploit light in a hitherto unappreciated way. All living organisms – including us – are solar-powered.

Sunlight has long been understood to be critical to life on Earth. But the fact that light is also used to oil the wheels of metabolism is only just, er, coming to light. Long wavelengths, which come from red and infrared (IR) light, are particularly beneficial for creating energy, and are readily available from sources including sunlight and incandescent bulbs.

But changes in lighting intended to help save energy have inadvertently deprived us from this crucial supply. The irony is that just as we have discovered the benefit of red light, we are unintentionally starving ourselves of it.

The story begins in the early 2000s with the adoption of two now-ubiquitous energy efficiency technologies. The first was the light-emitting diode (LED), which largely replaced energy-guzzling incandescent bulbs. Although this change helped conserve energy, it had other unforeseen consequences. The second was window glass that filters out IR, designed to prevent heat leaking into or out of buildings. Together, these dramatically narrowed the



spectrum of light we are exposed to indoors, an environment where most humans spend up to 90 per cent of their time. "We lost about 95 per cent of the spectrum," says neuroscientist Glen Jeffery at University College London. "Suddenly, without warning, boom, the long wavelengths go. And that's a problem."

For the vast majority of human existence, those wavelengths were unavoidable. Daylight is rich in visible red light, which covers about 650 to 750 nanometres. It also emits vast and invisible (to us, at least) quantities of IR, which extends out to about 2500 nanometres.

People who spend much of the day outside are naturally exposed to these long wavelengths, even when fully clothed. When long-wavelength light hits a human body, it sails through clothing and penetrates deep into tissues (short-wavelength light such as UV, in contrast, is absorbed by clothing, which is why covering up helps prevent sunburn). Red and IR are also abundant in moonlight and in the glow of a campfire. Indoor light, too, used to be full of these wavelengths, either from sunlight streaming through windows or light sources such as open fires, candles and oil and gas lamps. The invention of the electric light didn't change that, as the spectrum of an incandescent light bulb closely matches that of the sun.

But the adoption of energy-efficient lighting and windows robbed us of longer parts of the spectrum. Glass that filters out IR obviously blocks that portion of sunlight, and while LEDs throw out a lot of visible light, they produce nothing beyond about 750 nm. "LEDs are completely dark in the infrared," says Fosbury. Scott Zimmerman, founder of the lighting company Silas Inc. in New Jersey who collaborates with Fosbury and Jeffery, calls LED light "ultra-processed", an analogy with ultra-processed food. The combined effect of ultra-processed light and modern glass means that the average human today receives much less long-wavelength light than their ancestors did.

21st-century scurvy

At the same time, conditions such as obesity, type 2 diabetes, dementia and early-onset cancers are on the march. The usual suspects for this are poor diet and lack of exercise. But according to Fosbury, Jeffery and others, these are only a piece of the puzzle; another reason, perhaps the principal one, is red-light deprivation. "There's not a single cause, but I do increasingly think that light is the most fundamental and dominant one," says Fosbury. "And it's probably the easiest one to solve."

To understand why light is so vital, we have to go back in time again, to the Soviet Union of the late 1980s, where, at the USSR Academy of Sciences in Moscow, a biophysicist called Tiina Karu was experimenting with red and near-infrared light as a therapy. She discovered that they were useful in wound healing and pain management and wondered what the mechanism was. Eventually she hit on energy metabolism, specifically the pace at which mitochondria inside the body's cells produce a molecule called ATP. Red light, she found, accelerated this process.

Karu's work never found a wide audience, mainly because she came from the wrong side of the Iron Curtain, according to Jeffery. But she was right, and today red-light therapy is everywhere, used to promote wound healing and treat skin conditions, hair loss, chronic pain and much more. The evidence of its efficacy is patchy, but growing, says John Mitrofanis, a neurologist at the University of Grenoble Alpes in France. There is much debate over the correct doses and wavelengths, but researchers agree that its effects are mediated by mitochondria.

The key to this is the electron transport chain, a complex and highly orchestrated metabolic process that takes in energetic ›

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electrons and passes them down a chain of proteins, creating ATP in the process. ATP is biology's principal energy currency, analogous to cash in an economy. When a cell needs energy to perform a task – say, building new proteins – it uses ATP.

When mitochondria are bathed in red or IR light, the electron transport chain runs a little faster and more ATP is produced – a process Fosbury calls "photometabolism". The exact mechanism by which ATP production is accelerated remains a point of contention, but what's certain is that diseased cells are often short of ATP, so a boost can make up the deficit. That, says Jeffery, explains why red-light therapy is beneficial.

It also explains why taking away red light can be harmful. Jeffery points out that all life on Earth evolved in an environment rich in red light and IR, but humans now mostly live in one stripped of those wavelengths. The result is more sluggish ATP production. To add insult to injury, we have also flooded our indoor environment with shorter wavelengths in the form of blue light from screens and LEDs. Blue light inhibits ATP production by slowing down the electron transport chain. Lose, lose.

The effects are insidious. Fosbury likens long-wavelength light to a vitamin and calls the effects of deprivation "21st-century scurvy", a nod to the disease of vitamin C deficiency that killed and sickened tens of thousands of sailors in the 18th century. Like scurvy, it creeps up on you. "It's something that accumulates over a period of time," says Jeffery.

It isn't just the general benefits of being outside, but red light specifically that is proven to have benefits. One of the symptoms of 21st-century scurvy is elevated blood sugar, which, if left unchecked, can progress to type 2 diabetes. This is due to the slowing down of the electron transport chain, which burns glucose as its primary fuel. A couple of years ago, Jeffery showed that a 15-minute burst of red light blunts the blood sugar spike after a large dose of glucose. He has also done real-world experiments in windowless, LED-illuminated offices at University College London. When he added long-wavelength light from a dimmed incandescent bulb, he found that the office occupants had lower blood sugar, on average, than their colleagues labouring under pure LED light. "Their mitochondria are being kick-started by the red light," says Jeffery. A study published in January found something similar; researchers at Maastricht University in the Netherlands exposed 13 individuals with type 2 diabetes to 4.5 solid working days of LED light in an office environment, then 4.5 days of natural light in the same location. The participants' blood sugar control was much better during the daylight days.



GETTY IMAGES/WESTEND61

The pink LEDs in this greenhouse and even campfires emit red wavelengths

"The success of red-light therapy may be down to the correction of a deficiency"

Jeffery also has concerns about other diseases and health problems usually associated with ageing, especially neurodegenerative conditions. One of the causes of these, he says, is mitochondrial dysfunction, which is effectively induced by red-light deficiency. Clinical trials have found that near-infrared light can slow down age-related cognitive impairment. A recent study of almost 88,000 people in their sixties found that, over the course of eight years, those who spent more time in daylight were significantly less likely to develop dementia, though the underlying causes of this relationship aren't yet fully understood. Mitrofanis, meanwhile, has shown that red light can prevent Parkinson's in a primate model of the disease.

Cancer and cardiovascular diseases, too, have been linked to a lack of daylight. When dermatologist Richard Weller at the University



CLASSICSTOCK/ALAMY

of Edinburgh, UK, and his colleagues analysed data from more than 400,000 adults in a yet-to-be-published study, they found that people with higher habitual UV exposure – a proxy for sunlight exposure in general – were less likely to die from cancer and cardiovascular disease.

Indeed, says Mitrofanis, the success of red-light therapy may simply be down to correction of a red-light deficiency. "Maybe all this is doing is rescuing processes that have gone awry because we're inside all the time, getting illuminated with blue light."

The fact that longer-wavelength light speeds up energy production isn't a happy accident. Fosbury and Jeffery argue that it is a design feature of living systems. Life, they say, evolved to feed off this once-abundant resource to maximise the efficiency of ATP production. "Life on Earth has evolved for 4 billion years in sunlight and it's adapted exquisitely to the properties of sunlight," says Fosbury.

One of those adaptations is the ability to harvest and store photons. "The body literally is designed to absorb as much as possible in the infrared," says Zimmerman. The amount of light energy we take in every day is staggering, he says. "Sunlight is the number one energy input into the body. It's at least twice, if not three times, as much as food."

Once sunlight enters the body, it scatters, bouncing off cells and organelles repeatedly – perhaps tens or hundreds of times, says Fosbury – until it hits a molecule that can absorb it, dumping energy in the process. This scattering means that a photon of red or IR light remains inside the body for much longer than it would if it passed straight through. This is what you see when you press your fingertip to a flashlight.

The photon's final destination is somewhat random, but occasionally it is absorbed by a component of the electron transport chain. Scientists are currently evaluating whether water molecules in the mitochondria are key to converting light into energy. When they absorb energy from a photon, they vibrate faster and lubricate the passage of electrons down the chain. Remarkably, says Fosbury, each step in the chain requires the electrons to overcome an energy barrier of roughly 0.75 electron volts, which is almost precisely what a photon of long-wavelength light delivers. Without the supply of red light we evolutionarily developed for, we're getting far less energy.

Fortunately, the solution to this modern-day scourge is simple: recharge your light battery whenever you can, either with daylight or an incandescent bulb. There are red-light therapy devices, but some of these are overpowered, which can send cellular energy production into overdrive and lead to inflammation. Of course, exposing yourself to sunlight also carries its own risk. But clothing and sunscreen help block cancer-causing UV, while letting red and IR through.

For people stuck in modern offices, Jeffery recommends buying a light fitting with a dimmer switch and putting it on your desk with an incandescent bulb in it. "Even when it [the incandescent bulb] is very, very, very dim, it still produces a vast amount of IR," he says. There's no specific magic wavelength and so a red LED light would likely be better than no red light at all, but nowhere near as effective as full-spectrum red light from incandescent light bulbs or the sun.

A London hospital has created an outdoor ward to help patients and staff get more red light exposure



KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST

What would really make a difference, says Jeffery, is a change in attitude among the people who design and manage buildings. The pursuit of energy efficiency is laudable but has unintended consequences. And in any case, energy efficiency need not be sacrificed. True, incandescent bulbs are extremely inefficient as a source of visible light, producing mostly infrared, aka heat. But the energy consumption of a heavily dimmed incandescent bulb is no more than an LED, so there are no extra costs – and shedloads of savings in the form of a healthier workforce. "We can do masses for public health just by bringing back the long wavelengths of light you're being denied in your office environment," says Jeffery.

"There's a real need for change," says Alistair Nunn, director of science at the Guy Foundation in London, which supports research on quantum biology and its medical applications. "At the moment, everybody's going down this road of 'let's get lots of LEDs', but it's not doing us any good at all."

There are signs of institutional change, with hospitals at the forefront. Studies have shown that infrared light in hospital wards leads to improved clinical outcomes, including shorter stays. And it has long been known that inpatients who have access to daylight are discharged sooner, on average, than those kept in windowless rooms. Now, some hospitals are taking action. Jeffery and his team recently did a light survey of the critical care unit at King's College Hospital in London. "It's a beautiful building, but there's absolutely no long-wavelength light in there," he says. "I said to them, 'obviously I'm concerned about your patients, but I'm concerned about your staff too.'" The hospital managers took heed and, in May, opened a new six-bed ward on the roof. Two other London hospitals are considering outside space for their critical care patients, says Jeffery. "I think they'll follow because they can't afford not to."

And even if you aren't a patient in a critical care ward, you can't afford to risk 21st-century scurvy through a steady diet of ultra-processed light. "You can live your life without red light," says Jeffery, "but you cannot live healthily without it." ■



Graham Lawton is a consultant for *New Scientist*. He is the author of *Mustn't Grumble: The surprising science of everyday ailments*

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 857123, 8 pages
doi:10.1155/2012/857123

Research Article

Stimulation of TRPV1 by Green Laser Light

Quanbao Gu,[1] Lina Wang,[1,2] Fang Huang,[3] and Wolfgang Schwarz[1,4]

Low-level laser irradiation in the mW/cm2 range of visible and near-infrared (NIR) light had been introduced as a medical treatment already in the late 60s, but its medical application still remains controversial.

Photo biostimulation particularly in the red and NIR range have been attributed to absorption by cytochrome oxidase C.

The stimulation by the green light is dose-dependent, but after about 2min a steady state is reached.

Detailed investigations have elucidated that irradiation of peripheral nerve with red or NIR laser light may also be of relevance for analgesic effects. In particular, decreased conduction velocities have been reported in experiments on humans and animals with involvement of Aδ and C fibres.

In our experiments, we could demonstrate the effectiveness of green laser light on TRPV1. Interestingly, TRPV1 is highly expressed in peripheral Aδ and C fibers.

We, therefore, like to suggest that in addition to red and blue laser light also green light with its intermediate penetration depth might be a useful tool in medical treatment.





Photomedicine and Laser Surgery
Volume 00, Number 00, 2016
© Mary Ann Liebert, Inc.
Pp. 1–8
DOI: 10.1089/pho.2015.4025

Mesenchymal Stem Cells Synergize with 635, 532, and 405 nm Laser Wavelengths in Renal Fibrosis: A Pilot Study

Megan O'Connor, MS,[1] Rachana Patil, MS,[1] Jiangzhou Yu, MD, PhD,[1]
Richard Hickey, BS,[1] Kavitha Premanand, MS,[1] Andre Kajdacsy-Balla, MD, PhD,[2]
Enrico Benedetti, MD,[1,3] and Amelia Bartholomew, MD, MPH, FACS[1]

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, and the [illegible]

Acknowledgments

This study was supported by the University of Illinois, Department of Surgery. We thank Steve Shanks for the use of research-grade Erchonia lasers for this study.

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Date: Tuesday, November 17, 2026 at 7:00 PM
To: Michelle Schaer <michelle@danmurphydc.com>

Subject: Thank you

Good evening, my name is ••••••••••. I am a chiropractor and just finished reviewing Dr Dan Murphy's assessment notes for "Risk of Vertebrobasilar Stroke and Chiropractic Care: Results of a Population-Based Case-Control and Case-Crossover Study".

The information and assessment by Dr Murphy was fantastic. I make decisions based off of good information, Dr Murphy is reliable and trustworthy and I just want to thank him for his long term association with promoting facts and truths with regards to chiropractic care.

He is invaluable.

Thank you very much

D.C.
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