

The WAVE

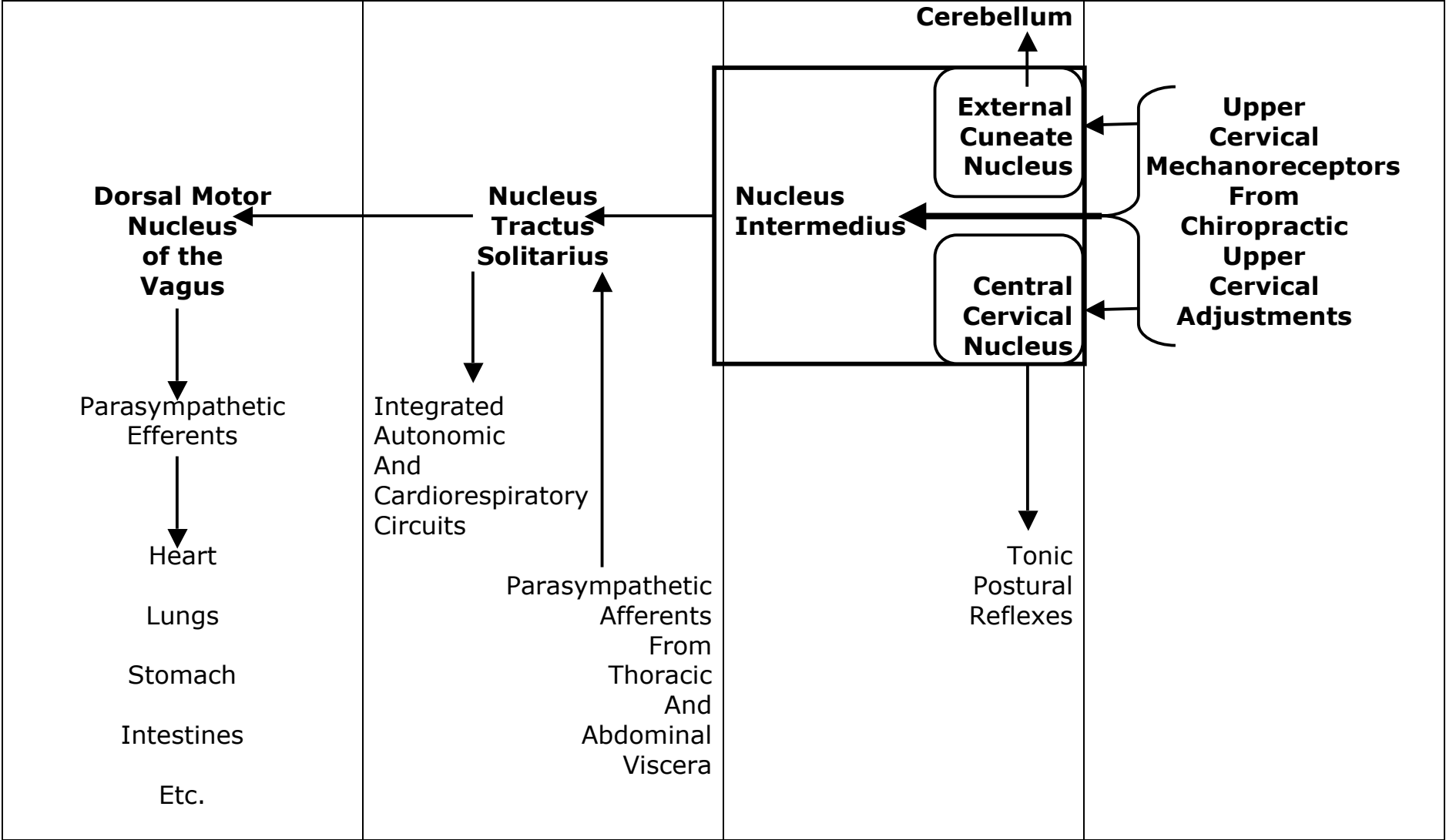
2026

The Vagus Nerve

Dan Murphy, DC

The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarii

**The Journal of Neuroscience
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Acetylcholine

AI Overview

Google

Acetylcholine is a **primary** chemical messenger (neurotransmitter) that carries signals between nerve cells in both the brain and the body.

It is essential for **learning, memory**, attention, arousal, and every voluntary muscle movement you make.

Key Functions

- **Muscle Movement:** It triggers the contraction of skeletal muscles, including those involved in breathing and movement.
- **Brain Function:** It acts as a neuromodulator in the brain, **consolidating memory**, shaping attention, and controlling REM sleep cycles.
- **Autonomic Control:** It regulates involuntary body functions such as heart rate, digestion, and glandular secretion.

How It Works:

- **Synthesis:** It is produced by the body using choline (an essential nutrient found in foods like eggs and meats) and acetyl-CoA.
- **Receptors:** It communicates by binding to two main types of receptors: **nicotinic** and **muscarinic**.

Health Implications:

- **Deficiencies:** Low levels of acetylcholine in the brain are linked to cognitive decline and conditions like Alzheimer's disease.
- **Medications & Toxins:** Many drugs and toxins interact with the acetylcholine system.

Acetylcholine and Vagus Nerve

Acetylcholine (ACh) is the primary neurotransmitter of the vagus nerve, which drives the body's parasympathetic (rest-and-digest) nervous system.

When the vagus nerve is activated, it releases ACh at target organs to slow the heart rate, stimulate digestion, and reduce systemic inflammation.

Core Functions & Pathways

- **Heart Rate:** ACh binds to muscarinic receptors on the heart, slowing the heart rate and stabilizing blood pressure.
- **Digestion:** The vagus nerve uses ACh to trigger the release of stomach acid, digestive enzymes, and stimulate gut motility.
- **The Cholinergic Anti-inflammatory Pathway (CAP):** Vagal nerve activation triggers the release of ACh in organs like the spleen and intestines. This ACh binds to alpha-7 nicotinic receptors on immune cells, shutting down the production of pro-inflammatory cytokines.

Vagus Nerve Stimulation (VNS)

When vagal tone is low, it can lead to chronic inflammation, poor digestion, or an elevated heart rate. You can naturally boost vagal ACh signaling and tone in your daily routine through a few accessible methods:

- **Deep Breathing:** Slow, diaphragmatic breathing (especially with prolonged exhalations) stimulates the vagus nerve to slow your heart rate.
- **Cold Exposure:** Brief exposure to cold water on the face or a cold finish to a shower activates the vagus nerve.
- **Vocal Toning:** Humming, singing, or gargling engages the vocal cords, which are controlled by branches of the vagus nerve.

Chiropractic and Vagus Nerve

Chiropractors focus on spinal adjustments—particularly in the upper neck (cervical spine)—to relieve physical stress on the nervous system. By removing spinal misalignments, they aim to reduce physical irritation on the vagus nerve, potentially improving parasympathetic ("rest and digest") function, reducing anxiety, and aiding digestion.

The Core Connection

The vagus nerve is the longest cranial nerve and runs directly alongside the upper cervical vertebrae, including the atlas (C1) and axis (C2). Chiropractors suggest that when these bones are misaligned (subluxations) or stiff, they can impinge neural flow or trigger the body's "fight or flight" response.

Potential Benefits & Mechanisms

- **Vagal Tone Enhancement:** By gently manipulating the cervical spine, chiropractors aim to "unkink" physical stress on the nerve pathways, allowing signals to flow freely from the brain to the rest of the body.
- **Heart Rate Variability (HRV):** Chiropractors often measure HRV to track vagal activity. Research suggests that chiropractic adjustments can improve HRV, which is a key indicator of a resilient nervous system and an improved ability to recover from stress.
- **Gut Health & Digestion:** Because the vagus nerve heavily innervates the digestive tract, better nerve signaling is frequently linked by practitioners to improved gut health and reduced gastrointestinal discomfort.
- **Pain Management & Inflammation:** Proper vagus nerve stimulation is tied to anti-inflammatory properties, and many patients report reduced chronic pain and headaches following cervical adjustments.
-

Adjunct Vagal Stimulation Techniques

In addition to manual spinal manipulation, chiropractors often recommend at-home practices to further stimulate the vagus nerve, such as:

- Deep, slow abdominal breathing
- Cold exposure (e.g., cold water splashing on the face)
- Singing, humming, or gargling (which activate the vocal cords closely tied to the vagus nerve)

Intermedius Nucleus

Intermedius Nucleus of the Medulla (InM)

Located in the lower brainstem, this perihypoglossal nucleus plays a critical role in integrating sensory information from the neck, vestibular system, and head.

- **Function:** It coordinates autonomic responses with changes in posture and relays this information to the solitary nucleus.
- **Projections:** It connects heavily with the hypoglossal nucleus to influence movements of the tongue and upper airways, linking spinal-visceral reflexes with head movement.

Intermedius Nucleus and Chiropractic

The **Nucleus Intermedius (InM)** is a small sensory relay station in the brainstem that processes nerve signals from the upper neck. In chiropractic, particularly upper cervical care, this area is highly significant because it serves as a bridge connecting spinal movement to automatic body functions, such as heart rate and breathing.

The Anatomical Connection

The upper cervical spine (the neck) contains a very high concentration of muscle spindles. When these muscles are tense, misaligned, or manipulated, they send sensory signals directly to the Nucleus Intermedius in the brainstem.

The Nucleus Intermedius then relays this information to two vital areas:

- **Nucleus Tractus Solitarius (NTS):** The primary sensory center for the parasympathetic nervous system (which controls rest, digestion, and heart rate).
- **Hypoglossal Nucleus:** Which controls tongue movement and airway patency.

Chiropractic Relevance

Chiropractic principles suggest that adjusting the spine—specifically the Atlas (C1) and Axis (C2) vertebrae—releases tension in the suboccipital muscles. This sensory change is believed to stimulate the Nucleus Intermedius, which may trigger a neurological reflex.

Proponents and some neurophysiological studies suggest this reflex loop can:

- **Influence the Autonomic Nervous System:** Downregulate an overactive sympathetic response ("fight or flight") and boost parasympathetic tone.
- **Affect Cardiorespiratory Function:** Influence blood pressure, heart rate variability (HRV), and breathing patterns.

Anticholinergic Drugs

Anticholinergic drugs are medications that block the neurotransmitter acetylcholine in the nervous system. This inhibition prevents nerve impulses responsible for involuntary muscle movements, digestion, and bodily secretions. Because they quiet the "rest and digest" system, they are widely used to treat conditions ranging from overactive bladder to Parkinson's disease.

Common Uses

- **Overactive Bladder:** Reducing involuntary bladder contractions (e.g., oxybutynin, tolterodine).
- **Parkinson's Disease:** Controlling tremors and muscle stiffness.
- **Chronic Obstructive Pulmonary Disease (COPD) & Asthma:** Relaxing and opening the airways (e.g., ipratropium).
- **Motion Sickness & Vertigo:** Blocking signals to the brain's vomiting center (e.g., scopolamine).
- **Gastrointestinal Disorders:** Reducing stomach acid and intestinal spasms.

Types of Drugs

While many are prescription-only, several are available over-the-counter (OTC), including:

- **Allergy & Cold Medications:** Diphenhydramine (Benadryl)
- **Overactive Bladder Medications:** Oxybutynin (Ditropan)
- **Motion Sickness:** Scopolamine
- **Asthma Inhalers:** Ipratropium (Atrovent)

Side Effects & Risks

Because these drugs broadly block acetylcholine, they often cause the classic "dry" side effects, commonly summarized by the medical mnemonic: *"Blind as a bat, mad as a hatter, red as a beet, hot as a dry, full as a flask, and dry as a bone."*

- **Physical:** Dry mouth, blurred vision, constipation, and difficulty urinating.
- **Cognitive:** Confusion, memory issues, and drowsiness.

Older adults are highly sensitive to these medications.

Taking multiple medications with anticholinergic properties (known as an "anticholinergic burden") has been consistently linked to an increased risk of cognitive decline and dementia.

Anticholinergic Burden

Anticholinergic burden is the cumulative cognitive and physical toll caused by taking multiple medications that block the neurotransmitter acetylcholine. Over time, this cumulative load increases the risk of falls, confusion, dementia, and mortality, particularly in older adults.

Understanding the Burden

- **The Mechanism:** Acetylcholine is essential for parasympathetic nervous system functions and brain health. Blocking it disrupts memory, learning, and basic bodily functions.
- **Cumulative Effect:** While a single medication with weak anticholinergic properties may be fine, taking several can lead to an additive (and sometimes dangerous) total load.
- **The ACB Scale:** Providers often measure this using the **Anticholinergic Cognitive Burden (ACB) Scale**

Many widely used over-the-counter and prescription drugs possess anticholinergic properties, including:

- First-generation antihistamines (e.g., diphenhydramine)
- Certain tricyclic antidepressants (e.g., amitriptyline)
- Overactive bladder medications (e.g., oxybutynin)
- Specific antipsychotics and anti-Parkinson medications
- Some gastrointestinal agents

Short-Term Side Effects

High burdens often present with recognizable peripheral and central side effects.

- **Physical (Peripheral):** Dry mouth, blurred vision, constipation, urinary retention, and fast heart rate (tachycardia).
- **Mental (Central):** Drowsiness, confusion, impaired concentration, and even hallucinations or delirium.

Long-Term Risks

- **Cognitive Decline:** Prolonged exposure is strongly associated with an increased risk of developing dementia and long-term memory impairment.
- **Physical Decline:** Increased dizziness and poor coordination directly lead to higher rates of falls and fractures in the elderly.

Anticholinergic Drugs and Alzheimer's

Taking medications with strong anticholinergic properties over long periods is linked to an increased risk of dementia and Alzheimer's disease. These drugs block acetylcholine—a vital brain chemical for memory. Older adults should avoid chronic use and consult a doctor to explore safer, non-medication alternatives.

The Link to Alzheimer's

Anticholinergic drugs block the action of acetylcholine, a neurotransmitter that is already critically low in the brains of people with Alzheimer's disease.

- **Cumulative Risk:** Research indicates a strong dose-response relationship. People who take higher cumulative doses or use these medications over extended periods face a substantially higher risk of developing dementia.
- **Potential Mechanism:** Laboratory and brain-imaging studies have found that blocking acetylcholine activity is associated with brain shrinkage, memory decline, and structural abnormalities similar to the amyloid plaques and neurofibrillary tangles seen in Alzheimer's.

Common Anticholinergic Drugs

Many prescription and common over-the-counter (OTC) drugs have strong anticholinergic effects, including:

- **First-Generation Antihistamines:** Diphenhydramine (Benadryl)
- **Sleep Aids:** Medications that contain diphenhydramine (e.g., ZzzQuil, Unisom)
- **Tricyclic Antidepressants:** Amitriptyline, doxepin
- **Bladder Medications:** Oxybutynin (Ditropan)

- **Gastrointestinal Meds:** Medications for motion sickness or stomach cramps
- **Certain Muscle Relaxants and Antipsychotics**

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Harvard Health Newsletter

Harvard Medical School

January 9, 2025

Modified

Common Anticholinergic Drugs Like Benadryl Linked to Increased Dementia Risk

A report published in *JAMA Internal Medicine* highlighted a link between long-term use of anticholinergic medications like Benadryl and dementia.

We do know that anticholinergic drugs can cause confusion and increase fall risk in older people.

Anticholinergic drugs block the action of acetylcholine.

In the brain, acetylcholine is involved in learning and memory.

In the rest of the body, it stimulates muscle contractions.

Anticholinergic drugs include some antihistamines, tricyclic antidepressants, medications to control overactive bladder, and drugs to relieve the symptoms of Parkinson's disease.

What the study found regarding Benadryl and dementia

A team led by Shelley Gray, a pharmacist at the University of Washington's School of Pharmacy, tracked nearly 3,500 men and women ages 65 and older who took part in a long-term study conducted by the University of Washington and Group Health, a Seattle healthcare system.

They used Group Health's pharmacy records to determine all the drugs, both prescription and over-the-counter, that each participant took the 10 years before starting the study.

They found that people who used these drugs were more likely to have developed dementia as those who didn't use them.

Moreover, dementia risk increased along with the cumulative dose.

Taking an anticholinergic for the equivalent of three years or more was associated with a 54% higher dementia risk than taking the same dose for three months or less.

Alzheimer's Disease

The results add to mounting evidence that anticholinergics aren't drugs to take long-term if you want to keep a clear head and keep your head clear into old age.

The body's production of acetylcholine diminishes with age, so blocking its effects can deliver a double whammy to older people.

It's not surprising that problems with short-term memory, reasoning, and confusion lead the list of side effects of anticholinergic drugs, which also include drowsiness, dry mouth, urine retention, and constipation.

Many drugs have a stronger effect on older people than younger people.

With age, the kidneys and liver clear drugs more slowly, so drug levels in the blood remain higher for a longer time.

People also gain fat and lose muscle mass with age, both of which change the way that drugs are distributed to and broken down in body tissues.

Older people tend to take more prescription and over-the-counter medications, each of which has the potential to suppress or enhance the effectiveness of the others.

"A MONUMENTAL WORK."

—DAVID PERLMUTTER, MD,
author of the #1 New York Times bestsellers *Grain Brain* and *Brain Maker*

The End *of* Alzheimer's

"In Alzheimer's Disease, there is a reduction in acetylcholine."

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The First Program to
Prevent and Reverse
Cognitive Decline



2017

DALE E. BREDESEN, MD

Professor and Founding President, Buck Institute; Professor, UCLA

ORIGINAL ARTICLE

Atlas vertebra realignment and achievement of arterial pressure goal in hypertensive patients: a pilot study

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Anatomical abnormalities of the cervical spine at the level of the Atlas vertebra are associated with relative ischaemia of the brainstem circulation and increased blood pressure (BP). Manual correction of this malalignment has been associated with reduced arterial pressure. This pilot study tests the hypothesis that correcting mal-alignment of the Atlas vertebra reduces and maintains a lower BP. Using a double blind, placebo-controlled design at a single center, 50 drug naïve ($n=26$) or washed out ($n=24$) patients with Stage 1 hypertension were randomized to receive a National Upper Cervical Chiropractic (NUCCA) procedure or a sham procedure. Patients received no antihypertensive meds during the 8-week study duration. The primary end point was changed in systolic and diastolic BP comparing baseline and week 8, with a 90% power to detect an

8/5 mm Hg difference at week 8 over the placebo group. The study cohort had a mean age 52.7 ± 9.6 years, consisted of 70% males. At week 8, there were differences in systolic BP (-17 ± 9 mm Hg, NUCCA versus -3 ± 11 mm Hg, placebo; $P < 0.0001$) and diastolic BP (-10 ± 11 mm Hg, NUCCA versus -2 ± 7 mm Hg; $P = 0.002$). Lateral displacement of Atlas vertebra (1.0 , baseline versus 0.04° week 8, NUCCA versus 0.6 , baseline versus 0.5° , placebo; $P = 0.002$). Heart rate was not reduced in the NUCCA group (-0.3 beats per minute, NUCCA, versus 0.5 beats per minute, placebo). No adverse effects were recorded. We conclude that restoration of Atlas alignment is associated with marked and sustained reductions in BP similar to the use of two-drug combination therapy.

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Keywords: atlas; vertebra; antihypertensive therapy

Introduction

It is well known that achievement of blood pressure (BP) goals in more than 70% of hypertensive individuals requires two or more antihypertensive agents.¹ Based on the most recent NHANES 1999–2000 data, BP control in the US has not improved significantly.² Moreover, many people have searched for alternative methods for lowering arterial pressure.

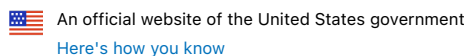
Since the early 1940s, a small cadre of chiropractic specialists have foregone typical ‘full-spine manipulations’, limiting their practice to precise, delicate manual alignment of a single vertebra, C-1 or Atlas; these practitioners make up the National Upper Cervical Chiropractic Association (NUCCA). Unlike other vertebrae, which interlock one to the next, the

Atlas relies solely upon soft tissue (muscles and ligaments) to maintain alignment; therefore, the Atlas is uniquely vulnerable to displacement. Displacement of C-1 is pain free and thus, remains undiagnosed and untreated, whereas health-related consequences are attributed to other aetiologies.

Minor misalignment of the Atlas vertebra can potentially injure, impair, compress and/or compromise brainstem neural pathways. The relationship between hypertension and presence of circulatory abnormalities in the area around the Atlas vertebra and posterior fossa of the brain has been known for more than 40 years.^{3–5} Studies by Jannetta *et al.*⁶ note arterial compression of the left lateral medulla oblongata by looping arteries of the base of the brain in 51 of 53 hypertensive patients who underwent left retromastoid craniectomy and microvascular decompression for unrelated cranial nerve dysfunctions. Such compression was not present in normotensive patients. Treatment by vascular decompression of the medulla was performed in 42 of the 53 patients and amelioration of hypertension was noted in 76%.⁶ Moreover, studies to clarify the

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FULL TEXT LINKS



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Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults

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Abstract

Importance: The use of anticholinergic (AC) medication is linked to cognitive impairment and an increased risk of dementia. To our knowledge, this is the first study to investigate the association between AC medication use and neuroimaging biomarkers of brain metabolism and atrophy as a proxy for understanding the underlying biology of the clinical effects of AC medications.

Objective: To assess the association between AC medication use and cognition, glucose metabolism, and brain atrophy in cognitively normal older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Indiana Memory and Aging Study (IMAS).

Design, setting, and participants: The ADNI and IMAS are longitudinal studies with cognitive, neuroimaging, and other data collected at regular intervals in clinical and academic research settings. For the participants in the ADNI, visits are repeated 3, 6, and 12 months after the baseline visit and then annually. For the participants in the IMAS, visits are repeated every 18 months after the baseline visit (402 cognitively normal older adults in the ADNI and 49 cognitively normal older adults in the IMAS were included in the present analysis). Participants were either taking (hereafter referred to as the AC+ participants [52 from the ADNI and 8 from the IMAS]) or not taking (hereafter referred to as the AC- participants [350 from the ADNI and 41 from the IMAS]) at least 1 medication with medium or high AC activity. Data analysis for this study was performed in November 2015.

Main outcomes and measures: Cognitive scores, mean fludeoxyglucose F 18 standardized uptake value ratio (participants from the ADNI only), and brain atrophy measures from structural magnetic resonance imaging were compared between AC+ participants and AC- participants after adjusting for potential confounders. The total AC burden score was calculated and was related to target measures. The association of AC use and longitudinal clinical decline (mean [SD] follow-up period, 32.1 [24.7] months [range, 6-108 months]) was examined using Cox regression.

Results: The 52 AC+ participants (mean [SD] age, 73.3 [6.6] years) from the ADNI showed lower mean scores on Weschler Memory Scale-Revised Logical Memory Immediate Recall (raw mean scores: 13.27 for AC+ participants and 14.16 for AC- participants; $P = .04$) and the Trail Making Test Part B (raw mean scores: 97.85 seconds for AC+ participants and 82.61 seconds for AC- participants; $P = .04$) and a lower executive function composite score (raw mean scores: 0.58 for AC+ participants and 0.78 for AC- participants; $P = .04$) than the 350 AC- participants (mean [SD] age, 73.3 [5.8] years) from the ADNI. Reduced total cortical volume and temporal lobe cortical thickness and greater lateral ventricle and inferior lateral ventricle volumes were seen in the AC+ participants relative to the AC- participants.

Conclusions and relevance: The use of AC medication was associated with increased brain atrophy and dysfunction and clinical decline. Thus, use of AC medication among older adults should likely be discouraged if alternative therapies are available.

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Figures



Figure 1. Association of Anticholinergic (AC) Medication...



Figure 2. Effect of Anticholinergic (AC) Medication...

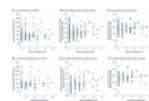


Figure 3. Association of Total Anticholinergic (AC) Medication...

FULL TEXT LINKS

Neurology

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Association of anticholinergic medications and AD biomarkers with incidence of MCI among cognitively normal older adults

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Abstract

Objective: To determine the cognitive consequences of anticholinergic medications (aCH) in cognitively normal older adults as well as interactive effects of genetic and CSF Alzheimer disease (AD) risk factors.

Methods: A total of 688 cognitively normal participants from the Alzheimer's Disease Neuroimaging Initiative were evaluated (mean age 73.5 years, 49.6% female). Cox regression examined risk of progression to mild cognitive impairment (MCI) over a 10-year period and linear mixed effects models examined 3-year rates of decline in memory, executive function, and language as a function of aCH. Interactions with APOE ε4 genotype and CSF biomarker evidence of AD pathology were also assessed.

Results: aCH+ participants had increased risk of progression to MCI (hazard ratio [HR] 1.47, *p* =

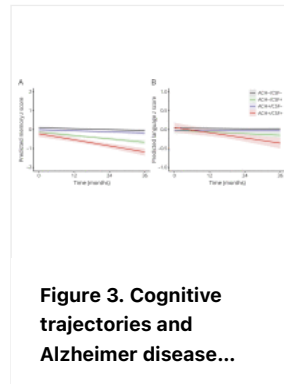
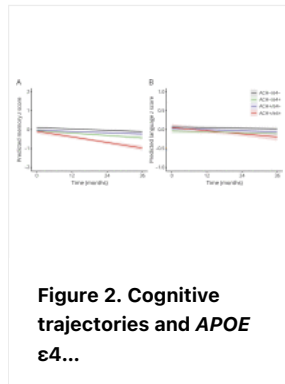
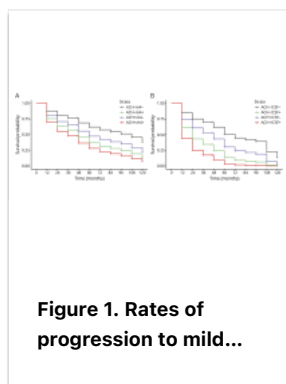
0.02), and there was a significant aCH $\times$ AD risk interaction such that aCH+/ ϵ 4+ individuals showed greater than 2-fold increased risk (HR 2.69, $p < 0.001$) for incident MCI relative to aCH-/ ϵ 4-, while aCH+/CSF+ individuals demonstrated greater than 4-fold (HR 4.89, $p < 0.001$) increased risk relative to aCH-/CSF-. Linear mixed effects models revealed that aCH predicted a steeper slope of decline in memory ($t = -2.35$, $p = 0.02$) and language ($t = -2.35$, $p = 0.02$), with effects exacerbated in individuals with AD risk factors.

Conclusions: aCH increased risk of incident MCI and cognitive decline, and effects were significantly enhanced among individuals with genetic risk factors and CSF-based AD pathophysiologic markers. Findings underscore the adverse impact of aCH medications on cognition and the need for deprescribing trials, particularly among individuals with elevated risk for AD.

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Clear your mind

As we start to understand the effects of chronic inflammation on the brain – from depression to dementia – we are unlocking new treatments, says **Manuela Callari**

GOLAM KHANDAKER's mother has had arthritis for as long as he can remember. She also lives with depression, and it always struck Khandaker how precisely her arthritis flare-ups coincide with her most severe episodes of low mood.

Perhaps it isn't surprising that these bouts of painful inflammation might cause her to feel low. But as Khandaker, then studying for a PhD at the University of Cambridge, investigated more closely, it became clear there was more going on.

In fact, research is revealing the profound effect persistent low-level inflammation has on the brain – which was once thought largely impervious to the fires burning elsewhere in the body – and what this means not only for depression, but for anxiety, schizophrenia, Alzheimer's disease and more. By unpicking the mechanisms driving these connections, researchers are coming up with new ways to protect people's brains and mental health, on top of the many day-to-day ways we can help ourselves.

Our immune defences are vital for survival. When the body detects an infection or injury, it activates an immune response, characterised by a cascade of inflammatory proteins called cytokines, to eliminate the pathogen and promote tissue repair. "Sickness behaviour" can also be triggered – a constellation of symptoms such as fatigue, social withdrawal and loss of appetite that is strikingly similar to major depression. In the acute phase of an illness, this behaviour is beneficial and signals the need to rest and recover during times of

physical injury or infection.

Sometimes, however, the acute immune response doesn't fade, and cytokines linger long after the initial battle is won, resulting in chronic low-grade inflammation. This is one of the scourges of the modern world, contributing to heart disease, type 2 diabetes, kidney disease and more. Now, the toll this takes on our brains is also becoming evident.

High levels of inflammatory markers are often found in people with acute mental health conditions. One 2020 study of more than 5000 people with depression, for instance, found they had elevated levels of inflammatory molecules in their blood compared with a control population, leading the study's authors to conclude that "depression is... a pro-inflammatory state".

The fire within

Elevated cytokine levels have also been found in people with schizophrenia and bipolar disorder, and in June, the link between chronic inflammation and mental health conditions was confirmed on a massive scale. An analysis of 1.5 million people from the UK's Our Future Health cohort found that people with conditions associated with chronic inflammation – such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease – have almost double the risk of experiencing anxiety and depression, even after adjusting for factors like chronic pain and income.

"The surprising part was that the risk for all

the different mental health conditions was pretty much identical [regardless of which inflammatory condition they had]," says Arish Mudra Rakshasa-Loots at the University of Edinburgh, UK, who led the study. "This indicates there is something more going on there beyond just the experience of chronic pain or social isolation." The consistent link across different conditions strengthens the case that a shared biological mechanism – inflammation – is at play.

But teasing apart cause and effect is tricky: does the inflammation cause the illness, or is it a consequence of it?

One of the first researchers to begin to untangle this question was Andrew Miller at Emory University in Atlanta, Georgia, based on observations in the early 2000s that people receiving interferon-alpha (IFN-alpha), an inflammatory cytokine used as a cancer therapy, were developing severe depression. "We knew there was a relationship between increased inflammatory markers and depression, but we didn't know which was the chicken and which was the egg," says Miller.

To find out, Miller and his colleagues carried out a randomised controlled trial, in which people were randomly assigned to receive either the treatment or a placebo. They found that pre-treatment antidepressants decreased the incidence of depression associated with IFN-alpha treatment in people with melanoma, and this causal link has since been replicated with at least two other inflammatory stimuli – endotoxin and typhoid vaccination.

Another way to tease apart causality is to ➤

analyse long-term monitoring studies to test whether pre-existing inflammation increases the risk of subsequent mental health conditions. For instance, Khandaker – now a psychiatrist at the University of Bristol, UK – and his colleagues used data from the Avon Longitudinal Study of Parents and Children in the UK, which measured levels of the inflammatory protein IL-6 in about 4500 children when they were 9 years old. They found that higher levels of this inflammatory marker in childhood were associated with 50 per cent higher odds of depression and a nearly two-fold increased risk of psychosis at age 18. “That clearly suggested that inflammation can precede mental illness,” says Khandaker.

The team then used a genetic technique called Mendelian randomisation, which tests whether the association between two things is likely to be a causal relationship or due to some third factor that influences the likelihood of both, such as lifestyle or another illness. In a study published earlier this year, the researchers sifted through 735 immune-related proteins and found strong evidence that specific inflammatory pathways have a causal role in depression, schizophrenia and Alzheimer’s disease. Of course, other factors are likely to be at play, too. “We know depression is a psychologically stressful condition, so the associated stress could itself cause inflammation,” says Khandaker.

Still, for Miller, the evidence is compelling enough that he expresses frustration with the persistence of the idea that inflammation isn’t a cause of depression, but merely a secondary symptom resulting from the lifestyle habits that often accompany it, such as smoking, poor diet and inactivity. “But [research] has shown that inflammation can cause depression,” he says.

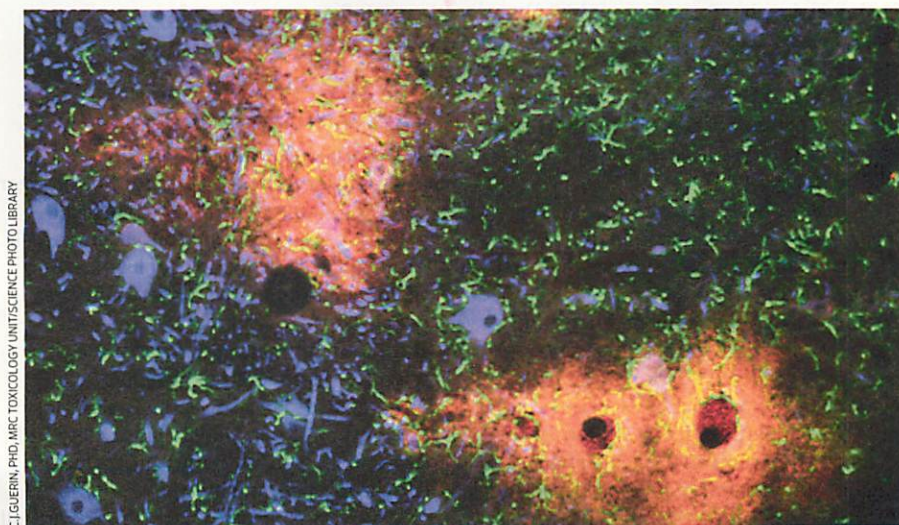
So, if chronic exposure to systemic inflammation affects our brain and mental health, the question is: how?

When Khandaker attended medical school in the 1990s, the brain was considered an immune-privileged fortress. “It was shielded from the rest of the body by the blood-brain barrier, our professors told us,” he recalls.

This barrier – a tightly regulated perimeter of cells – is designed to allow essential nutrients, such as glucose and oxygen, to pass through, while blocking toxins, pathogens, inflammatory cells and proteins. But research is revealing that under conditions of chronic

“This relentless friendly fire ultimately leads to cognitive decline”

When the blood-brain barrier breaks, leakage (orange) occurs from blood vessels (round black holes) into brain tissue



C. GUERIN, PHD, MRC TOXICOLOGY UNIT/SCIENCE PHOTO LIBRARY

QUENCHING THE FIRE

Many lifestyle factors influence our levels of chronic inflammation. Here are some key findings:

SEDENTARY BEHAVIOUR

More time spent seated or reclining, whether watching TV, sitting in a car or working at a computer, is associated with higher levels of chronic inflammation. This effect is likely to be due to many factors, including reduced activity of an enzyme in load-bearing muscles in our legs and core, leading to abnormal metabolism of fats.

DIETARY FIBRE

Many studies show that a high fibre intake is associated with decreased inflammation. Fibre covers a broad range of different plant-derived compounds that feed our gut microbiome. This promotes gut bacteria to produce helpful substances called short-chain fatty acids, which help maintain the gut lining and have an anti-inflammatory effect on the body.

OBESITY

Obesity is a key risk factor for chronic inflammation, due to the pro-inflammatory effect of excess subcutaneous fat. This means that losing weight is one of the most effective lifestyle changes we can make. One study found that, for people with a form of chronic inflammatory arthritis, weight loss alone leads to significant improvement in symptoms, while also reducing the underlying inflammation.

inflammation or stress, this protective wall can become leaky.

Caroline Ménard at Laval University in Quebec is investigating how this happens using an animal model of social stress – mice that can develop both high inflammation and behaviours akin to depression and anxiety. Using microscopy, Ménard's team saw that in healthy control mice, the barrier appears as a solid, continuous line, whereas in the stressed, inflamed mice, it looks as if it has been "ripped to shreds".

It is through these gaps that inflammatory molecules like cytokines are "sneaking" into the brain, where they can cause oxidative stress and disrupt neurotransmitter production, she says. In 2022, her team discovered similar structural damage in post-mortem brain samples from people who had depression.

The idea is that stress causes a large drop in levels of a protein called claudin-5, which holds the cells of the barrier together. With claudin-5 depleted, the barrier tears, letting inflammatory cytokines enter the brain. Once inside, they can disrupt key neurotransmitters such as dopamine and serotonin in certain areas, leading to reduced activity in brain circuits responsible for motivation.

Inflammatory signals can also trigger the brain's own specialised immune cells, the microglia

Under normal conditions, microglia act as vigilant housekeepers, cleaning up debris and protecting neurons. However, chronic exposure to inflammatory signals can cause these cells to flip from a protective state to a destructive, pro-inflammatory one, initiating a vicious cycle.

This neuroinflammatory state creates the conditions for the development and accumulation of amyloid-beta plaques, a hallmark of Alzheimer's disease. The presence of these plaques then further activates the microglia, which unleash a storm of inflammatory cytokines, such as IL-1beta, IL-6 and TNF-alpha, as well as oxidative molecules in response. This "inflammatory soup" not only causes direct harm to neurons through oxidative stress, but also recruits more microglia to the fight, amplifying the inflammation, says Ravinder Nagpal at Florida State University.

This mechanism also impairs the microglia's ability to perform their primary duty: clearing the very amyloid-beta plaques that are driving



GUERILLA/LAMY

Eating a Mediterranean diet could reduce levels of inflammation

the problem, making the situation progressively worse, he says. "This relentless friendly fire ultimately leads to widespread neuronal death and cognitive decline."

Another major **pathway through which inflammation affects the mind originates in our gut**. For starters, **gut bacteria can produce many different neurotransmitters, which can influence the brain via the vagus nerve**. So, when the gut microbiota is in an imbalanced state, known as **dysbiosis, caused by a poor diet or antibiotics**, this can affect the production of neurotransmitters, says Nagpal. As well as this, "bad" microbes can produce toxins, such as lipopolysaccharides, that damage the gut lining, allowing inflammatory molecules and bacteria to escape into the bloodstream and trigger systemic inflammation, which can, in turn, make the blood-brain barrier leaky.

In contrast, when the gut is in a healthy state, **beneficial microbes produce anti-inflammatory compounds, such as short-chain fatty acids, that help maintain a strong intestinal barrier**.

This has led some researchers to wonder whether transforming or replacing the gut

microbiome could offer a new form of treatment for mental health conditions and neurodegenerative conditions. Emerging evidence, albeit from small-scale trials, suggests that a **faecal microbial transplant** can alleviate symptoms of anxiety and depression.

A less drastic way to tip our gut microbiome in a healthier direction is via our diet, and there is good evidence **that anti-inflammatory eating patterns really do work**. The most well-researched is the Mediterranean diet, which entails eating plenty of fruits, beans, nuts, whole grains and fish, **with generous amounts of olive oil**, while limiting red and processed meats. For instance, one study of nearly 15,000 people in Italy found that a closer adherence to this dietary pattern correlated with reduced levels of inflammatory markers.

The secret isn't a single superfood, but rather the combined effect of the entire dietary pattern, says Rosa María Casas Rodriguez at the University of Barcelona in Spain. "We think it is the combination of different foods that, with different synergies, increases the effects."

We don't yet know about the impacts on the brain, but some other studies show that adhering to a Mediterranean-style diet is associated with a reduced risk of depression, and further large-scale trials are under way.

The benefits of an anti-inflammatory diet may even extend to shielding the brain from dementia. A 2024 study of data from more than 84,000 older adults with pre-existing conditions such as heart disease or type 2 diabetes who participated in the UK Biobank study found that those eating the most anti-inflammatory diet had a 31 per cent lower risk of developing dementia.

To delve into the mechanisms of these effects, Nagpal and his colleagues conducted a small, randomised trial of older adults with mild cognitive impairment. They found that, compared with controls, **following a Mediterranean diet that was also ketogenic (very low in carbs and high in fat)** for six weeks increased the production of beneficial short-chain fatty acids, particularly butyrate, which is known to be neuroprotective and improve gut barrier health. These changes in the gut microbiome were associated with improvements in Alzheimer's disease biomarkers, such as amyloid plaques, in the participants' cerebrospinal fluid.

Of course, diet isn't the only lever we can pull. What about **regular physical activity?**



Although higher-intensity exercise can cause a normal, temporary spike in inflammation for muscle repair, there is evidence that, in the long run, physical activity dampens chronic inflammation. It is also clear that a lack of exercise is linked to chronic inflammation.

One study from earlier this year of nearly 16,000 people found that sedentary behaviour is correlated with chronic systemic inflammation – which the study's authors called a "sedentary disease". The less you move, the greater the risk.

Sedentary behaviour is also a risk factor for obesity, which has strong associations with chronic inflammation (see "Quenching the fire"). Age is another risk factor, as well as chronic stress, which has a direct impact on the body's inflammatory state by triggering the sustained release of the hormone cortisol.

While cortisol normally acts as a potent brake on inflammation, prolonged exposure can lead to a condition where immune cells become less sensitive to anti-inflammatory signals, triggering a cascade of inflammatory cytokines that can disrupt neurotransmitter metabolism and exacerbate depression. To combat this stress response, there is evidence that mindfulness and meditation can help, but Nagpal's advice is to find an activity you genuinely enjoy, as "happiness is one of the key components that can directly reduce stress".

And then there are medications. In the past decade or so, Miller, Khandaker and others have tested anti-inflammatory drugs typically

"Happiness is one of the key components that can directly reduce stress"

used for conditions such as rheumatoid arthritis to treat depression, and they have generally found a positive impact. However, perhaps unsurprisingly, these medications have by far the greatest impact on those for whom persistent, low-grade inflammation is driving their illness – perhaps up to 1 in 4 people with depression. "The most pressing question in our field right now is how to identify this group," says Khandaker. This isn't straightforward, because there isn't yet a standard biomarker to measure chronic inflammation, which is a complex process involving a range of different immune substances and cells.

Miller argues that a common blood test for C-reactive protein, a general marker of

inflammation, is the "lowest-hanging fruit" for identifying people who might respond to anti-inflammatory treatments, and that this approach is already being trialled in clinics.

But perhaps the most talked-about new approach involves drugs that mimic the satiety hormone GLP-1, such as semaglutide (sold as Ozempic and Wegovy), best known for their dramatic effects on weight loss. While these drugs were originally used to treat diabetes and then obesity, their ability to combat inflammation has put them at the centre of research into cognitive decline and mental health conditions.

Several large observational studies link the use of these drugs to a reduced risk of dementia, depression and anxiety, though, so far, the findings from clinical trials are more of a mixed bag. But all eyes are on the results of two large-scale phase III trials, evoke and evoke+, which are investigating whether semaglutide can modify the course of early-stage Alzheimer's disease, with results expected later this year.

A key question is whether the anti-inflammatory effects of GLP-1 drugs are mainly due to weight loss and better blood glucose control, both of which dampen inflammation, or via a direct effect on the immune or nervous system. Studies presented at the Society for Neuroscience meeting in Chicago last October by the research company Neurofit in Strasbourg, France, show that in mouse models of Alzheimer's, GLP-1 drugs improve cognitive deficits even in healthy-weight animals. "This demonstrates that the beneficial effect occurs directly in the brain, rather than being a secondary consequence of weight loss," says Emile Andriambeloson at Neurofit.

All this highlights how there is still a way to go before we have a full understanding of how inflammation messes with our minds – but the research is already beginning to translate into tangible clinical progress. The other good news is that, for the majority of us who may be unknowingly experiencing long-term low-level inflammation, there are many lifestyle factors that can help simmer down the heat burning within. ■

Exercise is another way to dampen down inflammation



REUTERS/CARLOS JASSO



Manuela Callari is a freelance science writer

Local v. Systemic inflammation A Courtroom Experience

When one treats whiplash-injured patients, occasionally chiropractic testimony will become necessary. Treating chiropractors testify as experts for the plaintiff (injured patient). Insurance defense attorneys usually attempt to minimize (challenge, discredit, refute, embarrass, etc.) the importance and relevance of the plaintiff chiropractor testimony.

In a recent case of uncontested injury and liability, the defense essentially conceded these classic chiropractor testimony issues:

- Injury causes local inflammation
- Local inflammation alters the nociceptive afferent threshold (causes pain)
- The resolution of inflammation is fibrosis
- Fibrosis reduces injured joint movement parameters, and alters the instantaneous axis of rotation (creating the orthopedic component of the subluxation complex)
- Reduced and/or altered joint movement parameters proportionally reduces mechanical afferentation (proprioception) towards the central neural axis, rendering the pain gate chronically open and resulting in chronic pain
- Applied, specific line-of-drive mechanical forces (chiropractic adjustment), would realign the developing fibrosis tissue along the direction of the applied forces, improving joint movement parameters, improving mechanoreception (proprioception), closing the pain gate, and reducing pain perception
- And that this line of reasoning and evidence is supported by history, complaint, examination, imaging (especially stress radiography), and standard functional measurement outcome assessments

So where did the defense go during the cross-examination of the treating chiropractic expert? They went to issues pertaining to **systemic inflammation** (as contrasted to **local inflammation**), as impacting the magnitude of the patient's pain, the duration of the patient's pain, the recovery of pain and function, and the residuals documented on functional measurement outcomes. Their basic argument was this:

Total Inflammation = Local Inflammation + Systemic inflammation

Their argument (simplified) was that the patient's pain and disability are established by the patient's **Total Inflammation**. Yet, the injury caused only the **Local Inflammatory** component of the patient's total inflammation. Therefore, they

argued that any component of the patient's clinical status attributed to **Systemic Inflammation** was not their responsibility.

This argument is weak, as attorneys often state that all injured people get equal protection under the law, including the frail, (including those with pre-injury **systemic inflammation**). Hence, they used an extension of the argument by claiming that the standard of care in chiropractic is to treat not only the **local inflammation**, but also the **systemic inflammatory** issues in order to optimize recovery rates and reduce residual pain and functional problems.

The attorney was well educated, articulate, and very knowledgeable about a number of related **systemic inflammatory** variables. These included diet (consumption of alcohol, refined carbohydrates, red meat, etc.), exercise, sleep hygiene, antioxidant supplements, and more. His primary line of questioning centered around the ratio of omega-6 to omega-3 fatty acids. His eloquent argument was that the standard of care for chiropractors was to assess and recommend omega-3 fatty acid supplementation for all patients in pain, including those injured in a whiplash accident. His argument included:

- If the treating chiropractor does not assess the omega-6 to omega-3 ratio and intervene appropriately, the chiropractor is practicing below the standard of care. As such, any nociceptive and/or functional residuals are ascribed to substandard chiropractic care and **not** to the injuries sustained in the accident.
- If the patient does not follow the advice of the treating chiropractor in reducing his systemic inflammatory profile (like taking omega-3 supplements), any nociceptive and/or functional residuals is ascribed to the patient and **not** to the injuries sustained in the accident.

The Bottom Line:

We advocate assessing the omega-6 to omega-3 ratio in all patients (we do). It is a quick, simple finger prick analysis that is very informative. The most anti-inflammatory component of fish oil is eicosapentaenoic acid (EPA); as such, we prefer a formula that has a higher level of EPA, preferably a ratio of 2:1 of EPA:DHA. (DHA = docosahexaenoic acid). Classically, dosing is determined by the labs, but in general, supplementation is not likely to achieve an anti-inflammatory profile without consuming 3000 mg daily of EPA + DHA (EPA = 2,000 mg; DHA = 1,000 mg).

There are other interesting factors that warrant review and discussion, but for another time.

References that support these concepts are included after the graph:

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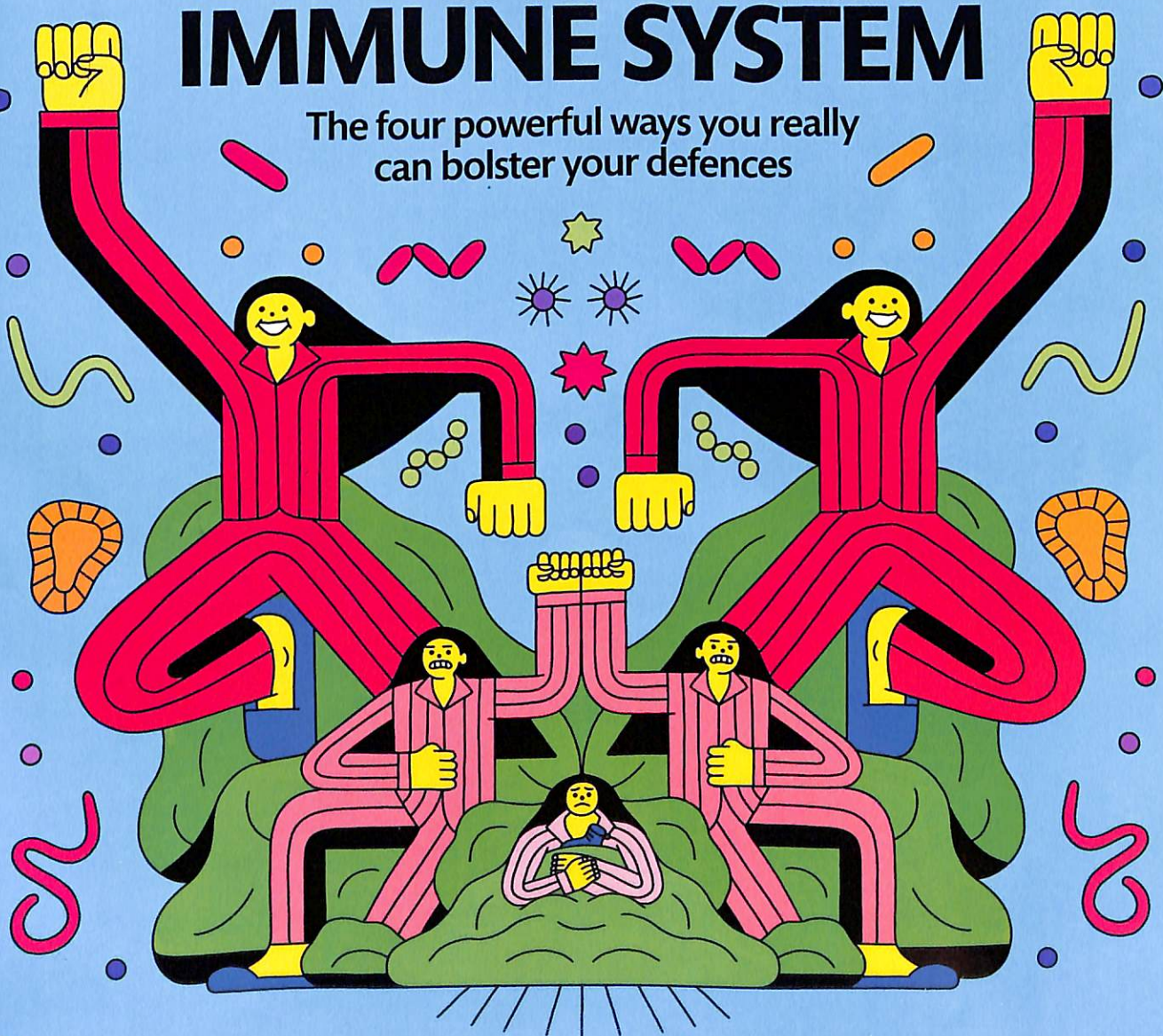
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Improve your immunity

You can upgrade your immune system to help fight off infection, but not in the way you think, discovers **Helen Thomson**

I AM lying under a blanket, feeling rough, staring at a bowl of oranges. Every fibre of my being is urging me to devour the lot. I can hear my mum – and medical friends at university – insisting that a megadose of vitamin C will head off my oncoming cold.

The thing is, I know it isn't true. Despite the common belief, vitamin C doesn't prevent colds. At best, it may shave a few hours off your symptoms. Still, the myth endures, because who wouldn't want an easy way to supercharge their immune system?

Over the past weekend, friends have also suggested I drink ginger tea and gobble down some turmeric. It got me thinking: what, if anything, really helps strengthen the immune system to aid it in warding off potential invaders? To find out, I decided to take stock of my own immune health and find an evidence-based approach to improving it. Along the way, I learned how absent bacteria, the contents of my spice rack and even my outlook on life play a critical role in enhancing my immune defences – and uncovered the one thing that might harm immunity more than anything else.

We often talk about “boosting” our immune

system, but, taken literally, that would be a terrible idea. Immunity isn't a dial you can just turn up, says immunologist Daniel Davis at Imperial College London.

Your immune system is made up of a diverse network of cells, proteins and organs that must be powerful enough to attack invaders but restrained enough not to target healthy cells or harmless molecules – overreactions that underlie autoimmune conditions and allergies. “You don't want to boost your immune system. You want to help it respond appropriately,” says Davis. “That's a lot harder to do.”

But before I start tinkering with my immunity, I need some idea of what shape it is in. According to immunologist Jenna Macciochi at the University of Sussex, UK, a rough gauge is simply counting your colds. “An average person experiences a few mild illnesses a year,” she says. “More frequent or severe illness can indicate an underlying immune dysfunction or heightened susceptibility.”

By that measure, my immune system is worse than average: I had a couple of colds at the beginning of the year, plus a recent





Sauerkraut and fresh ginger are tasty ways to help your immunity

A high CD4 count is good: it means plenty of generals to organise any potential immune battle. High CD8 is helpful if you are currently fighting an infection, but chronically high levels indicate an overactive immune system and increased inflammation, which is linked with several serious health problems. CD8 levels increase with age and with lifestyle factors like smoking, heavy drinking and lack of physical activity.

Making the immune grade

These numbers are inadequate on their own. Instead, you need to work out their ratio by dividing CD4 by CD8. A ratio above 1 suggests CD8 levels are being kept in check, or "restrained", as Ahuja calls it. A ratio below 1 suggests they are "unrestrained", something you want to avoid. Combine this result with your CD4 level, which ideally should be above 800 cells per microlitre, and you have your grade (see "Immunity score", right). My ratio was 2.66, meaning my CD8 levels are being kept in check, but my CD4 count was 691 per μL , which translates to a grade of 2a. Respectable, but could do better.

Immune grade is a meaningful measure: over the past decade, Ahuja's team has tracked the immune grade of more than 10,000 people. Those with better scores respond well to vaccines, are less susceptible to infections and have lower rates of hospitalisation from infections. "During the pandemic, we found that 80-year-olds with a good immune grade were less likely to be hospitalised with covid-19 than people of any age with the lowest

"For long-term immune power, we must look to our microbiome"



Immunity score

For a high immune grade, you need good levels of CD4+ cells, and you also need your CD8 cells to be kept in check, or "restrained"

	Score	CD4+ T-cells (cells/mm ³)	
Immune Health Grades	I	≥800	Restrained
	IIa	≥500 <800	
	IIb	>200 <500	
	IIc	≤200	
	III	≥800	Unrestrained
	IVa	≥500 <800	
	IVb	>200 <500	
	IVc	≤200	

immune grade," says Ahuja. Having a bad grade also puts your mortality on the fast track: 40-year-olds with grade 4 – the weakest grade – face the same mortality risk at that age as healthy 55-year-olds with a grade 1 result.

So, how do I move from 2a towards grade 1? I don't smoke, which has a negative impact on almost every type of immune cell studied, so my first instinct is diet.

Here, our mass ignorance about vitamin C is a cautionary tale – particularly as we live in a world where inaccurate health advice spreads so easily on social media. This myth actually began in the 1970s with Nobel prize-winner Linus Pauling, whose book *Vitamin C and the Common Cold* spread the message that high doses could prevent colds. "He was always on TV, always on the radio, everyone was listening to him," says Davis. Later analyses suggested that his data was flawed and cherry-picked, but the message stuck.

There is something that might give me a quick fix, however. A 2013 review concluded that 75 milligrams of zinc taken daily within 24 hours of getting your first sniffle reduced the duration of a cold, with significantly fewer people still experiencing symptoms on day 7 than those who took placebos.

For long-term immune power, though, we need to look to our microbiome. The trillions of bacteria inhabiting our gut influence the action of all the main cell types in our immune army. Vitally, they maintain the integrity of the gut lining, preventing leakiness and inflammation, and churn out beneficial chemicals such as short-chain fatty acids, which can modify T-cells' response to viruses like influenza or HIV.

The simplest way to build a healthy microbiome is to ensure microbial diversity by feeding them plenty of whole foods, plus at least 30 grams of fibre per day. Another easy intervention is gardening. Healthy soil is teeming with beneficial bacteria that get transferred directly from our hands to our guts and are linked to better immune health. Amish communities who farm manually, for instance, tend to have stronger immune systems than similar Hutterite groups who use industrialised farming.

Then there are probiotics – live microorganisms – that you can drink or consume through fermented foods like natural yogurt, kimchi or kefir. During the covid-19 pandemic, Tim Spector, co-founder of the nutrition app Zoe, and his colleagues

“Your immune system must be powerful enough to attack invaders but not target healthy cells”

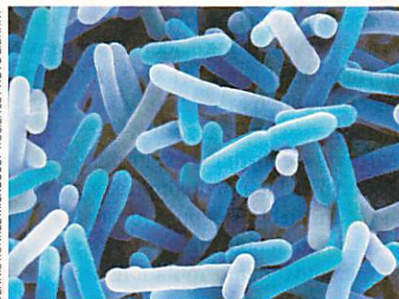
surveyed almost half a million people and found those taking probiotics or eating fermented food regularly had less severe covid-19 symptoms than those taking vitamin C, zinc, garlic or nothing.

Of course, correlation isn't causation, but other studies add to its weight. In a 2021 trial, 36 people were randomly assigned to eat five to six daily portions of fermented foods or a high-fibre diet for 10 weeks. The fermented food group saw bigger shifts in immune cells and a significant decrease in inflammatory proteins in just a few weeks, compared with the fibre group.

I have recently started eating around three portions of kefir and the like each day. The Zoe researchers tell me that fewer servings of fermented food should still be beneficial, though specific doses haven't been tested. For the sake of my immune system, I am motivated to try more. Five to six servings of fermented food a day sounds excessive, but each serving doesn't need to be large, it is about 300 calories altogether, says Christopher Gardner at Stanford University in California, who led the trial. “[It] isn't as much as it might sound.”

While it also seems a little excessive to delve much deeper into your microbiome, I recently happened to be approached by researchers at

DENNIS KUNKEL MICROSCOPY/SCIENCE PHOTO LIBRARY



Bifidobacterium in the gut helps prevent over-inflammation

Gardening can expose you to more beneficial bacteria



the Functional Gut Clinic in London, the first microbiome clinic in the UK, with the offer of being their first patient to receive a full gut MOT. So, over a few days, I took a battery of stool, breath and glucose tests. Alongside some interesting revelations about bad bacteria that had taken up residence in my small intestine, giving me insight into some recent health issues, the results also offered a surprising window into my immune health. It turned out that my gut was completely devoid of four types of beneficial bacteria that are normally a significant part of the adult gut microbiome.

Their absence was concerning. For instance, one of the missing bacteria, *Bifidobacterium bifidum*, supports immune health by preventing over-inflammation and boosts the activity of immune cells that kill pathogens, as well as increases the production of certain antibodies. Anthony Hobson, clinical director at the Functional Gut Clinic, suggests that it could be my childhood dairy intolerance that led to these helpful bacteria – which are often consumed first through breast milk, then in other dairy products – failing ever to find a niche.

Most people with a healthy, balanced diet shouldn't need to take probiotic supplements – or, for that matter, spend £900 (\$1180) on advanced microbiome tests unless they have significant gut issues. But armed with this information, I have refocused my diet and now take daily probiotics to feed my gut its missing microbes. Reseeding the microbiome is challenging after the first five years of life, but I'm hoping that topping up with bacteria-rich foods will help my immune health in the long run.

Spice up your diet

As I cast a thankful eye on some homemade sauerkraut in need of burping, I consider what else might earn its space in my store cupboard. I drink fresh ginger and turmeric tea daily, vaguely aware of supposed immune benefits. But is this, like vitamin C, largely wishful thinking?

Perhaps not. A recent review suggests that ginger does have anti-inflammatory properties, triggering the release of chemicals called cytokines that help regulate immune responses. “I do recommend people eat ginger in order to improve the health of their immune system,” says Fitriyono Ayustaningwarno at Diponegoro University in Semarang, ➤



Indonesia, lead author of the review. He adds, however, that its anti-inflammatory properties will only be effective when consumed in adequate amounts. “The best way to get the bioactive compounds in the ginger is by eating it fresh,” he says.

Turmeric also has a wealth of research on the immune benefits of its active compound, curcumin – in animals at least. The molecule that gives the spice its distinct orange colour protects against pneumonia by regulating immune responses and dampens inflammation. It also boosts the immune system’s ability to fight a range of cancers.

In humans, however, results are limited. Curcumin may improve symptoms of rheumatoid arthritis by influencing the activity of macrophages, immune cells that digest pathogens, and there are trials

testing whether it can improve the efficacy of chemotherapy. But strong evidence is severely lacking. The problem – and it’s a big one – is its bioavailability. When we eat turmeric, barely any curcumin is actually absorbed.

Researchers are currently exploring ways around this. Taking curcumin alongside piperine, found in black pepper, prevents the body from metabolising it so quickly, for example, and other formulations are being developed to improve absorption.

“You wouldn’t use curcumin to prevent getting the flu or other infectious disease,” says Claus Schneider at Vanderbilt University in Nashville, Tennessee. But he says there is good evidence that its breakdown products can act on pathways crucial for regulating immune response and inflammation. He points to a small study of people on haemodialysis,

which showed that 2.5 g of turmeric added to a daily fruit juice for three months reduced inflammatory proteins in their body compared with a placebo.

So my fresh ginger and turmeric tea is no miracle cure, but it is probably doing more good than harm.

While diet is a powerful but complex modulator of immune health, exercise is more straightforward. A wealth of evidence shows that moderate, regular physical exercise is one of the most effective ways to improve your immune system.

Moderate exercise is anything that raises your heart rate and makes you a bit sweaty: brisk walking, swimming, gentle running. These activities improve immune surveillance – increasing the number of circulating immune cells that scan for abnormal cells and pathogens – boost antibody production and help the body return to normal after an immune response. In July, Yang Li at Beijing Normal University in China and her colleagues performed a large-scale review of all the evidence of exercise on the immune system and their conclusion was frank: “Exercise minimises the chance of becoming sick... Exercise is considered a naturally built-in immune booster.”

But more isn’t always better. High-intensity training can raise levels of the stress hormone cortisol, which temporarily suppresses our immune system. When mice infected with a parasitic infection swam for 60 to 90 minutes, five times a week, it exacerbated symptoms by 50 per cent, whereas those that did so for 30 minutes, twice a week boosted helper T-cells and improved clearance of the parasite. In people with depression, spending 40 minutes walking, four times a week has been found to lower markers of inflammation in the brain by up to 25 per cent, whereas more intense exercise increased them.

Because of this, some advice has warned against daily exercise, arguing it could have negative effects on immune function. In 2018, however, John Campbell and James Turner at the University of Bath, UK, disproved this idea, showing that daily exercise increased T-cell production by up to 25 per cent and decreased inflammatory markers by up to 35 per cent.

So, how much is too much? Li and her colleagues concluded that negative effects on immune health are particularly noticeable in athletes who engage in high-intensity interval training, which involves short

A brisk walk is one way to raise antibody production



“Exercise is considered a naturally built-in immune booster”

Psychological Stress and Susceptibility to the Common Cold

New England Journal of Medicine

August 29, 1991; Vol. 325; No. 9; pp. 606-612, 654

Cohen S, Tyrrell DA, Smith AP.

Department of Psychology, Carnegie Mellon University, Pittsburgh

These authors prospectively studied the relation between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses.

After completing questionnaires assessing degrees of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses.

The subjects were then quarantined and monitored for the development of evidence of infection and symptoms.

The rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in the degree of psychological stress.

CONCLUSIONS:

Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness.

ALSO NOTED IN ARTICLE AND ITS FOLLOW-UP:

"Psychological stress is thought to influence immune function through autonomic nerves innervating lymphoid tissue, or hormone-mediated alteration of immune cells."

"In biomedical terms, 'stress' refers to any adverse physical, mental, or emotional stimulus (stressor) that upsets the organism's homeostasis."

"At the physiological level, stress has been the subject of study going back to Walter B. Cannon's description of the 'fight or flight' response involving actions of the sympathetic nervous system and the adrenal medulla."

How the

2023

Immune System Works

Seventh Edition

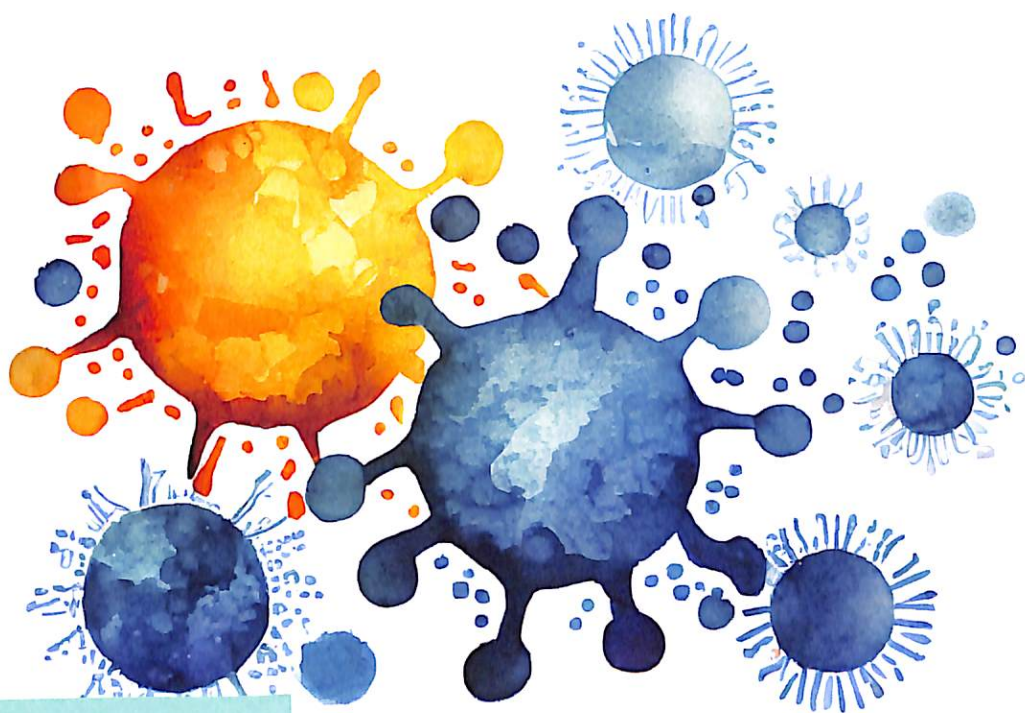
Lauren Sompayrac



WILEY Blackwell

The Logic of Immunity

Deciphering an Enigma



2024

B. J. Cherayil

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occupies the colon and causes a severe and very treatment-resistant form of diarrhea.

Defenders in Residence

K Although the epithelium is a robust, self-repairing barrier, it can be weakened by mechanical, chemical, thermal, or other types of injury and allow the entry of pathogens or potentially virulent members of the microbiota that are normally kept in check. Significant breaches of the epithelium, whether they are secondary to weakened barrier functions or the result of active intrusion by pathogens, are handled by a second line of defense consisting of the immune cells that reside in almost all tissues, including in the vicinity of epithelial surfaces. There are many types of resident immune cells—macrophages, dendritic cells, and mast cells, to name a few—and new ones are still being discovered. Even cells that are not traditionally considered to be part of the immune system, such as the endothelial cells that line blood vessels, nerve cells, and the fibroblasts that contribute to the general background “stuff” or stroma of most tissues, can be co-opted to carry out immunological functions when needed. All these cells may become involved in the immune response in one way or another depending on the circumstances, and we will encounter several of them in later sections. But from the perspective of dealing with microorganisms that have made their way through the epithelium, one of the most important cell types is the macrophage.

MP
MP
MP As its name indicates, the macrophage is the big eater of the immune system. This amoeba-like cell is singularly skilled at ingesting (or phagocytosing, to use the more scientific term) any particulate material—dead cells, cellular debris, foreign bodies, microorganisms—that it encounters as it crawls slowly through tissue spaces. During phagocytosis, the macrophage extends protrusions of the plasma membrane that engulf the particle being targeted, ultimately enclosing it in a membrane-bound compartment or organelle called the phagosome. The phagosomal cargo is then subjected to a barrage of caustic chemicals, including highly reactive radicals of oxygen and

Ros

nitrogen, before being delivered to another organelle—an acidic sub-cellular compartment called the lysosome—where its destruction is completed as a result of exposure to degradative enzymes. There are very few microorganisms that can survive this harsh treatment. Consequently, tissue macrophages are efficient defenders of their territory, rapidly eliminating any microbes that might make their way through the epithelium. If the number and virulence of the microbial intruders is low, they are cleared by macrophages with little or no fuss and we are often unaware that a problem has occurred. In fact, it is likely that such trivial skirmishes between intruders and defenders occur several times a day in our skin and other barrier tissues because of minor breaks in the epithelium. That they do so silently, without becoming apparent as a clinical abnormality, is a testament to the effectiveness of macrophage antimicrobial functions. It is only when these functions are missing or defective do we realize how important they are. Consider, for example, the plight of individuals with an inherited condition known as chronic granulomatous disease (CGD), which is caused by a genetic mutation that renders macrophages and other phagocytic cells incapable of generating the reactive oxygen radicals necessary to kill microorganisms that they have engulfed. Patients with CGD are plagued by recurrent infections of the lungs and of the soft tissues beneath the skin, often involving organisms that are not particularly virulent and that the rest of us are able to shrug off thanks to the quiet efficiency of our phagocytic cells.

The person who is widely credited with recognizing the importance of macrophages and phagocytosis in antimicrobial defense is the nineteenth-century Ukrainian zoologist Élie Metchnikoff. He appears in most photographs as a grandfatherly figure, with kindly eyes, a hint of a smile, and the unkempt hair and bushy beard that marked serious men of that period. But by his own account his early life was spent under the shadow of recurrent episodes of depression. He attempted suicide twice: the first time, by morphine overdose, following the death of his beloved wife and the second, by auto-infection with pathogenic bacteria, in response to work-related stress. Yet, he was deeply

illness and that we associate with the feeling of being sick: fever, dis-
taste for food, and the desire to get away from it all and crawl into bed.
The various sickness behaviors, as well as the fever, are manifestations
of the underlying inflammatory process and are the result of the cyto-
kines that are released at the site of infection. The cytokines make
their way into the circulation and induce cells in the brain—endothelial
cells and macrophage-like cells known as microglia—to secrete addi-
tional molecules, including small lipids, that act on specific nerve
cells. These neurons are wired into neural circuits that control body
temperature, appetite, mood, and social interactions. Depending on
the particular network that they are connected to, activation of the
nerve cells can make you unwilling to eat, reluctant to interact with
other people, or unable to look on the bright side of life. Some of the
activated circuits can also fool your brain into thinking that your body
temperature is too low and that it needs to be raised by shivering and
reducing blood flow to the skin (which is why you develop a fever).

The importance of fever and sickness behaviors in dealing with in-
fection is not entirely clear, but there is some evidence to suggest that
elevated body temperature may inhibit the growth of pathogens and
increase immune cell activity. Social withdrawal may help to decrease
transmission of pathogens from one individual to another, and loss of
appetite can alter metabolism in ways that enhance the ability to tol-
erate the presence of certain types of pathogens. Some of these ideas
are speculative or based on a limited number of animal experiments,
so they are not fully substantiated. But what is undeniable is that fe-
ver and sickness behaviors have been conserved through evolution
(they occur in most animals, and even cold-blooded ones like lizards
and snakes, which cannot regulate their own body temperature, will
move to a warm location when they are sick), suggesting that these re-
sponses probably have some survival value.

Resolution: Cooling Off

Once the microorganisms that initiated the inflammatory process have been eliminated, something that is usually accomplished only after the



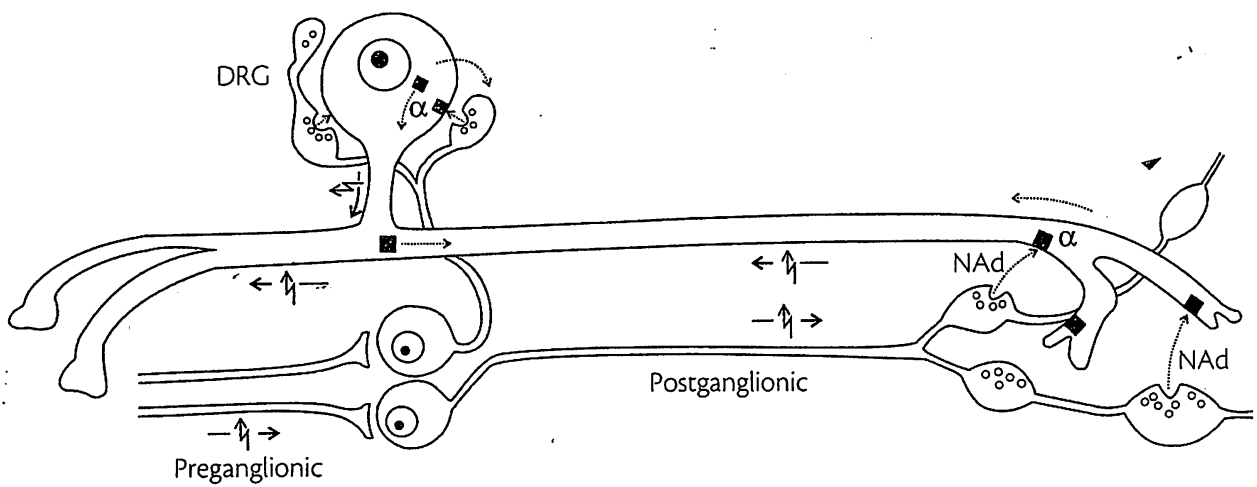
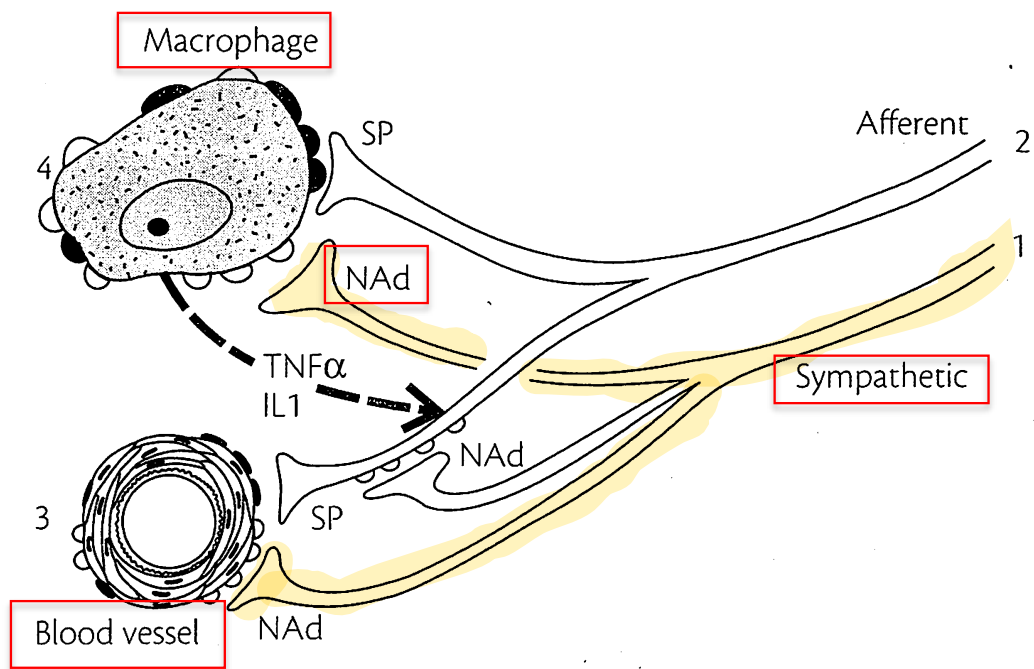
2013

EDITED BY
Christopher J. Mathias
Sir Roger Bannister

Autonomic Failure

*A Textbook of Clinical Disorders of
the Autonomic Nervous System*

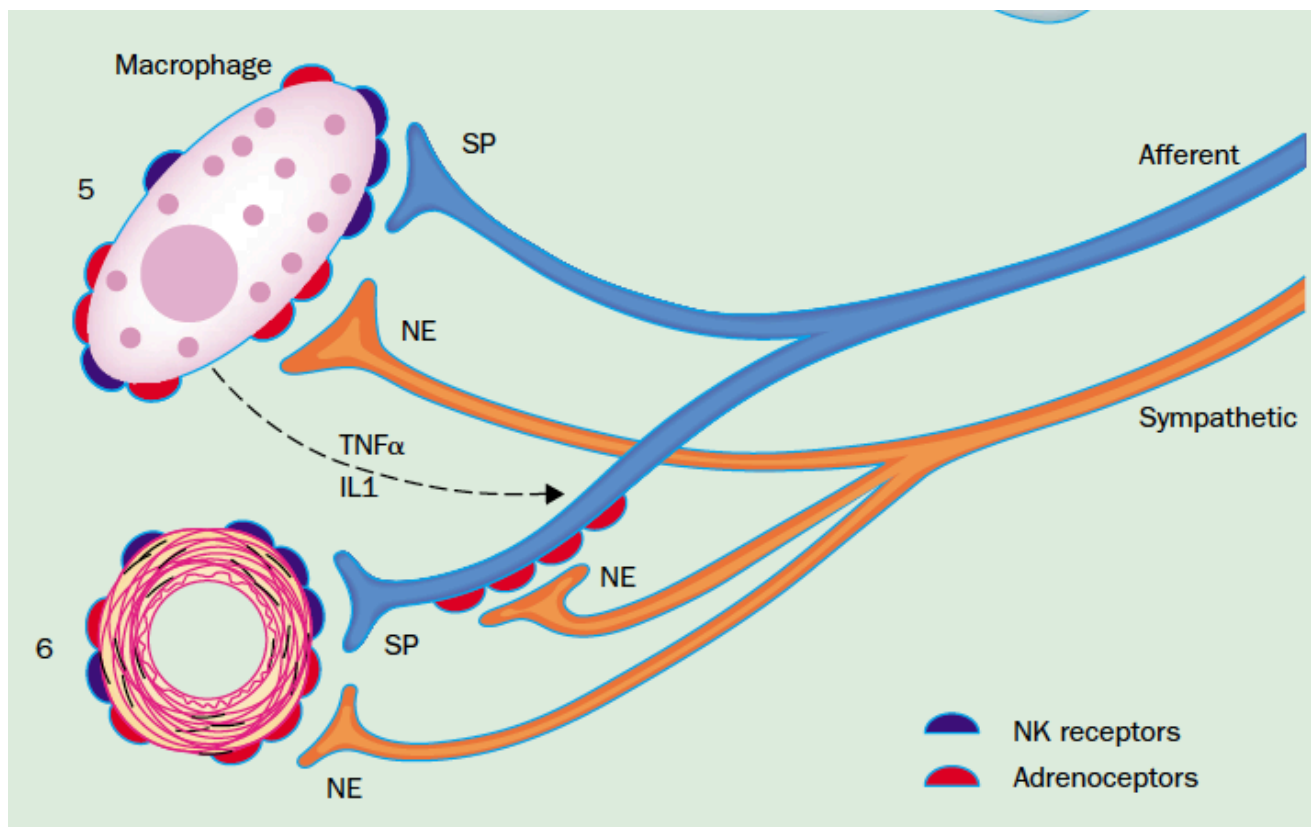
Fifth Edition



Complex Regional Pain Syndrome: Mystery Explained?

THE LANCET, Neurology
November 2003; Vol. 2; No. 11; p. 691

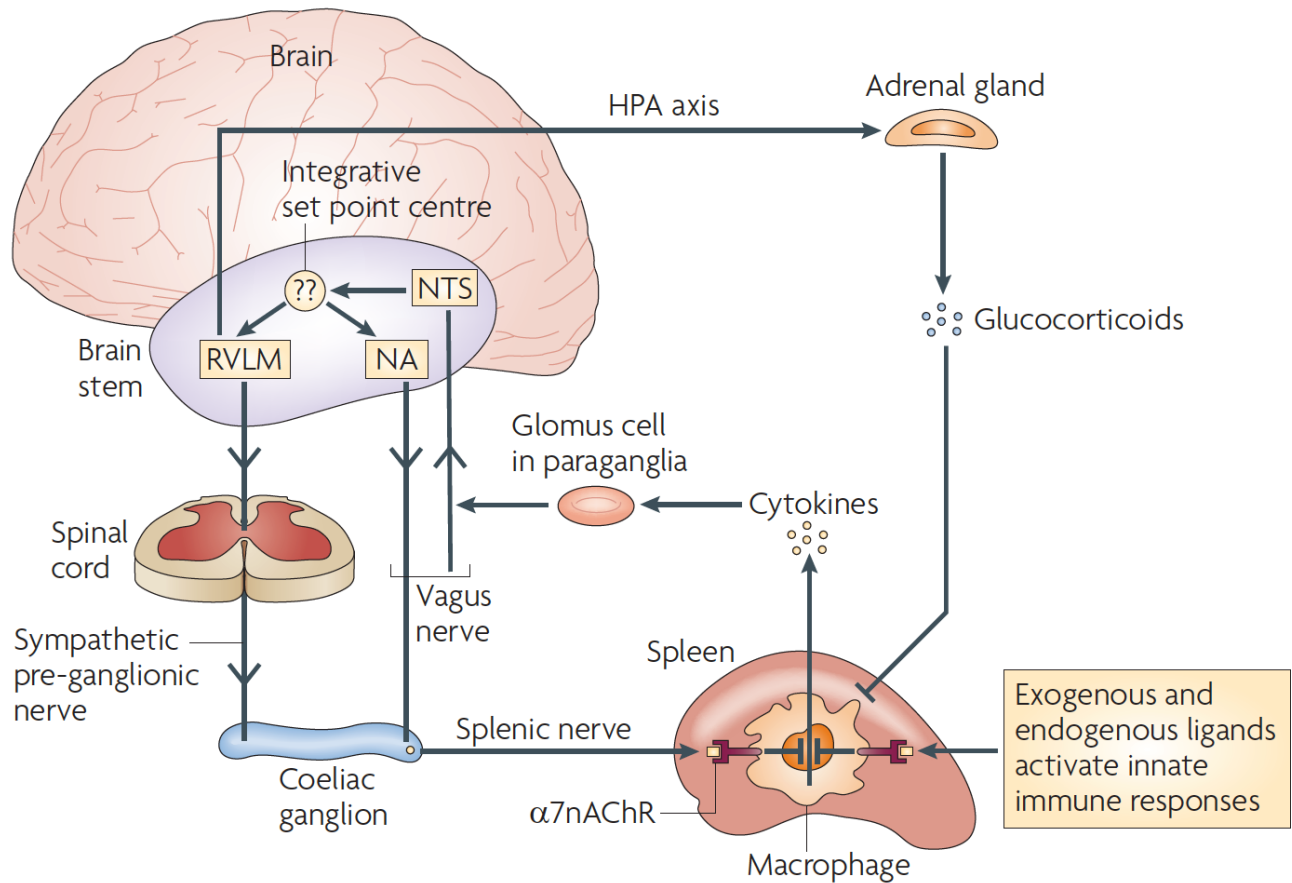
Wilfrid Jänig and Ralf Baron:
Department of Physiology, Christian-Albrechts
University of Kiel, Germany



Reflex Control of Immunity

Nature Immunology
June 2009

Kevin Tracey



By Bernadine Healy, M.D.

The Dangerous Art of the Tattoo



TATTOOS ARE FAST BECOMING A MARK of the 21st century, with one quarter or more of those under the age of 30 adorning their skin with at least one. Whether driven by the urge for personal expression or just plain youthful impulsiveness, most people get tattooed without a clue about the health implications of this invasive skin-puncturing procedure. I'd suggest that all tattooing require a signed consent form outlining risks—the most obvious one being a major case of remorse.

Upwards of 50 percent of those who get tattoos later wish they hadn't. Their regrets become medical when they visit a dermatologist to have the tattoos removed, which is both painful and expensive. In the July issue of the *Archives of Dermatology*, researchers at Texas Tech University Health Sciences Center report on what's behind the change of heart: moving on from the past, problems wearing clothes, embarrassment, and concerns that tattoos could adversely affect job or career.

But tattooing is designed to last forever, delivering permanent ink deep under the epidermis. The skin reacts by protectively encapsulating the alien clumps of pigment in dense fibrous tissue while a few nearby lymph nodes collect what migrates out. For a long time, removal meant surgical excision or deep abrasion of the skin, invariably causing scarring and sometimes the need for skin grafting. In the preferred approach now, the tattoo gradually fades away under many months of laser treatments tailored to the wavelength of the pigments. Sounds easy. But with disruption, the fading tattoo becomes more like a toxic chemical dump.

Chemists from several laboratories, including the government's National Center for Toxicological Research, have identified low levels of carcinogens in tattoo ink. But the laser removal process, which demolishes the pigment by scorching it with heat, triggers chemical reactions that generate carcinogenic and mutation-inducing breakdown products, which are then absorbed by the body. Recently, German scientists reported that concentrations of toxic molecules from red and yellow pigments increased up to 70-fold after laser irradiation. And the bigger the tattoo, the greater the toxic release. This

can only make one wonder whether it's better to let the sleeping paint lie, walled off by the body's own protective devices. Only time and a lot more study will tell.

We know so woefully little about tattoos. The Food and Drug Administration, which goes after cosmetics with a vengeance, does not regulate the tattoo industry. In fact, no one really knows exactly what's in the numerous commercial and home-made inks. But they do contain solvents and metals like lead and mercury and a range of impurities acceptable for computer printers or car paint—but not for human injection.

Allergic reactions and skin infections can occur after tattooing. And though they may be coincidental, skin cancers, including melanomas, have been reported within tattoo sites, bearing very close watching. The FDA warns about the risk of tattoo parlors transmitting viruses like HIV and the cancer-causing hepatitis C. Because of this, blood banks typically ban donations from people who have been tattooed in the previous 12 months. The FDA also warns patients that if they have an MRI scan, their tattoos can swell or burn, presumably related to the metal in some inks.

Stigma. Once mainly a guy thing, tattoos now decorate men and women equally, and increasingly they are a women's health issue. It should be obvious that getting or removing tattoos during pregnancy is not a good idea. And some anesthesiologists have expressed concerns about performing epidurals, used during labor, through those symmetrically designed female lower-back tattoos because of the slim possibility that the needle might carry pigment into the spinal canal. Perhaps not surprisingly, most patients seeking removal are women, prompted by a disproportionate level of psychological distress and even tattoo stigma.

Witness the tasteless moniker used to describe those lower-back tattoos: "tramp stamp."

I asked a few of my *U.S. News* colleagues about their take on women and tattoos. One said there was something trendy if not sexy about them—but maybe not for his fiancée. Another said he'd date a girl with one if it were not too obvious. A third saw only harmless self-expression. I'm with one young reporter who visited a tattoo parlor for a piece she was writing. She's down on tattoos because of the murky risks—and the idea of looking at the deeds of her youth for 80 years. ●

Laser removal, which demolishes tattoo pigment, may sound easy. But it opens up a toxic chemical dump.



CARY JOBE—AURORA

The effect of tattoos on the body is more than skin deep

Christa Lesté-Lasserre

TATTOO ink collects in lymph nodes and **interferes** with the immune system, causing potentially lifelong changes to the body's disease-fighting mechanisms.

That is the conclusion of a study in mice, in which tattooed animals showed **chronic inflammation** in their lymph nodes – which were pigmented with the ink – and had **altered antibody responses** to vaccines. Human lymph nodes from tattooed individuals had similar inflammation and colouring.

"When you're tattooing, you're actually injecting ink into your body," says Santiago González at the University of Lugano in Switzerland. "It's not just a cosmetic effect... there are effects on the immune system as well."

Tattooing has become a global trend. Between 30 and 40 per cent of people in Europe and the US under the age of 40 have at least one tattoo.

González says he and his colleagues were working on an unrelated research project on inflammation in mice when they realised the animals developed "**crazy inflammatory reactions**" after being given small tattoos for identification.

To find out more, they used standard commercial inks in black, red and green to tattoo a 25-square-millimetre patch of skin on the hind feet of dozens of mice. With specialised imaging equipment, they watched the ink travel along the lymphatic vessels inside the leg up to the nearby lymph nodes almost immediately.

There, the team saw that **macrophages** – immune cells that clean up debris, pathogens and dead cells – captured the ink, tinting the nodes and



provoking acute inflammation. Within about 24 hours, those macrophages died, releasing the ink, which then got captured by other macrophages. Those, too, would die and release ink, which would get taken up by yet other macrophages – **creating a cycle of chronic inflammation** that lasted well after the tattoo site had healed (*PNAS*, doi.org/qhd9).

By the end of the experiment, two months after tattooing, the mice's lymph nodes still had

"Tattooing is not just cosmetic, there are effects on the immune system as well"

levels of inflammatory markers up to five times higher than normal, says González.

To investigate whether this inflammation affected immune function, they injected vaccines directly into the tattooed skin. The tattooed mice's antibody response to a covid-19 mRNA vaccine was noticeably weaker than in control mice, but their response to an influenza vaccine was stronger.

Tattooing has now become a global trend

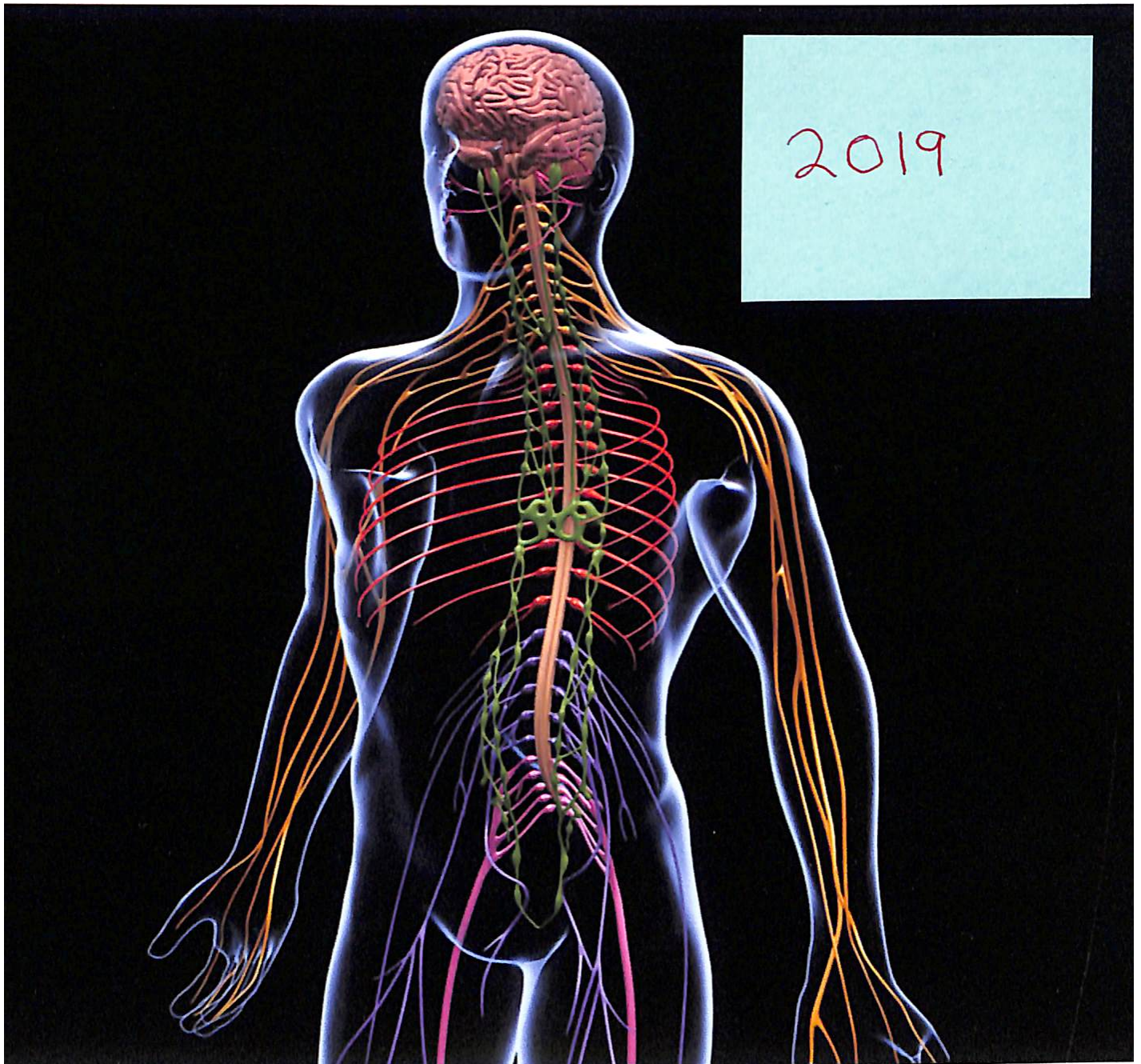
Further analyses showed the lymph node macrophages of tattooed mice were so full of ink, they captured less of the covid-19 vaccine – which, as an mRNA vaccine, needs processing by macrophages to be functional. For the protein-based influenza vaccine, however, inflammation boosted the antibody response, perhaps because there were more immune cells recruited to the tattooed site.

Finally, they examined a small set of lymph node biopsies from people who had been tattooed in regions near the nodes. Even two years after tattooing, the nodes still contained visible pigment, packed into the same kinds of macrophages as seen in the mouse study.

Michael Giulbudagian at the German Federal Institute for Risk Assessment in Berlin says "the relevance for human health, in particular after the complete healing of the wound, must be further investigated". ■

COLD SPRING HARBOR PERSPECTIVES IN MEDICINE

Bioelectronic Medicine



EDITED BY Valentin A. Pavlov
Kevin J. Tracey

Bioelectronic Medicine

Every organ in the human body is innervated by the nervous system and communicates with the brain via electrical signals. Various devices can be used to modulate these electrical signals and elicit changes in organ function with the aim of treating injury or disease. This approach is the basis of the rapidly emerging field of bioelectronic medicine, which has the potential to diagnose and treat medical conditions more precisely and effectively than ever before.

OPINION

THE WEEKEND INTERVIEW with Kevin Tracey | By Allysia Finley

Electricity Is the New Medical Miracle

Kelly Owens was a medical mystery, her teens and 20s blighted by a cascade of seemingly unrelated health problems that left her debilitated. For a decade and a half she was put on one medication after another—22 in all—to little effect. Then electricity saved her.

"I didn't even remember how 'healthy' felt, since it had been 15 years," Ms. Owens, 33, says. Now she and her husband are talking about having a child, something she had thought impossible. She credits Kevin Tracey, an innovative neurosurgeon she found through Facebook.

Ms. Owens was an athletic 13-year-old when she twisted her ankle tap-dancing. A few weeks later, her ankle was still swollen and she began experiencing severe nausea and diarrhea. A year or two later, her other ankle swelled up, though she'd never injured it. Then her knees grew inflamed.

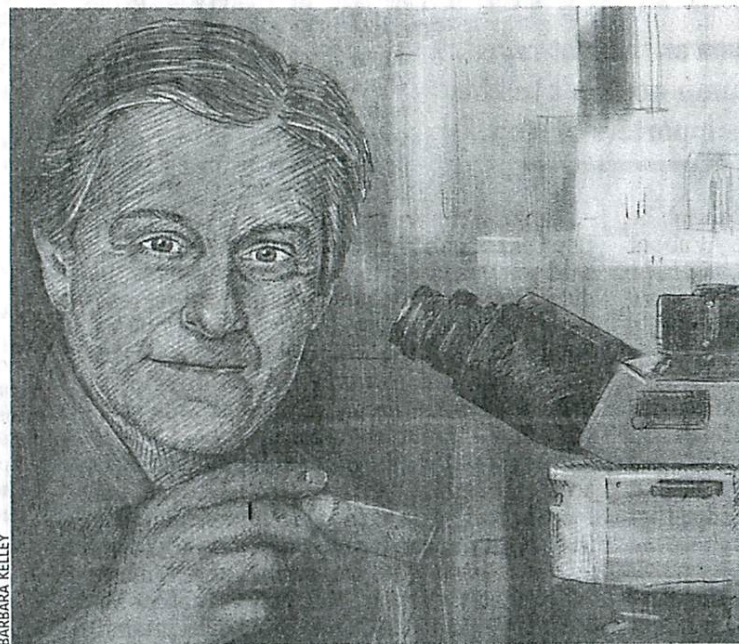
Stimulating the vagus nerve can relieve arthritis, Crohn's disease and other inflammatory conditions—perhaps someday even Alzheimer's disease.

family and friends, she and her husband moved to Amsterdam, one of the sites where the trial took place. The trial's principal investigator was Geert D'Haens, a global expert in inflammatory bowel disease based at the Amsterdam University Medical Center.

SetPoint implanted a pace-maker-sized device in her chest cavity that sends stimulation to electrodes surgically placed on her vagus nerve. Her symptoms began to improve within weeks. Soon she was able not only to walk but to run. Two months after the device was implanted, doctors deemed her in clinical remission. Her ailments have remained at bay, and her doctors weaned her from steroids.

Scientists have long known that the vagus nerve carries signals between the brain and internal organs that regulate physiological processes such as digestion, breathing and heart rate. When you exercise, for instance, your heart speeds up. Then your brain sends a signal via the vagus nerve directing your heart to slow down so it doesn't beat out of control.

Dr. Tracey's breakthrough two decades ago was the discovery that the brain also controls the immune system through the vagus nerve. By using electrical stimulation to hack into neural networks, it's possible to regulate the im-



BARBARA KELLEY

the molecule that killed Janice was made by her own immune system. It's a molecule that's known today as TNF—tumor necrosis factor.

TNF is a cytokine, a protein made by the immune system to send signals that can cause or reduce inflammation. But the discovery of TNF explained only part of the mystery behind sepsis. Questions remained, Dr. Tracey said: "What is it that controls the

can overproduce cytokines," which can result in autoimmune conditions like rheumatoid arthritis and Crohn's disease, Dr. Tracey says. Hence the treatment: "You can implant a device on the vagus nerve of humans, or animals, and by controlling the activity of the nerve with the nerve stimulating device, you can control the magnitude of the cytokine response."

The vagus nerve is actually a

Eight of the 16 patients in Ms. Owens's trial showed improvement after four months, and she and three others went into complete remission. SetPoint plans to conduct larger randomized controlled trials on patients who haven't responded to biologic drugs. Such trials can take many years to complete, as they do for drugs, but the Food and Drug Administration has been helpful in supporting the innovation. Last year the FDA approved the technique to help people who have suffered damage to motor skills caused by strokes.

Vagus-nerve stimulation might also help some people suffering from "long Covid," Dr. Tracey says, although he cautions more research is needed. A study earlier this year found that most long-Covid patients had signs pointing to vagus-nerve dysfunction, including diarrhea, dizziness and rapid heart rate. Many also showed signs of vagus-nerve damage on medical imaging.

Some patients may shudder at the idea of getting implanted with a device that sends electrical pulses up to their brains and back down to the body. "Some have been quick to say, well, vagus-nerve stimulation is invasive," Dr. Tracey says. "Well, I would say that biologics are invasive too. They're administered with needles." He adds that the 150,000 or

year-old when she twisted her ankle tap-dancing. A few weeks later, her ankle was still swollen and she began experiencing severe nausea and diarrhea. A year or two later, her other ankle swelled up, though she'd never injured it. Then her knees grew inflamed.

Stimulating the vagus nerve can relieve arthritis, Crohn's disease and other inflammatory conditions—perhaps someday even Alzheimer's disease.

After a colonoscopy and endoscopy, she was diagnosed with Crohn's disease, an inflammatory bowel condition. Blood tests and a physical examination revealed spondyloarthropathy arthritis, which attacked her spine, joints and organs. She developed blood clots and skin ulcers. By the time she finished college, she says, there wasn't a joint in her body that didn't hurt. Her myriad ailments made it difficult to walk and forced her to quit her job as a teacher. To control her joint inflammation, she was prescribed steroids, which made her bones as brittle as a 70-year-old woman's.

She was 25 when she stumbled on a Facebook video of Dr. Tracey, CEO of the Manhasset, N.Y.-based Feinstein Institutes for Medical Research, discussing how electricity could replace medication. Dr. Tracey, 64, pioneered research showing that electrical stimulation of the vagus nerve—the nervous-system “motherboard” that originates at the back of the neck, which connects the brain to the rest of the body—could suppress inflammation that causes chronic diseases such as Crohn's and rheumatoid arthritis.

She enrolled in a vagus-nerve stimulation trial by SetPoint Medical, a California-based biotech startup that Dr. Tracey co-founded in 2007. With financial help from

Scientists have long known that the vagus nerve carries signals between the brain and internal organs that regulate physiological processes such as digestion, breathing and heart rate. When you exercise, for instance, your heart speeds up. Then your brain sends a signal via the vagus nerve directing your heart to slow down so it doesn't beat out of control.

Dr. Tracey's breakthrough two decades ago was the discovery that the brain also controls the immune system through the vagus nerve. By using electrical stimulation to hack into neural networks, it's possible to regulate the immune response and perhaps someday cure inflammatory conditions such as multiple sclerosis, lupus and even Alzheimer's disease.

The story of this novel insight begins with Dr. Tracey's painful childhood. His mother died of an inoperable brain tumor when he was 5. That sparked his interest in neurosurgery. He wanted to develop treatments so that other children wouldn't have to suffer the way he and his two younger siblings had. He went to medical school and joined a New York hospital as a neurosurgery resident.

In 1985 he was caring for an 11-month-old girl named Janice.

“She'd been crawling across the kitchen floor when her grandmother was cooking dinner. And grandma turned to drain boiling water in the sink and spilled the boiling water on her granddaughter,” Dr. Tracey recalls. “We didn't think she was going to survive. But she did—she survived for a month—and then inexplicably went into shock and died in my arms. And so I was haunted by her death. She died of septic shock.”

Septic shock occurs when a nonfatal injury or infection leads to organ failure and dangerously low blood pressure. Sepsis causes 1 in 5 deaths worldwide. In 1985 scientists didn't understand what causes the condition. Janice's death spurred Dr. Tracey to research sepsis' biological underpinnings: “What we discovered is that

the molecule that killed Janice was made by her own immune system. It's a molecule that's known today as TNF—tumor necrosis factor.

TNF is a cytokine, a protein made by the immune system to send signals that can cause or reduce inflammation. But the discovery of TNF explained only part of the mystery behind sepsis. Questions remained, Dr. Tracey said: “What is it that controls the amount of cytokines being produced? Why do some people, like Janice, make massive amounts of cytokines that can kill them?”

While testing an experimental drug that blocked TNF production in mice with strokes, his lab stumbled on a clue. The drug not only blocked TNF production in the rodents' brains, which helped the strokes heal; it also turned off TNF and other cytokines made in the rest of the body. That led to the discovery that “the brain communicates to these organs by sending signals through the vagus nerve.”

His lab performed two more experiments in mice that confirmed this hypothesis. “So now we knew the vagus nerve could transmit this off-switch to the immune system.” He postulated that “if there's an off-switch in the vagus nerve, there must be an on-switch, which is how a reflex works.” More experimentation and research proved his hunch true.

In the case of sepsis, bacteria activate white blood cells to produce cytokines, which can help heal wounds. An inflammatory condition like Ms. Owens's can also trigger the release of cytokines. Problems arise when the nervous system fails to regulate the production of cytokines. “If the nervous system doesn't control that response, the immune system

can overproduce cytokines,” which can result in autoimmune conditions like rheumatoid arthritis and Crohn's disease, Dr. Tracey says. Hence the treatment: “You can implant a device on the vagus nerve of humans, or animals, and by controlling the activity of the nerve with the nerve stimulating device, you can control the magnitude of the cytokine response.”

The vagus nerve is actually a network of some 160,000 nerve fibers, 80,000 on either side of the neck. Each fiber has a specific job—for instance, controlling heart rate. These fibers also deliver information to the brain, which processes them and sends signals back down the vagus nerve or to nearby structures such as the pituitary gland, which regulates hormone production.

How do doctors know which fiber or fibers to stimulate? Dr. Tracey explains a “cool trick called optogenetics,” which involves genetically engineering mice so that the fibers in their brain stem are stimulated to send signals to the body when activated by a laser beam. Researchers can then figure out which fibers control which processes by shining a laser on the neurons.

More than 100 trials worldwide are being conducted using vagus-nerve stimulation for an array of conditions. SetPoint has conducted three small trials on vagus-nerve stimulation for rheumatoid arthritis and Crohn's. “The same device implanted in the same location can be used for other diseases,” says CEO Murthy Simhambhatla. (Dr. Tracey resigned from the company's board in 2011 to spend more time in his lab after meeting the first rheumatoid-arthritis patient treated in a SetPoint clinical trial who experienced complete remission. He continues to work as a consultant for SetPoint.)

Search is needed. A study earlier this year found that most long-Covid patients had signs pointing to vagus-nerve dysfunction, including diarrhea, dizziness and rapid heart rate. Many also showed signs of vagus-nerve damage on medical imaging.

Some patients may shudder at the idea of getting implanted with a device that sends electrical pulses up to their brains and back down to the body. “Some have been quick to say, well, vagus-nerve stimulation is invasive,” Dr. Tracey says. “Well, I would say that biologics are invasive too. They're administered with needles.” He adds that the 150,000 or so epilepsy patients who have been treated with vagus-nerve stimulation over the decades have very rarely experienced side effects.

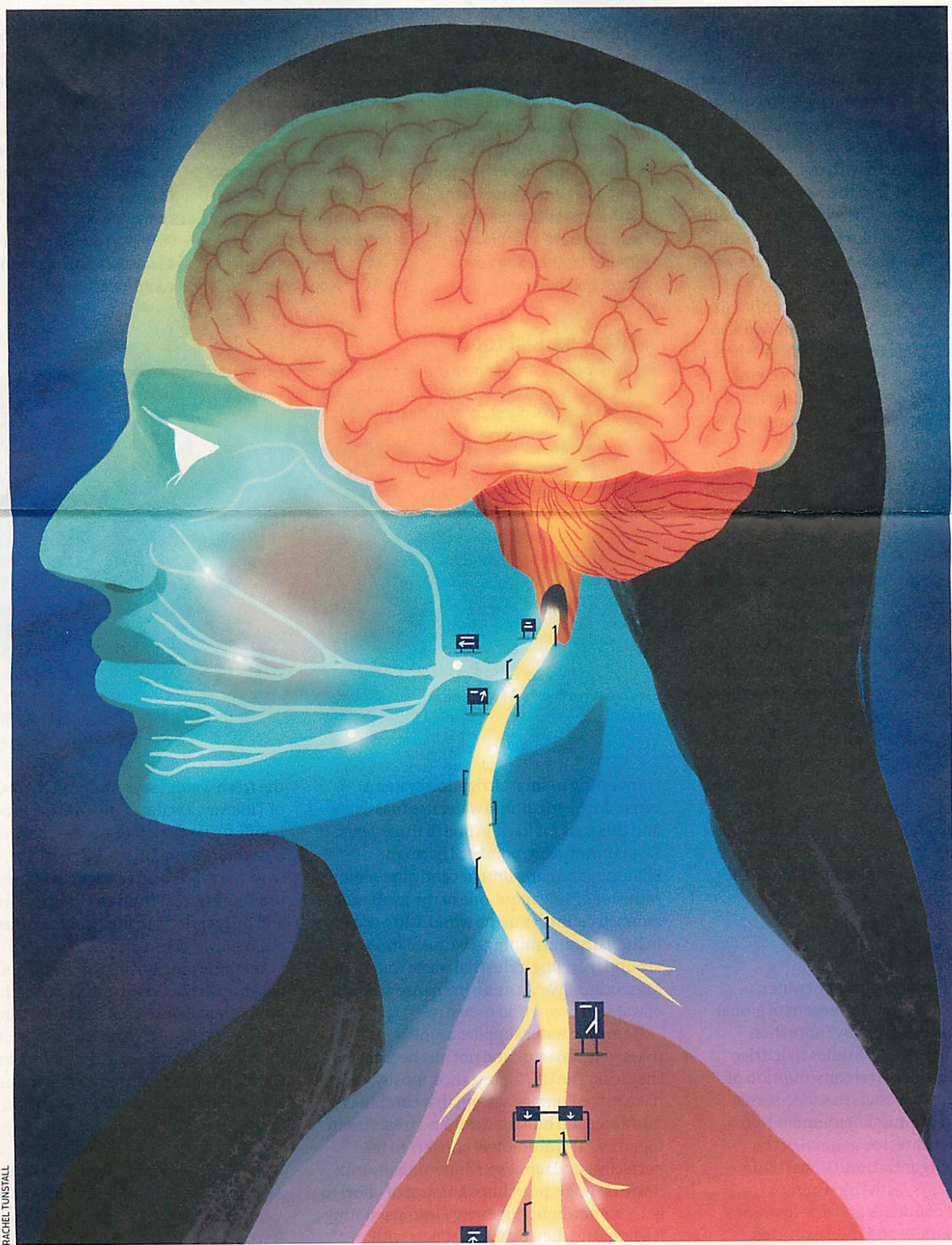
Some drugs also work by chemically stimulating the vagus nerve and may carry potential to treat conditions other than those for which they were originally developed. Dr. Tracey conducted a small trial that found famotidine (also known by the brand name Pepcid) can reduce the duration of acute Covid in patients with mild to moderate symptoms by activating the vagus nerve and suppressing the cytokine storm.

Healthy behaviors like exercise and meditation can also stimulate the vagus nerve, Dr. Tracey says, but they may not help patients whose nerve fibers are damaged or who have a genetic predisposition. The latter might have caused Ms. Owens's ailments.

Dr. Tracey is reluctant to say she's cured: “She might be. We don't know. How do you know if she's cured? No one wants to turn the device off.” But she feels like a normal, healthy 33-year-old, and she hopes her story will inspire others with similar conditions: “Patients really need to have hope.”

Ms. Finley is a member of the Journal's editorial board.

Features



RACHEL TUNSTALL

AS I peered at its sinewy, tentacle-like tendrils, I thought the pale structure splayed on the table before me resembled a huge tapeworm, or perhaps a scrawny squid.

Its lacklustre appearance didn't match with the wonder of what I knew it to be: a human vagus nerve, the sensory superhighway that connects our brain to most of our vital organs and helps regulate everything from the movement of food through our intestines to the steady beating of our heart.

I was at the Feinstein Institutes for Medical Research in New York, viewing one of 30 vagus nerve samples being diced, sliced and imaged by Stavros Zanos and his colleagues. The goal? To create a detailed map of the roughly 160,000 nerve fibres along its structure.

This ambitious effort comes after recent research has revealed the vagus nerve's role in a wider array of processes than we ever realised – not only monitoring organ function, but helping discern facial expressions and even regulating mood. Most enticingly, we are starting to understand how it governs

inflammation, the immune response that runs rampant in conditions ranging from heart disease to Parkinson's.

Already, electrical devices called vagus nerve stimulators are used to treat epilepsy, depression, migraines and obesity. But they are limited by our rudimentary understanding of the nerve's complex structure. Now, efforts to untangle its mysteries are allowing us to map each of its branches and even discover specialised cell types we never knew existed. Not only might these insights enable us to control inflammation, they could open a whole new frontier for precision medicine.

The vagus nerve is a bundle of neural fibres that starts at the brain stem. It splits into two channels that run along either side of the neck, then rejoin at the heart before descending to the gut and other organs.

The earliest evidence of its crucial function dates back almost 2000 years to when the ancient Roman physician Galen accidentally severed a sheaf of nerves in a pig, stopping its squeals but not its squirms. It turned out he had sliced a branch of the vagus nerve

responsible for transmitting signals from the brain to the vocal cords.

Subsequent experiments revealed that the vagus nerve regulates functions of the heart, stomach, lungs, liver and more. But it wasn't until about three decades ago that we began to tap into it for medical treatments.

The earliest success was with epilepsy. In the late 1980s, J. Kiffin Penry and Joan Christine Dean, then at Wake Forest University in North Carolina, showed that implanting a vagus nerve stimulator reduces or even eliminates seizures for some people with the condition. Most of these stimulators use a pulse generator slightly larger than a poker chip, which is implanted under the skin on the chest. This sends electrical impulses via a wire to a cuff wrapped around the vagus nerve in the neck. The first such stimulator was approved by the US Food and Drug Administration (FDA) in 1997 for treating drug-resistant epilepsy.

Since then, the FDA has approved an implantable device for treatment-resistant depression, after trials showed that it lessened symptoms for about 40 per cent of people who had already tried four or more other treatments without success. A device called VBLOC has also been approved for treating obesity: people using it lost about 8 per cent more excess weight than those in a control group. Most recently, the FDA approved a stimulator for regaining upper body movement after a stroke. Research also indicates that stimulators can be used to regulate blood pressure and lower blood sugar.

Most tantalising is the role the vagus nerve plays in controlling inflammation. Hints of this first emerged in the 1990s, when Kevin Tracey, now at the Feinstein Institutes for Medical Research, and his colleagues developed an anti-inflammatory drug to block production of proteins called cytokines, which spur the body's immune response to infection or illness. In modest amounts, cytokines and the ensuing inflammation fend off foreign pathogens and heal injuries, but an overabundance of them has the opposite effect, damaging tissues and potentially causing chronic illness or even organ failure.

Tracey and his team injected their new drug into the brains of rats experiencing stroke from bacterial infections. As they hoped, it dampened inflammation in the brain. But to their surprise, the effect also extended throughout the rodents' whole bodies.

YOUR BODY'S SECRET SUPERHIGHWAY

The vagus nerve influences everything from your heartbeat to your immune system. Unravelling its secrets could usher in a new era of medicine, finds **Grace Wade**

You are electric

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With drugs given orally or intravenously, you would expect widespread effects, but the researchers weren't anticipating this after injecting the medication directly into the brain. "For months, we agonised over what the mechanism could be," says Tracey. Eventually, they tried severing the animals' vagus nerves. "When we did that, the drug in the brain no longer turned off inflammation," he says. "Scientists don't say 'eureka' any more, they say 'holy shit', and that's what happened."

Tracey dubbed the vagus nerve's ability to mediate inflammation the inflammatory reflex. It kicks in when specialised neurons detect cytokines and send signals to the brain, which in turn relays messages to the spleen to start churning out white blood cells. The discovery suggested that we might be able to interrupt inflammation with an electrode, not just drugs, he says.

In 2012, a device using an electrode that Tracey designed while at SetPoint Medical, a biotechnology company in California, was tested in a small group of people with the chronic inflammatory condition rheumatoid arthritis. Of those, 70 per cent had at least a 20 per cent reduction in symptoms, and almost half saw a 50 per cent improvement.

The effect is similar to that of some drugs, but there is a major advantage: anti-inflammatory medications often severely suppress immune function, leaving people vulnerable to infection. Not so with this

approach. Vagus nerve stimulation causes white blood cells to shut down cytokine production enough to avoid runaway inflammation, but not so much that our immune system is disarmed completely, says Tracey.

Mysterious fibres

SetPoint Medical is now conducting a trial of the device in about 250 people. Tracey is hopeful that the FDA could approve the treatment for rheumatoid arthritis within a few years. Meanwhile, similar devices have also shown promise in treating conditions characterised by chronic inflammation, including inflammatory bowel disease, multiple sclerosis and Parkinson's disease.

"What diseases are affected by inflammation? Pretty much every chronic illness," says Zanos. "I'm not saying vagus nerve stimulation will work for every single one of them, but it makes sense to test it out in some way or another."

There is just one hiccup in all of this: how exactly these treatments work is largely a mystery. It is unclear which fibres the stimulators even target. Is it those closest to the electrode? The ones furthest away? The small ones? The large ones? We simply don't know. We just turn on the device and hope for the best.

With obesity, for instance, the stimulator is meant to work by mimicking signals that travel along the vagus nerve to tell the brain to stop eating when the stomach is full. In people with epilepsy, though, vagus nerve devices

may provide benefits by stimulating nerve cells that increase blood flow to a brain region called the thalamus, which processes information from most senses. It may also work in part by triggering the release of the neurotransmitter noradrenaline, which can reduce seizure symptoms. Boosting noradrenaline may be the way stimulation eases depression symptoms, too. But which particular nerve fibres play a role in this is unknown.

It is even trickier to pin down exact targets of devices that zap the vagus through the skin. Today, these transcutaneous stimulators can be purchased in many countries without a prescription from about \$200. They are often marketed as a way to boost "vagal tone", a supposed measure of vagal activity. But researchers say the concept isn't terribly scientific (see "What is vagal tone?", right).

Some transcutaneous stimulators have been rigorously tested, though. In 2018, the FDA approved one for treating chronic migraines and cluster headaches after research showed that it significantly lowered the number of days that people experience them. Tracey says it is important to talk with your doctor before using this kind of technology. These devices may not be suitable for some people with heart conditions, as they can affect heart rhythms.

Therein lies the problem. The extraordinary complexity of the vagus nerve is what makes it an avenue for improving so many aspects of health, but the lack of specificity in treatments also means they can have unintended side effects. It may also be why some applications simply fail.

"The way neuromodulation has been done for many years is creating an electrode and then placing it on a nerve or in the brain and hoping for the best," says Zanos. For more consistent results, and to expand the potential applications, we need a much more detailed understanding of what we are aiming for.

All of which explains how I find myself staring at the stringy tissue in Zanos's lab. He and his colleagues are embarking on a three-year, \$6.7-million project funded by the US National Institutes of Health to map the vagus in its entirety. That involves identifying every single nerve fibre and tracking its location along the structure's meandering pathway.

It is painstaking work, beginning with the process of extracting the vagus nerve from a cadaver. At points, it is thinner than a cotton thread, and researchers must carefully label

Cold water swimming is supposedly a way to enhance "vagal tone"



RON BINTANG/GETTY IMAGES

What is vagal tone?

Contemplative activities, including yoga, tai chi and meditation, can slow respiration and, in turn, affect signals travelling along the vagus nerve. Extreme athlete Wim Hof, for example, swears by his daily dunks in ice-cold water and militant breathing routine to reduce inflammation by improving vagal tone, a supposed measure of electrical activity along the vagus nerve.

But what is vagal tone really, and is it actually something you can strengthen? When I ask Kevin Tracey at the Feinstein Institutes for Medical Research in New York, he cradles his head in his hands and groans. "It is a non-scientific term that is difficult to define, and because it is difficult to define, I think it is misappropriated," he says.

One issue is that it is almost impossible to directly gauge vagus nerve activity, so another measure called heart rate variability – or the variation in timing between heartbeats – is used as a stand-in. But research in rats shows heart rate variability doesn't correlate well with vagal output.

Even if people could reliably calculate the vagus nerve's firing capacity, it probably wouldn't do much good given the structure's dizzying complexity.

"People tend to think and talk about the vagus nerve like a single, solid copper wire," says Tracey. "But it's more like 160,000 wires, each of which can control a very specific function."

"Vagal tone implies that there is one function of the vagus nerve," says Stephen Liberles at Harvard University. But many fibres in the vagus have opposing effects (see main story). "So there is no vagal tone. It is a bit of a misnomer," he says.



GRACE WADE

Sections of the vagus nerve are encased in wax, then sliced thinly

what organs its many branches connect to.

The researchers then chop it into pieces that, at their thickest, resemble cannellini beans, which are moulded into blocks of wax. These are placed into what is essentially a deli meat slicer, where the encased nerve sections are shaved into slivers as thin as a human hair.

Finally, the team bathes the segments in staining solutions to reveal their inner complexity. Zanos shows me an image on his computer. What was once a rather dull, brown blob is now a motley of red, green and blue fluorescence. Each colour correlates to a different type of nerve fibre, yielding clues to its function, he says.

We can tell what types of signals neurons ferry based on their distinct anatomical features. Afferent neurons transmit sensory information towards the brain, while efferent neurons relay signals for controlling movement from the brain to our muscles. Fibres that are insulated in a fatty coating called myelin generally fire faster than those without it. "So, if it is myelinated and efferent, we know that most likely mediates muscle contractions," says Zanos.

Mapping the vagus nerve's anatomy won't only allow us to better predict the effects of placing an electrode anywhere along the nerve's structure, but could also lead to the creation of ultra-selective stimulators that act only on certain fibres, he says.

Zanos and his colleagues have already shown proof of this concept. After they mapped the vagus nerve of pigs, they developed an ultra-selective vagus nerve stimulator with 10 separate contact points. In research published earlier this year, they showed that, when implanted into live pigs, the device altered the animals' breathing while minimising effects on other organs.

Mapping the vagus nerve is just the first step, says Cristin Welle at the University of Colorado. "The next step is going to be, how do each of those fibre types then interact with the rest of the nervous system?" she says. She and her team are charting the vagus nerve in the opposite direction, identifying which brain regions it activates. Last year, they showed that vagus nerve stimulation targets neurons in the primary motor cortex of mice, enhancing the animal's ability to learn motor skills.

Stephen Liberles at Harvard University believes we can achieve even greater precision by elucidating the mechanisms of specific neurons with genetic sequencing. Of particular interest are sensory neurons, which constitute about 80 per cent of all nerve fibres in the vagus and use specialised receptors to detect changes in an environment. "Some of our landmark discoveries in the external senses were discovering odourant receptors or vision receptors," says Liberles. "We don't know the receptors for almost any internal organ sense."

Conducting traffic

Already, he and his colleagues have identified previously unknown types of vagal neurons that mediate breathing, control blood pressure and detect nutrients in the gut. He believes we will eventually be able to develop drugs that act only on specific vagal cells. If the vagus nerve is our body's superhighway, such drugs would control the movement of individual cars, while vagus nerve stimulators would dictate general traffic flow across multiple lanes.

"When you understand how all these vital body-to-brain communication pathways operate, that will open the door to therapies by which you can toggle [these] different pathways with greater selectivity," says Liberles. Being able to modulate inflammation or other physical functions with this level of precision would be nothing short of game-changing for modern medicine.

As I leave Zanos's lab, I steal a final look at the ribbon of white tissue, marvelling at its extraordinary potential – and the power of science to map it and manipulate it. ■



Grace Wade is a health reporter for *New Scientist*



Neuro-Immunity Controls Obesity-Induced Pain

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The prevalence of obesity skyrocketed over the past decades to become a significant public health problem. Obesity is recognized as a low-grade inflammatory disease and is linked with several comorbidities such as diabetes, circulatory disease, common neurodegenerative diseases, as well as chronic pain. Adipocytes are a major neuroendocrine organ that continually, and systemically, releases pro-inflammatory factors. While the exact mechanisms driving obesity-induced pain remain poorly defined, nociceptor hypersensitivity may result from the systemic state of inflammation characteristic of obesity as well as weight surplus-induced mechanical stress. Obesity and pain also share various genetic mutations, lifestyle risk factors, and metabolic pathways. For instance, fat pads are often found hyper-innervated and rich in immune cell types of multiple origins. These immunocytes release cytokines, amplifying nociceptor function, which, in turn, via locally released neuropeptides, sustain immunocytes' function. Here, we posit that along with mechanical stress stemming from extra weight, the local neuro-immune interplay occurring within the fat pads maintains the state of chronic low-grade inflammation and heightens sensory hypersensitivity. Overall, stopping such harmful neuro-immune crosstalk may constitute a novel pathway to prevent obesity-associated comorbidities, including neuronal hypersensitivity.

Keywords: obesity, pain, white adipose tissue, ILC1, T_H2, neuro-inflammation

OBESITY

Obesity is defined as an excessive accumulation of fat associated with adverse health consequences and results from the complex interaction of socioeconomic, genetic, epigenetic, and lifestyle factors (WHO, 2018). Obesity prevalence has now reached epidemic proportions, affecting up to 1.9 billion adults worldwide, including 650 million patients who are clinically obese. The body mass index (BMI) is used to stratify adult patients as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), or obese (>30). The severity of obesity is further classified as class: I (30–34.9), II (35–39.9), or III (>40) (WHO, 2018).

In terms of mortality, it has been projected that obesity and obesity-associated chronic diseases will account for almost three-quarters of all deaths worldwide by 2020 (WHO, 2013). Thus, obesity is highly comorbid and constitutes a key risk factor for developing insulin resistance and type II diabetes, cardiovascular diseases, cancer, and dementia (Khaodhiar et al., 1999). In addition to these, obesity is now considered an important pain facilitator, as BMI and pain perception are strongly correlated (Table 1). For example, 40% of obese suffer from chronic pain, and the pain they report is more severe, often intractable, seeking more medical attention and consuming more

TABLE 1 | Pain sensitivity correlate with obesity status.

Patient sample	Pain site	Obesity prevalence among patients (%)	References
1 million adults	Diverse	44	Stone and Broderick, 2012
5,724 elderly	Knee	58	Andersen et al., 2003
721 adults	Headache	30	Tietjen et al., 2007
300 children and teenagers	Musculoskeletal	56	Taylor et al., 2006
182 adults	Diverse	40	Coaccioli et al., 2014
100 adult women	Fibromyalgia	45	Neumann et al., 2008

painkillers (Thomazeau et al., 2014). Inversely, patients suffering from chronic pain are also more likely to become obese (Stone and Broderick, 2012). Being highly prone to develop osteoarthritis (OA), they chiefly report musculoskeletal pain (King et al., 2013). Finally, obesity-induced pain varies with the patients' sex, diet, and body fat distribution.

While significant advances were made in the understanding of the molecular mechanisms driving persistent pain, this knowledge has yet to translate into effective therapies. Thus, the management of chronic pain still constitutes a significant unmet clinical need (Yekkirala et al., 2017). The following section will explore the molecular mechanism and the relative contribution of (i) mechanical stress; (ii) chronic low-grade inflammation; and (iii) neuro-immunity to obesity-induced pain; and whether targeting such mechanism may constitute a therapeutic strategy to alleviate sensory hypersensitivity.

ORGANIZATION OF THE NERVOUS SYSTEM AND PAIN SENSATION

The nervous system is designed to quickly detect stimuli and direct avoidance behavior (Basbaum et al., 2009). In the periphery, autonomic neurons monitor and regulate organ functions (involuntary) while the somatic (voluntary) system provides sensitivity and motor control. In addition to these, nociceptors are a peripheral population of unmyelinated (C-fibers) or thinly myelinated (A δ fibers) neurons specialized in sensing potentially damaging stimuli (pressure, temperature, chemical). These signals are transduced in electrical impulses, which are integrated centrally. In turn, effector signals are produced and transmitted to motor neurons activating muscle contraction (Albright et al., 2000) and occasionally tuning immune responses.

Upon activating nociceptor, the host generally experienced pain, which is defined as an unpleasant sensory and emotional experience (IASP, 2018). Pain is either acute, serving a protective physiological response to a harmful stimulus, or chronic, when physically debilitating and lasting over 3 months (IASP, 2018). Pain can also be stratified as (i) nociceptive, associated with the

detection of potentially harmful tissue-damaging stimuli (Woolf and Ma, 2007); (ii) neuropathic, triggered by an injury/disease to the somatosensory nervous system (Costigan et al., 2009); (iii) dysfunctional, when associated to a disease state of the nociceptive nervous system (i.e., fibromyalgia) (Nagakura, 2015); or (iv) inflammatory, associated with tissue damage and active inflammation (Pinho-Ribeiro et al., 2017).

Nociceptors detect not just features typically thought of as causing a painful sensation, such as chemical and noxious temperature, but uncharacteristic signals ranging from cytokines, fungi, microbes, and immunoglobulins (Rajchgot et al., 2019). A revised portrait of neuron danger sensing include (i) ion channel transducers [transient receptor potential (TRP), Piezo]; (ii) receptor for sensitizing mediators [Mas-related G protein-coupled receptor (Mrgpr), prostaglandins (PG), protons (H), bradykinin (BK), etc.]; (iii) threat detectors including receptors for immunocyte-produced mediators (interleukins, chemokines, and immunoglobulins); and (iv) damage-associated molecular pattern (DAMP) detector (Crosson et al., 2019). Damage-associated molecular patterns, which include protease-activated receptors (PARs), toll-like receptors (TLRs), and pattern recognition receptors (PRRs), are families of specialized receptors for microbial proteins, and play an essential role in preserving mucosal homeostasis. Overall, nociceptors' transcriptional data show the enormous variety of threat detection competences of nociceptor neurons, including immunocyte-produced cues (Wilson et al., 2013; Riol-Blanco et al., 2014; Talbot et al., 2015; Oetjen et al., 2017; Foster et al., 2017).

Inflammatory pain is characterized by the influx of immunocyte-producing cytokines, chemokines, and growth factors. These mediators typically bind to G protein-coupled receptors (GPCRs) and/or tyrosine kinase receptors expressed by nociceptor terminals and lead to intracellular kinases activation. Subsequently, these kinases decrease the activation threshold of ion channel transducer [i.e., transient receptor potential vanilloid-1 (TRPV1); transient receptor potential cation channel, subfamily A, member 1 (TRPA1)] and voltage-gated sodium channels (Nav) (i.e., Nav1.7, Nav1.8, and Nav1.9) (Caterina, 2000; Kerr et al., 2001; Nassar et al., 2004; Amaya et al., 2006; Bautista et al., 2006) or increased their membrane expression (Julius, 2013). Consequently, these effects sensitized nociceptors, which results in hypersensitivity to non-noxious stimuli, a situation termed allodynia (Woolf et al., 1992; Woolf and Ma, 2007). Besides, the nerve terminal "sensitized" state intensifies the response to painful trigger (termed hyperalgesia). Such hypersensitivity focuses the host on the injury site and leads to alternative behavioral (i.e., gait change). These effects are typically limited to the inflammatory sites, while systemic hypersensitivities result from central sensitization (Talbot and Couture, 2012; Rajchgot et al., 2019); see detailed review by Woolf et al. (1992) and Woolf and Ma (2007).

Known nociceptor sensitizer includes prostaglandin E₂ (PGE₂) produced by cyclooxygenase 2 (COX2) and nerve growth factor (NGF). Nociceptors express receptors for and were found to be sensitized by interleukin (IL)-1 β (Binshtok et al., 2008) or Chemokine (C-C motif) ligand 3 (CCL3) (Zhang et al., 2005) in the context of pain, IL-5 in asthma (Talbot et al., 2015), IL-4

and thymic stromal lymphopoietin (TSLP) in atopic dermatitis (Oetjen et al., 2017), IL-31 during itch (Cevikbas and Steinhoff, 2012), IL-33 after contact with poison ivy (Liu et al., 2016), and IL-23 in the context of psoriasis (Riol-Blanco et al., 2014).

INFLAMMATION

Characterized by its pain, heat, redness, and edema (Larsen and Henson, 1983), inflammation suggests an immune-mediated phenomenon, but each of these characteristics can also stem from neuronal activation. Typically, noxious stimuli-induced action potential travels to the brain to initiate sensation (Talbot et al., 2016b; Azimi et al., 2017). When they reach the sensory neuron branch points, these electrical signals are also transmitted antidromically, back to the peripheral terminals, to initiate neurogenic inflammation via the local release of neuropeptides (Richardson and Vasko, 2002; Chiu et al., 2012). Subsequently, these peptides act on the endothelium to generate redness and heat (secondary to vasodilation) and edema (extravazation due to enhanced capillary permeability) (Foreman, 1987; Weidner et al., 2000).

IMMUNITY IN HOST DEFENSE

Innate immunity is the primary barrier against microbes (Janeway and Medzhitov, 2002), while adaptive immunity generated long-term antigen memory (Litman et al., 2010). Antigen-presenting cells integrate danger signals and communicate information to T helper cells driving either of type 1 (against intracellular microbes), type 2 (against parasites), or type 17 (against extracellular pathogens) responses (Iwasaki and Medzhitov, 2015). Other immunocytes include mast cells (type 2 effector cells) (Metcalf et al., 1997; Barbara et al., 2007), neutrophils (type 1 and 17 effector cells) (Mayadas et al., 2014), and macrophages (Hume, 2015). Macrophages have an incredible plasticity ranging from M1 macrophages (IL-1 β ⁺, TNF- α ⁺), which are involved in cell elimination, to M2 macrophages (IL-10⁺, TGF- β ⁺), partaking in tissue restoration. Besides, innate lymphoid cells (ILCs) are tissue-resident T_H cytokine-expressing cells (Lin⁻: TCR β ⁺, CD3e⁺, CD19⁺, TCR γ δ ⁺, Ly6G⁺, F4/80⁺) (Spits et al., 2013), and as CD4 T cells, they are divided into three groups. ILC1 are T_H1-like cells and produce INF- γ ; ILC2 are T_H2-like cells, express GATA3 and ROR α , and produce IL-4, IL-5, and IL-13, while ILC3 are T_H17-like, express ROR γ t, and secrete IL-17 and IL-22 (Artis and Spits, 2015). In the function of the cytokines they express, they guide response against pathogens, parasite, and fungi (Artis and Spits, 2015) and are also involved in autoimmune and inflammatory diseases (Fuchs and Colonna, 2013; Villanova et al., 2014).

MECHANICAL STRESS

Sustained overloading on the musculoskeletal structure of the lower back, hip, and knee joints prompts the development of OA in obese patients (King et al., 2013). Obesity-related

TABLE 2 | Obesity-mediated osteoarthritis (odds ratio).

Site	Obesity-related OR	References
Knee	1.6	Felson et al., 1988
Hip	2.0	Lieverse et al., 2002
Hands	1.3	Haara et al., 2004
Low back	4.3	Liuke et al., 2005

OA is multifactorial and involves direct joint damage as well as genetic, biological, and metabolic factors (Davis et al., 1988). For instance, increased mechanical load changes the chondrocyte mechanotransducer signaling (Haudenschild et al., 2008), promotes cytokine secretion (IL-1 β , IL-6, and TNF- α) and matrix metalloproteinases release, and contributes to establishing a pro-oxidative microenvironment (Stannus et al., 2010). These prompts the degradation of type II collagen, joint extracellular matrix, and hyaluronic acid fragmentation. These factors caused (i) imbalance between deterioration and repair of the cartilage; (ii) chondrocyte apoptosis; (iii) reduced synoviocyte fluid viscosity; and (iv) increased joint friction, all of which changed the patients' posture and gait, reducing their mobility and increasing pain scores (Jordan et al., 2003).

While OA affects 16% of adults, it is present in 23% of overweight and 31% of obese patients (Vincent et al., 2012). As such, obese patients are 35% and 11% more at risk of developing knee and hip OA, respectively (Table 2; Jiang et al., 2012). Knee radiograph showed smaller width of the medial and lateral joint space in obese patients (Çimen et al., 2004), resulting in a 35% greater risk to undergo knee arthroplasty (Bourne et al., 2007).

These effects may be partly explained by the production of adipose tissue (AT)-secreted adipokines (leptin and adiponectin) (de Boer et al., 2012). These adipokines, whose circulating and cartilage levels correlate with BMI, activate their cognate receptors on the surface of chondrocytes, increasing the production of matrix metalloproteinases, nitric oxide (NO), and cytokines (IL-1 β , IL-6, IL-8, TNF- α) (Figenschau et al., 2001). In turn, these mediators heighten synovial inflammation and pain hypersensitivity by driving fibroblast proliferation and immune cell infiltration (Francin et al., 2014).

OBESITY, A LOW-GRADE INFLAMMATION DISEASE

White adipose tissue (WAT) comprised pre-adipocytes, adipocytes, endothelial cells, and immunocytes and has a primary role in energy storage. Adipocytes originate from mesenchymal stem cells (Qian et al., 2010), and their production is mainly controlled by epigenetic regulators, growth factors, and CCAAT-enhancer-binding proteins (or C/EBPs) and peroxisome proliferator-activated receptor γ (PPAR γ) transcriptional regulators (Wu et al., 1999). Increased mitochondrial metabolism and biogenesis results in reactive oxygen species production, which initiate adipocyte differentiation in a mammalian target of rapamycin complex 1 (mTORC1)-dependent manner (Tormos et al., 2011). White adipose tissue content strikingly increases

accumulate within the dorsal root ganglion (DRG) of high-fat diet (HFD)-fed mice (Song et al., 2017).

Diet-induced obesity CD4⁺ T lymphocytes were found to have biased T cell receptor (TCR) repertoires, suggesting an antigen-specific expansion. Glucose homeostasis typically becomes dysregulated in diet-induced obesity, when numbers of IFN- γ -secreting T_H1 cells overwhelm the non-expanding pools of T_H2 (CD4⁺GATA-3⁺) and Tregs (CD4⁺CD25⁺Foxp3⁺). Through T_H2 cell increases, CD4⁺ T cell transfer into HFD Rag1^{-/-} animals reversed weight increase and insulin resistance. Transient CD3 depletion also restores the T_H1/Treg balance and reverses HFD-induced insulin resistance, suggesting an upstream role for CD4⁺ T cell in controlling obesity-associated metabolic abnormalities (Winer et al., 2009).

Adipose tissue macrophages (ATM) initiate WAT inflammation. However, recent data suggest that other tissue-resident innate immune cells, such as ILCs, also are major contributors (Yang et al., 2016). ILC2 number decreased in obese mice epididymis and human subcutaneous WAT (Brestoff et al., 2015). Being resident in lean AT, ILC2s maintain a T_H2-like status of AT (Molofsky et al., 2013), in which ILC2-produced IL-5 and IL-13 promote the beiging of WAT (Molofsky et al., 2013; Brestoff et al., 2015; Hashiguchi et al., 2015). These effects are present in Rag1 null mice and are, therefore, independent of tissue-resident M2 macrophages (Hams et al., 2013; Molofsky et al., 2013). Thus, IL-33-driven WAT biogenesis suggests another role for an ILC2-inducing cytokine in regulating obesity (Brestoff et al., 2015; Lee et al., 2015). In effect, IL-33 null mice gain more weight than their wild-type counterpart and have reduced frequency of ILC2s. This phenomenon is also present in IL-33 KO mice fed a normal diet (Brestoff et al., 2015). Exogenous IL-33 rescued WAT ILC2s number and M2 macrophage (Brestoff et al., 2015).

High-fat diet -exposed mice have enhanced IFN- γ levels (Wensveen et al., 2015). The depletion of natural killer (NK) cells decreased HFD-induced insulin resistance and M1 macrophage levels but stopped the onset of obesity. Inversely, the adoptive transfer of splenic NK cells into IFN- γ null animals restores HFD-mediated insulin resistance (Wensveen et al., 2015). Tissue-resident ILC1 may directly promote obesity-induced insulin resistance without the influence of natural killer T (NKT) or T cells (O'Sullivan et al., 2016). IL-12 activated ILC1 lead IFN- γ production and subsequent polarization of M1 macrophages (O'Sullivan et al., 2016). ILC1-derived IFN- γ balanced out the effect of IL-33 mediated ILC2 activation within visceral AT (Oboki et al., 2010), providing an *in situ* negative regulators of ILC2 anti-obesity effects.

While untested, ILC3-derived IL-17 may drive obesity-related comorbidities (Kim et al., 2014). Thus, Rag1 and IL-17, a double knockout mice, failed to develop asthma exacerbation when fed with a HFD (Kim et al., 2014). ILC3-producing IL-22 promote liver metabolism and help stop insulin resistance (Wang et al., 2014). Accordingly, IL-22R null mice were highly susceptible to HFD-induced obesity and insulin resistance. In obese mice, exogenous IL-22 tones down diabetes-induced oxidative stress and islet β inflammation, rescuing insulin secretion and glucose sensitivity (Hasnain et al., 2014).

Overall, the influx and polarization of immunocytes by WAT-derived mediators enhance fat accumulation, speed up joint damages, and may directly sensitize nociceptor, as discussed in the next section. Blocking the inflammatory component of obesity may, therefore, constitute a potential therapeutic avenue to stop obesity progression and its comorbidities.

INNERVATION OF THE WAT

Under the control of a complex set of humoral and neural factors (Ismael et al., 2008; Dias et al., 2010; Talbot et al., 2012, 2016a; El Midaoui et al., 2015), WAT-released mediators tuned the host energy status as well as the number and phenotype of immune, vascular, and structural cells (Ouchi et al., 2011). Along with blood-derived factors, adipocyte size, lipid mobilization, and paracrine secretion are controlled by sensory nerve terminals (Bartness et al., 2014). Thus, fat pad sensory innervation is increased in obesity (Bamshad et al., 1998; Vaughan et al., 2014). In addition, evidences suggest a dual, yet segregated, sympathetic and parasympathetic innervation of WAT (Kreier et al., 2002). We refer the reader's attention to the work of Bartness and colleagues for more information on WAT innervation (Bartness and Bamshad, 1998). Overall, neurons control WAT production of cytokines and immune influx, making fat innervation a central component player in obesity-induced low-grade inflammation.

AUTONOMIC NERVOUS SYSTEM IN OBESITY

Sympathetic neurons control catabolic functions (Migliorini et al., 1997) via neuropeptide Y (NPY) suppression of lipolysis and promotion of angiogenesis and heighten adipocyte differentiation (Kuo et al., 2007). It is worth noting that adipocytes and macrophage-produced cytokines increase sympathetic flow, while excessive cytokine levels, such as during severe inflammation, have the opposite effect (Pongratz and Straub, 2014).

Parasympathetic vagal neurons that innervate the fat pad have anabolic functions helping tune insulin-mediated glucose and free fatty acid uptake and help promote lipid accumulation (Bartness, 2002). Conversely, lipid accumulation further increases their anabolic functions (Bartness, 2002). In doing so, norepinephrine controls triacylglycerol lipolysis, NO production, and tissue remodeling (Nguyen et al., 2018). Fat pad denervation decreased transcript expression of resistin and leptin, without impacting the levels of adiponectin. It, therefore, supports an anabolic role for WAT-parasympathetic neurons (Bartness, 2002; Kreier et al., 2002).

These data support the long appreciated contribution of parasympathetic neurons as an inhibitor of splenic macrophage-mediated inflammation (Tracey, 2002; Andersson and Tracey, 2012). Thus, spleen innervating adrenergic activates acetylcholinergic T cells (Rosas-Ballina et al., 2011). By stimulating splenic macrophages' alpha-7 nicotinic

receptor, acetylcholine stops their production of TNF- α (Wang et al., 2003).

Harnessing such inflammatory reflex using bioelectronic devices (Chavan et al., 2017), non-invasive vagus neurons activate blunt inflammation in arthritic patients (Koopman et al., 2016) and mice with experimental inflammatory bowel disease (Ji et al., 2014). As such, parasympathetic neuron activation constitutes an innovative approach to tone down systemic inflammation, obesity progression, and obesity-associated comorbidities, such as pain hypersensitivity.

NEURO-IMMUNITY

The sensory nervous and immune systems work together to promote host defense and homeostasis (Talbot et al., 2016b) and interact through a common language of receptors, cytokines, neuropeptides, and enzymes (Cronin et al., 2018). While this crosstalk is adaptive, protecting the host from threat, it drives disease pathophysiology (Chiu et al., 2013; Wilson et al., 2013; Talbot et al., 2015, 2016b; Foster et al., 2017). In addition to prompting withdrawal reflexes, neurons' interaction with immunocytes controls host defenses (Barnes, 1996; Spiller, 2002; LaMotte et al., 2014; Talbot et al., 2016b).

Clinically, the denervation of an arthritic joint reversed inflammation in that joint, supporting a role for nociceptor regulation of inflammatory processes (Courtright and Kuzell, 1965). The somatosensory neurons are ideally positioned in lymphoid tissues and in the mucosal barrier to control immune responses (Talbot et al., 2015). Such microenvironment allows nociceptors to interact with tissue-resident immune cells via the local release of neuropeptides (Downing and Miyan, 2000; Rosas-Ballina et al., 2011; Foster et al., 2015; McMahon et al., 2015; Veiga-Fernandes and Mucida, 2016). The peptides generated and locally secreted during neurogenic inflammation promote lymphocyte polarization, controlling the extent and type (1, 2, or 3) of inflammation experienced (Ganea and Delgado, 2001; Goetzl et al., 2001; Cunin et al., 2011; Nussbaum et al., 2013; Talbot et al., 2015) as well as stimulating antigen trafficking in the lymph node (LN) (Valijan, 1989; Chiu et al., 2012; Roberson et al., 2013; Talbot et al., 2016b).

The effects of sensory neurons on immunity seem to vary between inflammatory context (T_H1/T_H17 vs T_H2), the neuron subpopulation implicated, as well as the nature of the peptides being secreted (Foster et al., 2015; Azimi et al., 2016, 2017; Talbot et al., 2016b). Typically, substance P (SP) promotes T cell activity and increased dendritic cell (DC) recruitment and recognition of non-self-antigens (Calvo et al., 1992; Siebenhaar et al., 2007). Calcitonin gene-related peptide (CGRP) have the inverse action, stopping T cell proliferation and reducing DC migration to LN (Mikami et al., 2011).

During allergic airway inflammation, IL-5, a type II effector cytokine secreted from several immunocytes, directly activates airway nociceptors, and this leads to the release of VIP. In turn, VIP stimulates ILC2 (Nussbaum et al., 2013; Talbot et al., 2015) and CD4⁺ cells to induce cytokine production,

including IL-5, which initiates a positive feedforward pro-inflammatory cycle (Talbot et al., 2015, 2016b; Foster et al., 2017). Neuromedin U (NMU) also stimulates ILC2s, and when given alongside IL-25, it enhances asthma severity (Cardoso et al., 2017; Klose et al., 2017; Wallrapp et al., 2017). Blocking the NMU–NMUR1 axis decreased ILC2 activity and allergic inflammation (Wallrapp et al., 2017). Besides, while CGRP supports ILC2 production of IL-5 (Wallrapp et al., 2019), it inhibits alarmin-driven type 2 cytokine production, constrains IL-13 expression, and blocks ILC2 proliferation (Nagashima et al., 2019; Wallrapp et al., 2019; Xu et al., 2019).

Within the WAT microenvironment, locally released neuropeptides (CGRP, SP) increase immune influx and polarization, heightening WAT inflammation and nociceptor sensitivity (Foster and Bartness, 2006). From the data obtained in mouse models of allergic inflammation, one would imagine that CGRP produced by fat pad-innervating sensory neurons would block the function of ILC2s cells, unbalancing the type 1/type 2 immunocyte ratio within the WAT. By favoring T_H1-mediated immunity, sensory neurons would enhance the influx of pro-inflammatory immune cells such as IL-1 β and TNF α -secreting M1 macrophages and IFN- γ -producing ILC1. On the one hand, these cytokines would sensitize nociceptor neurons TRP and Na_v channels, triggering pain hypersensitivity; on the other hand, the neurons would locally release more neuropeptides to further imbalance the fat pad local immunity (hypothesized integrated system in **Figure 1**). Blocking the neuro-immune interplay in such a context would have a twofold, yet synergistic, effect: (i) directly decreased obesity-induced pain trigger by inflammatory cytokines, and (ii) decreased chronic low-grade inflammation. We devised two translational approaches to do this.

TARGETING NEURO-IMMUNE CROSSTALK

First, we modified an efficient pain and itch neuron-blocking strategy to locally silence tumor-innervating nociceptors (Roberson et al., 2013). This strategy uses large pore TRP channels as a specific drug delivery device to transport charged local anesthetic (such as QX-314) into nociceptor neurons to stop Na⁺ currents. In the context of inflammation, as found in the fat pad micro-environment, TRP channels open, allowing QX-314 (263 Da) to enter these neurons, producing a specific and durable electrical silencing (Binshtok et al., 2007). Of note, QX-314 did not impact immune cell function (Talbot et al., 2015), confirming its selectivity for inflammation-activated nociceptors (Talbot et al., 2015, 2020; Foster et al., 2017). This strategy offers three major potential advantages: (1) high specificity (the effect is limited only to sensory neurons that express activated large pore channels), (2) long-lasting activity, and (3) limited side effects; the charge on QX-314 would limit diffusion through lipid membranes and redistribution outside of the respiratory epithelium.

Second, Bean and colleagues devised novel charged N-type Ca^{2+} channel blockers, including an NCE termed CNCB2. The latter induced a prolonged pain blockade and was more potent than its neutral analog at inhibiting nociceptor release of CGRP and acted at lower concentrations to stop the neurogenic inflammation component of asthma. Such cationic molecules are therefore suited to treat pain by stopping potential action generation in nociceptive neurons and reducing inflammation by blocking pro-inflammatory neuropeptide release (Lee et al., 2019).

CONCLUDING REMARKS

Peripheral sensitization is a major contributor to inflammatory pain (Albright et al., 2000; Woolf and Ma, 2007; Ji et al., 2014). Because several sensitizing mediators are released simultaneously during inflammation, stopping one of these mediators is likely to have a limited impact. Silencing sensitized neurons or shared downstream signaling pathways should therefore have larger and provide more prolonged pain relief. Among the others, QX-314, CNCB2, or activation of parasympathetic neurons using bioelectronic medicine, may constitute such broadly acting strategy in reversing the neuro-immune component of obesity-induced inflammation and pain.

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AUTHOR CONTRIBUTIONS

All authors wrote the manuscript.

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Vagus Nerve Stimulation in Musculoskeletal Diseases

Joint Bone Spine

May 2021; Vol. 88; No. 3; pp.105149

Alice Courties, Francis Berenbaum, Jérémie Sellam: from Sorbonne University and Saint-Antoine Hospital, both in Paris, France. This study cites 39 references.

CAP = Cholinergic Anti-inflammatory Pathway

VNS = Vagus Nerve Stimulation

Ach = Acetylcholine, also means Cholinergic Nerves

KEY POINTS FROM THIS ARTICLE:

- 1) The vagus nerve is the main nerve of the parasympathetic autonomic nervous system. It is a sensory, motor and visceral nerve. **[80% afferent; 20% efferent]**
- 2) The vagus nerve controls these functions:
 - Vegetative (visceral) functions
 - Anti-inflammatory and analgesic functions
 - These functions are dependent on the secretion of acetylcholine (Ach)
- 3) "Initially developed in the treatment of refractory epilepsy, vagus nerve stimulation (VNS) is currently being evaluated in several musculoskeletal diseases."
- 4) Nicotinic receptors are the primary control of systemic inflammation.
 - The main nicotinic receptor involved in the anti-inflammatory effect of the CAP is the homopentameric alpha 7 nicotinic Ach receptor (α7nAChR).
- 5) Three categories of vagus nerve stimulation include:
 - An invasive surgical placement of an electrode around the cervical vagus nerve which is connected to a generator implanted subcutaneously.
 - "Adverse events in relation with the procedure [have] occurred (e.g., dyspepsia [and] neuropathic pain around the stimulator)."
 - A non-invasive stimulation of the cervical vagus nerve branch percutaneously with a hand-held device targeted near the vagus nerve in the cervical spine (medial to the sternocleidomastoids muscle about C1-C4).

Current Directions in the Auricular Vagus Nerve Stimulation I: A Physiological Perspective

Frontiers in Neuroscience
August 2019; Vol. 13; Article 854

Eugenijus Kaniusas, Stefan Kampusch, Marc Tittgemeyer, and 17 more: this study cites 246 references.

The vagus nerve (VN) is cranial nerve ten (CNX). It is both sensory (80%) and motor (20%). The motor vagus nerve goes to both the *muscles* and *viscera* (heart, lungs, GI, etc.) This review “summarizes the contemporary views on the electrical stimulation of the auricular VN (aVNS) as a promising electroceutical therapy.”

ANS = autonomic nervous system

aVN = auricular vagus nerve

aVNS = auricular vagus nerve stimulation

NTS = nucleus tractus solitarius, the sensory nucleus of the vagus nerve

VN = vagus nerve

VNS = vagus nerve stimulation

KEY POINTS FROM THIS ARTICLE:

- 1) *Bioelectronic medicine* is a non-pharmaceutical treatment for diseases.
- 2) The vagus nerve is the 10th cranial nerve that starts at the brainstem and “widely meanders and loops within the neck, thorax and abdomen.”
- 3) “VN establishes a mutual connection between the brain and major body structures as pharynx, larynx, trachea, heart, aorta, lungs, and the entire gastrointestinal tract including esophagus, stomach, liver, pancreas, and spleen.”
 - The VN plays a crucial role in determining brain-body interactions.
- 4) “Modulation of the afferent vagus nerve affects a large number of physiological processes and bodily states associated with information transfer between the brain and body.” **[Key Point]**
 - These include disease mitigating effects, chronic pain diseases, neurodegenerative and metabolic ailments to inflammatory and cardiovascular diseases.
- 5) “The activity of VN is proportionally associated with health, wellbeing, relaxation, and even emotions like empathy, whereas it is negatively associated with risk factors such as morbidity, mortality, and stress.”
- 6) 80% of VN fibers are afferent sensory fibers carrying somatic and visceral information to the brainstem.

Article Review 3-11:

The Intermedius Nucleus of the Medulla: A Potential Site for the Integration of Cervical Information and the Generation of Autonomic Responses

Article Review 38-14:

Neck Muscle Afferents Influence Oromotor and Cardiorespiratory Brainstem Neural Circuits

Article Review 12-19:

The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases

Article Review 9-24:

Vagus Nerve Stimulation in Musculoskeletal Diseases
[This is a very important Review on this topic].

In addition to upper cervical chiropractic care, we stimulate the afferent vagus nerve at the cyma of the ear with low level laser therapy (Erchonia).

Important Additions

We should all recall the vagus nerve uses acetylcholine as its neurotransmitter. Many, many common drugs for colds, flu, and allergies, and other applications, are classified as anti-cholinergic drugs because they reduce the production of acetylcholine.

Credible publications claim a link between anti-cholinergic drugs and Alzheimer's disease. This is detailed in the following book and Article Reviews:

The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline

Dale Bredesen, MD [neurologist, UCLA]; 2017

Article Review 17-16:

Association Between Anti-Cholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults;
Journal of the American Medical Association Neurology

Article Review 49-20:

Association of Anti-Cholinergic Medication and Alzheimer's Among Cognitively Normal Older Adults
Neurology

This is an argument for taking acetylcholine enhancing supplements, as suggested By Dr. Bredesen. We take Complete Brain Charge and Complete Synapse from Nutri-West.

THE PLANT PARADOX



THE HIDDEN DANGERS IN "HEALTHY"
FOODS THAT CAUSE DISEASE
AND WEIGHT GAIN

STEVEN R. GUNDRY, MD

The Plant Paradox **The Hidden Dangers in "Healthy" Foods that Cause Disease and Weight Gain**

Steven Gundry, MD
2017

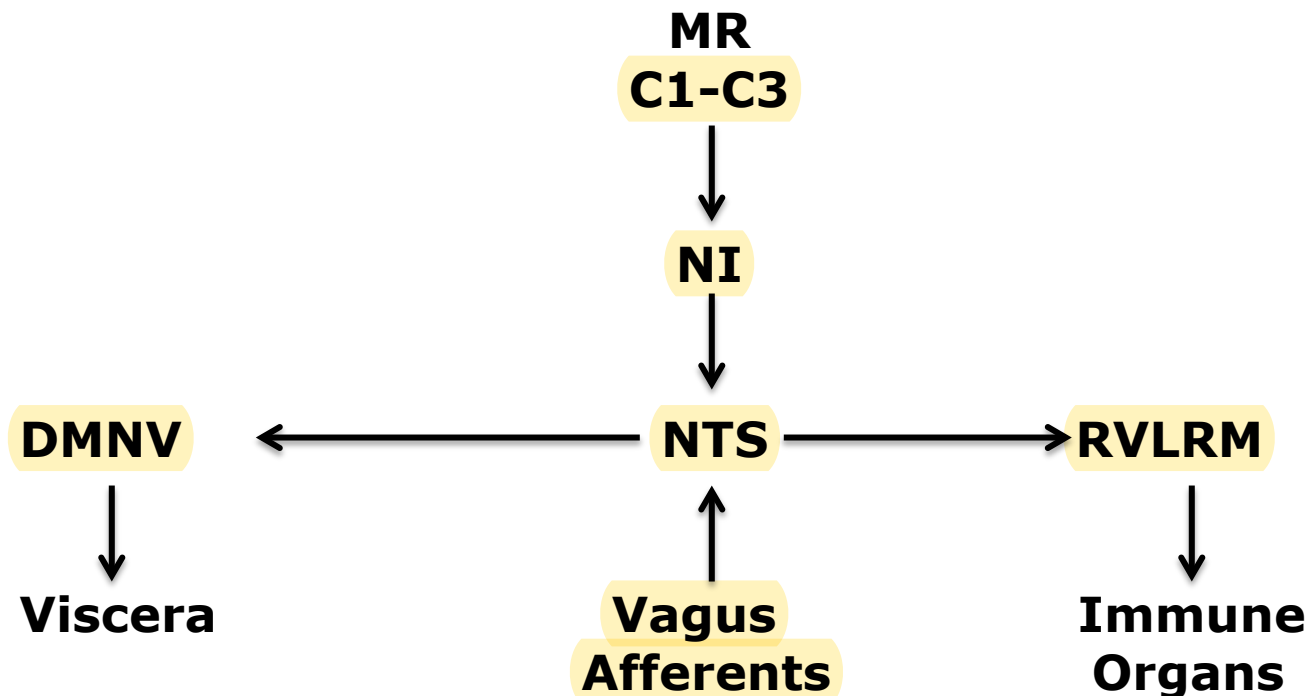
The vagus nerve, also called the parasympathetic nervous system, is the largest nerve coming from the brain to the gut.

It communicates orders to all the various organs in your body.

Exciting studies have shown that lectins reach the brain not only through the blood but, shockingly, also by climbing the vagus nerve from the gut into the brain.

It turns out that for every fiber leading from the brain to your heart, lungs, and your abdominal organs, there are nine times as many fibers leading up to the brain from the gut.

Unlike what I and most other doctors were taught in medical school, the vagus nerve exists to get information to the brain from the gut not the other way around.



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—JAMES NESTOR, AUTHOR OF THE *NEW YORK TIMES* BESTSELLER *BREATH*

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2024

STEVEN R. GUNDRY, MD

NEW YORK TIMES BESTSELLING AUTHOR OF
THE PLANT PARADOX

The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarius

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¹Institute of Membrane and Systems Biology, University of Leeds, Leeds LS2 9JT, United Kingdom, ²Department of Genetic and Behavioral Neuroscience, Gunma University Graduate School of Medicine, and Solution Oriented Research for Science and Technology, Japan Science and Technology Agency, Maebashi 371-8511, Japan, and ³Department of Gene Technology and Developmental Neurobiology, Institute of Experimental Medicine, H-1450 Budapest, Hungary

Sensory afferent signals from neck muscles have been postulated to influence central cardiorespiratory control as components of postural reflexes, but neuronal pathways for this action have not been identified. The intermedius nucleus of the medulla (InM) is a target of neck muscle spindle afferents and is ideally located to influence such reflexes but is poorly investigated. To aid identification of the nucleus, we initially produced three-dimensional reconstructions of the InM in both mouse and rat. Neurochemical analysis including transgenic reporter mice expressing green fluorescent protein in GABA-synthesizing neurons, immunohistochemistry, and *in situ* hybridization revealed that the InM is neurochemically diverse, containing GABAergic and glutamatergic neurons with some degree of colocalization with parvalbumin, neuronal nitric oxide synthase, and calretinin. Projections from the InM to the nucleus tractus solitarius (NTS) were studied electrophysiologically in rat brainstem slices. Electrical stimulation of the NTS resulted in antidromically activated action potentials within InM neurons. In addition, electrical stimulation of the InM resulted in EPSPs that were mediated by excitatory amino acids and IPSPs mediated solely by GABA_A receptors or by GABA_A and glycine receptors. Chemical stimulation of the InM resulted in (1) a depolarization of NTS neurons that were blocked by NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide) or kynurenic acid and (2) a hyperpolarization of NTS neurons that were blocked by bicuculline. Thus, the InM contains neurochemically diverse neurons and sends both excitatory and inhibitory projections to the NTS. These data provide a novel pathway that may underlie possible reflex changes in autonomic variables after neck muscle spindle afferent activation.

Key words: posture; neck; cardiovascular; respiration; medulla oblongata; autonomic

Introduction

Reflex changes in cardiorespiratory variables during body movements rely on interactions between the somatic and autonomic nervous systems. A prime example of such interaction is the somatosympathetic reflex, in which stimulation of thinly myelinated group III (Aδ) and unmyelinated group IV (C-fiber) limb muscle afferent fibers can reflexly increase cardiorespiratory output (Potts et al., 2000, 2003; Wilson, 2000). These reflexes are mediated via sensory afferent input to the spinal cord, which is then relayed to the nucleus tractus solitarius (NTS), a brainstem

site for cardiorespiratory integration (Potts et al., 2003). Cardiorespiratory changes can also be evoked by stimulation of neck muscle afferents (Bolton et al., 1998; Bolton and Ray, 2000), proposed to contribute to alterations in cardiorespiratory outflow in preparation for a change in posture (Bolton and Ray, 2000). In contrast to limb afferents, the sensory signals from these muscles appear to be mediated by group IA muscle spindle afferents (Bolton et al., 1998). However, the neural pathways that link these afferent signals to cardiorespiratory control are completely unknown.

One target for sensory information from neck muscles is the cervical spinal cord where terminations can be found in the dorsal horn (although sparse) and the central cervical nucleus (CCN) (Bakker et al., 1984; Pfaller and Arvidsson, 1988; Prihoda et al., 1991). The CCN projection is generally considered to underlie spinal somatic reflex circuits, such as those for the tonic neck reflex involved in postural control (Wilson et al., 1984; Brink et al., 1985; Hongo et al., 1988; Popova et al., 1995). There is also a strong direct neck muscle afferent projection to the medulla oblongata where fibers terminate in the external cuneate nucleus and a nucleus located at the lateral edges of the dorsal aspect of the hypoglossal motor nucleus (XII), referred to either as the

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*I.J.E. and M.L.D. contributed equally and significantly to this work.

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This study shows a separation of the afferent inputs to the INTERMEDIATE NUCLEUS of the MEDULLA from those to the CENTRAL CERVICAL NUCLEUS and vestibular nuclei, indicating that the INTERMEDIATE NUCLEUS of the MEDULLA participates in discrete circuits with a distinct functional role.

"Activation of neck muscle spindle afferents via neck flexion can initiate an increase in heart rate, muscle sympathetic nerve activity, and arterial blood pressure."

"This cervico-sympathetic reflex appears to originate from muscle spindles in the dorsal neck musculature, it is very likely that the suboccipital muscle group is involved in the reflex because these muscles have an extremely high muscle spindle content." **[Very Important]**

"Additional evidence for the involvement of the suboccipital muscle group in the cervico-sympathetic reflex comes from changes in blood pressure associated with chiropractic manipulations of the C1 vertebrae, which would result in altering the length of fibers in the suboccipital muscle group."

"The projection from the INTERMEDIATE NUCLEUS of the MEDULLA to the NUCLEUS TRACTUS SOLITARIUS identified in this study therefore places it in an ideal position to mediate cardiorespiratory changes to neck muscle afferent stimulation, because the NUCLEUS TRACTUS SOLITARIUS is a major integratory area for autonomic control circuits."

"The results from this study and others reveal that the INTERMEDIATE NUCLEUS of the MEDULLA is neurochemically rich."

This study is the first to investigate the neurochemistry of the INTERMEDIATE NUCLEUS of the MEDULLA, and show that the INTERMEDIATE NUCLEUS of the MEDULLA sends both excitatory and inhibitory projections to the NUCLEUS TRACTUS SOLITARIUS.

KEY POINTS FROM DAN MURPHY

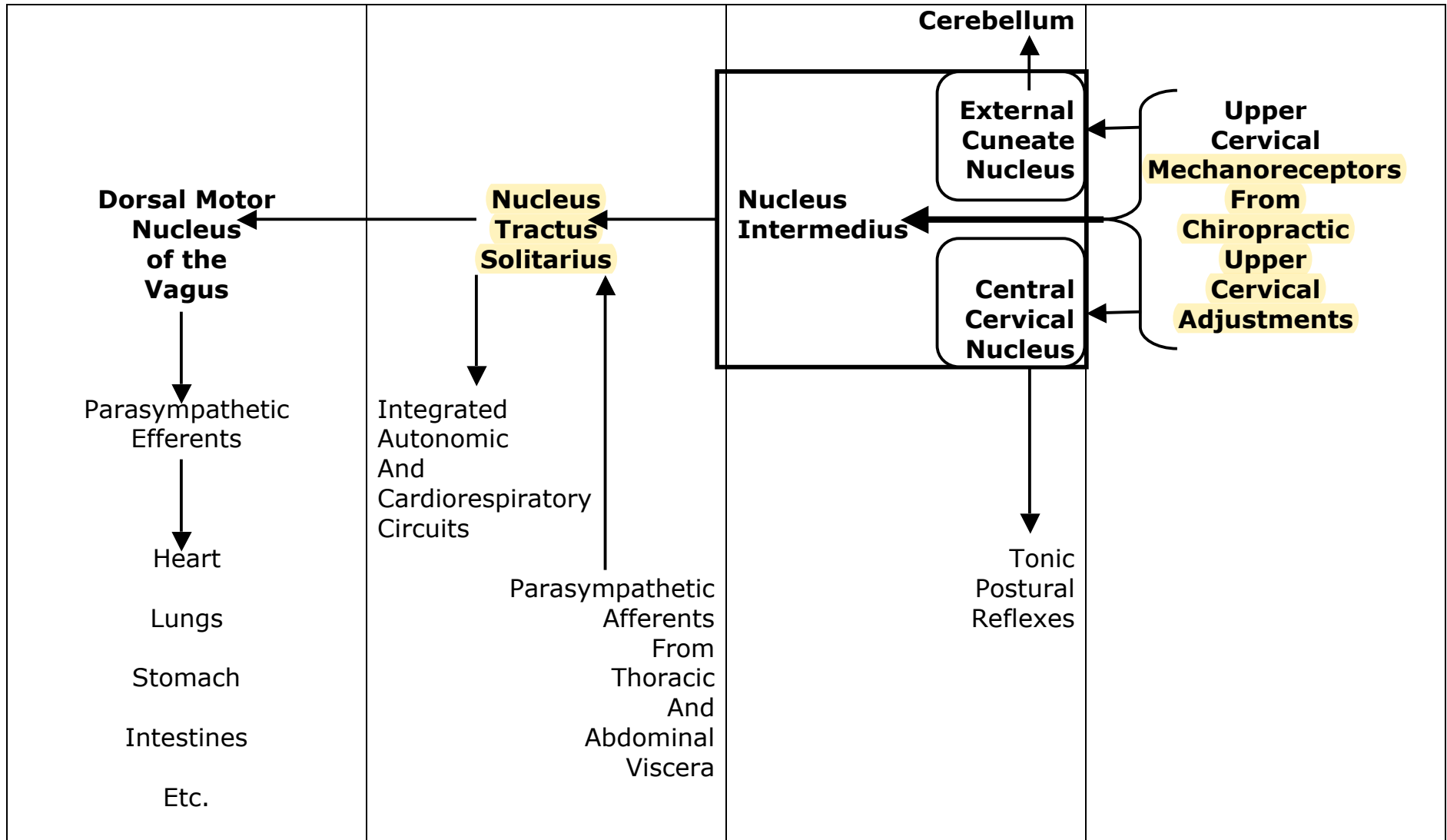
- 1) Sensory afferent signals from neck muscles are components of postural reflexes.
- 2) Sensory afferent signals from neck muscles influence central cardiorespiratory control.

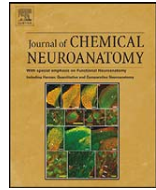
[This would suggest that if one could affect the sensory afferent from the neck muscles one could influence postural reflexes and cardiorespiratory control.]

- 3) The INTERMEDIATE NUCLEUS of the MEDULLA is a target of neck muscle spindle afferents and is ideally located to influence both postural reflexes and cardiorespiratory control.
- 4) The INTERMEDIATE NUCLEUS of the MEDULLA sends both excitatory and inhibitory projections to the NUCLEUS TRACTUS SOLITARIUS.
- 5) In the "somatosympathetic reflex," muscle afferent fibers reflexly alter cardiorespiratory output. "These reflexes are mediated via sensory afferent input to the spinal cord, which is then relayed to the nucleus tractus solitarius (NTS), a brainstem site for cardiorespiratory integration."
- 6) "Cardiorespiratory changes can also be evoked by stimulation of neck muscle afferents."
- 7) Neck muscle afferents enter the CENTRAL CERVICAL NUCLEUS and its rostral continuation, the INTERMEDIATE NUCLEUS of the MEDULLA. "There is a strong direct neck muscle afferent projection to the medulla oblongata where fibers terminate in the external cuneate nucleus [accessory cuneate nucleus] and the INTERMEDIATE NUCLEUS of the MEDULLA."
- 8) There are monosynaptic excitatory and inhibitory projections from the INTERMEDIATE NUCLEUS to the NUCLEUS TRACTUS SOLITARIUS.
- 9) The INTERMEDIATE NUCLEUS of the MEDULLA receives afferent inputs from neck muscles.
- 10) "Neck muscle afferent stimulation is involved in postural reflexes such as the cervicocollic reflex and interacts with information from the vestibular system to maintain posture."
- 11) "This cervico-sympathetic reflex [that can alter heart rate and blood pressure] appears to originate from muscle spindles in the dorsal neck musculature, it is very likely that the suboccipital muscle group is involved in the reflex because these muscles have an extremely high muscle spindle content." **[Very Important]**
- 12) "Additional evidence for the involvement of the suboccipital muscle group in the cervico-sympathetic reflex comes from changes in blood pressure associated with chiropractic manipulations of the C1 vertebrae, which would result in altering the length of fibers in the suboccipital muscle group." **[Very Important]**
- 13) "The projection from the INTERMEDIATE NUCLEUS to the NUCLEUS TRACTUS SOLITARIUS identified in this study therefore places it in an ideal position to mediate cardiorespiratory changes to neck muscle afferent stimulation, because the NUCLEUS TRACTUS SOLITARIUS is a major integratory area for autonomic control circuits." **[Very Important]**

The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarii

The Journal of Neuroscience
August 1, 2007





Review

The intermedius nucleus of the medulla: A potential site for the integration of cervical information and the generation of autonomic responses

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ABSTRACT

The **intermedius nucleus of the medulla** (InM) is a small perihypoglossal brainstem nucleus, which **receives afferent information from the neck musculature** and also descending inputs from the vestibular nuclei, the gustatory portion of the nucleus of the solitary tract (NTS) and cortical areas involved in movements of the tongue. **The InM sends monosynaptic projections to both the NTS** and the hypoglossal nucleus. It is likely that the InM acts to integrate information from the head and neck and relays this information on to **the NTS where suitable autonomic responses can be generated**, and also to the hypoglossal nucleus to influence movements of the tongue and upper airways.

Central to the integratory role of the InM is its neurochemical diversity. Neurones within the InM utilise the amino acid transmitters glutamate, GABA and glycine. A proportion of these excitatory and inhibitory neurones also use nitric oxide as a neurotransmitter. Peptidergic transmitters have also been found within InM neurones, although as yet the extent of the pattern of co-localisation between peptidergic and amino acid transmitters in neurones has not been established.

The calcium binding proteins calretinin and parvalbumin are found within the InM in partially overlapping populations. Parvalbumin and calretinin appear to have complementary distributions within the InM, with parvalbumin being predominantly found within GABAergic neurones and calretinin being predominantly found within glutamatergic neurones.

Neurones in the InM receive inputs from glutamatergic sensory afferents. This glutamatergic transmission is conducted through both NMDA and AMPA ionotropic glutamate receptors.

In summary the InM contains a mixed pool of neurones including glutamatergic and GABAergic in addition to peptidergic neurones. **Neurones within the InM receive inputs from the upper cervical region, descending inputs from brain regions involved in tongue movements and those involved in the co-ordination of the autonomic nervous system. Outputs from the InM to the NTS and hypoglossal nucleus suggest a possible role in the co-ordination of tongue movements and autonomic responses to changes in posture.**

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"Changes in the positioning of the head relative to the trunk, or sensory information arising from the neck musculature, have been clinically implicated in the control of heart rate and blood pressure."

When the sternocleidomastoid muscle loses (denervation) its normal proprioceptive input into the vestibular nucleus and/or NTS, there is an exaggerated vagal response subsequent to stimulation of the carotid sinus.

"The InM acts to integrate information from both the neck musculature and the vestibular system before relaying this information on to the NTS."

This pathway from the neck musculature to the NTS might be behind the "changes in heart rate and blood pressure observed following upper cervical chiropractic manipulations and autonomic disturbances observed in whiplash patients."

"Both excitatory and inhibitory neurones from the InM project to the NTS providing scope for the InM to evoke differential responses within NTS neurones according to the sensory information that it receives, rather than simply acting as a relay."

"InM neurones are strongly targeted by afferent fibres projecting via the upper cervical DRG," and this "information can manifest as changes in autonomic variables."

"The InM is a little investigated nucleus in the brainstem which has surprisingly diverse neurochemistry. It is possible that this complex nucleus plays a role in the generation of autonomic responses to movements of the head, especially as it is monosynaptically connected with both the NTS and hypoglossal nuclei."

KEY POINTS FROM DAN MURPHY

- 1) The intermedius nucleus of the medulla (InM) [nucleus intermedius] is in the medulla. It receives afferent information from:
 - A)) The neck musculature
 - B)) The vestibular nuclei
 - C)) The gustatory portion of the nucleus of the solitary tract (NTS)
 - D)) Cortical areas involved in movements of the tongue
- 2) The nucleus intermedius sends monosynaptic projections to:
 - A)) The nucleus of the solitary tract (NTS)
 - B)) The hypoglossal nucleus
- 3) The nucleus intermedius integrates information from the head and neck and relays this information on to the nucleus of the solitary tract where suitable autonomic responses are generated.

- 4) The nucleus intermedius also communicates with the hypoglossal nucleus to influence movements of the tongue and upper airways.
- 5) Nucleus intermedius neurones receive inputs from sensory afferents that use glutamate as a neurotransmitter. **[Some excitotoxin experts insist that dietary glutamate {MSG, hydrolyzed protein, etc.} will adversely influence the function of glutamatergic neurons]**
- 6) Outputs from the nucleus intermedius to the nucleus tractus solitarius and hypoglossal nucleus suggest a role in the co-ordination of tongue movements and autonomic responses to changes in posture. **[Very Important: the nucleus intermedius co-ordinates autonomic responses to postural changes]**
- 7) The nucleus intermedius has a spinal cord component called the "central cervical nucleus" or the "medullary portion of the central cervical nucleus" or the "intercalated nucleus" or the "nucleus intercalatus of Staderini."
- 8) The spinal cord component of the nucleus intermedius (central cervical nucleus) is "located lateral to the central canal at the border of the dorsal and ventral horns."
- 9) Sensory fibers from the upper cervical dorsal root ganglion (DRG) directly enter the nucleus intermedius. **[Very Important]**
- 10) Sensory nerves from the suboccipital muscles, the sternocleidomastoid muscle and the longus capitis muscle project to the nucleus intermedius via the upper cervical spine dorsal root ganglion. **[Very Important: the sensory projections from these muscles are mechanoreceptors and proprioceptors; alterations of mechanical afferent input from these muscles alters the input to the nucleus intermedius, then to the nucleus tractus solitarius and to subsequent autonomic responses]**
- 11) "These projections from the cervical DRG to the nucleus intermedius have been proposed to be proprioceptive, which suggests that activity within the nucleus intermedius is heavily influenced by the position of the head relative to the trunk." **[Very Important]**
- 12) "Chemical or electrical stimulation of the nucleus intermedius causes monosynaptic excitatory and inhibitory postsynaptic potentials in the nucleus of the solitary tract (NTS)."
- 13) The authors suggest that the greatest influence of the nucleus intermedius is to the "autonomic circuits relating to the cardiovascular system."
- 14) Nucleus intermedius neurones are "under the influence of information arising from the neck region, in particular the dorsal neck muscles."

15) One of the functions of the nucleus intermedius is to elicit autonomic responses to movements of the head to complement those triggered by the vestibular system.

16) The vestibular system regulates cardiovascular autonomic (sympathetic) responses to head movements.

17) Innocuous mechanical stimulation of the neck of humans that does not activate the vestibular system evokes changes in heart rate and blood pressure, perhaps through the nucleus intermedius.

[This is like saying that altered mechanical afferent input from the neck {innocuous mechanical stimulation} subsequent to the chiropractic subluxation alters the neurological influence to the nucleus intermedius, in turn influencing the autonomic control of heart rate and blood pressure. Recall that the study in the *Journal of Human Hypertension*, March 2007, showed that specific upper cervical chiropractic adjustments (NUCCA) significantly reduced blood pressure, and the outcomes remained stable during an 8 week follow-up period]

18) Low threshold stimulation of the nerves entering the C1 and C2 DRG can elicits changes in the activity of both sympathetic and respiratory nerves.

[Very Important: supports chiropractic adjustments influencing sympathetic neurology]

19) Proprioceptive information can play a role in modulating the autonomic nervous system. **[Very Important: this is a central theme to chiropractic clinical approaches to many non-musculoskeletal syndromes]**

20) "Neurons in the nucleus intermedius are under the influence of sensory afferent information arising from the neck region." **[Very Important]**

21) The nucleus intermedius receives afferent input from the vestibular nuclei.

[Important because the vestibular nucleus also receives monosynaptic inputs from upper cervical spine afferents]

22) The nucleus intermedius also receives descending inputs from the prefrontal cortex and the amygdala. **[This explains some of the emotional influences on the autonomic neurological activity]**

23) Upper cervical DRG afferent fibers project to the nucleus intermedius, and these fibers are "proprio- and mechano-ceptive afferents" and not nociceptors.

[This is very important because it implies that non-painful aberrant mechanical afferent input from the upper cervical spine can alter autonomic function. In the study from the *Journal of Human Hypertension*, March 2007, which showed a significant reduction of blood pressure with specific upper cervical chiropractic adjustments, the authors noted that none of the patients were suffering from neck or back pain]

24) The authors suggest the primary afferents influencing the nucleus intermedius are from the upper cervical muscles “adding weight to the theory that the nucleus intermedius is under the influence of cervical muscles.”

25) “The InM is a surprisingly complex nucleus which receives sensory inputs from the neck region via the upper cervical DRG.”

26) “Changes in the positioning of the head relative to the trunk, or sensory information arising from the neck musculature, have been clinically implicated in the control of heart rate and blood pressure.”

[Very Important: the upper cervical chiropractic subluxation is a change in the “positioning of the head relative to the trunk, or sensory information arising from the neck musculature”]

27) “The nucleus intermedius acts to integrate information from both the neck musculature and the vestibular system before relaying this information on to the nucleus tractus solitarius.”

28) This pathway from the neck musculature to the nucleus tractus solitarius might be behind the “changes in heart rate and blood pressure observed following upper cervical chiropractic manipulations and autonomic disturbances observed in whiplash patients.” **[Very Important: these authors acknowledge the ability of upper cervical chiropractic adjustments to influence heart rate and blood pressure, both autonomic functions]**

29) “The nucleus intermedius neurones are strongly targeted by afferent fibres projecting via the upper cervical DRG,” and this “information can manifest as changes in autonomic variables.”

30) The nucleus intermedius “plays a role in the generation of autonomic responses to movements of the head,” especially as it is monosynaptically connected with the nucleus tractus solitarius.

COMMENTS FROM DAN MURPHY

This is a very important article for chiropractors. It explains the neuroanatomical relationship between upper cervical spine subluxation (a mechanical problem) and visceral autonomic neurology. The authors use chiropractic adjustments of the upper cervical spine influencing cardiac function as support for their neuroanatomical findings. This study supports the 115 years of clinical observations of chiropractors. It shows the “biological plausibility” of the influence of chiropractic adjustments on non-musculoskeletal syndromes.

I would be unable to share this information with so many were it not for the efforts of ICA Board Member Dr. George Curry, an excellent chiropractor and scholar.

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A potential site for the integration of cervical information and the
generation of autonomic responses**

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**Proprioceptors / Mechanoreceptors
from**

**Sternocleidomastoid
Muscle**

**Suboccipital
Muscle**

**Longus Capitus
Muscle**

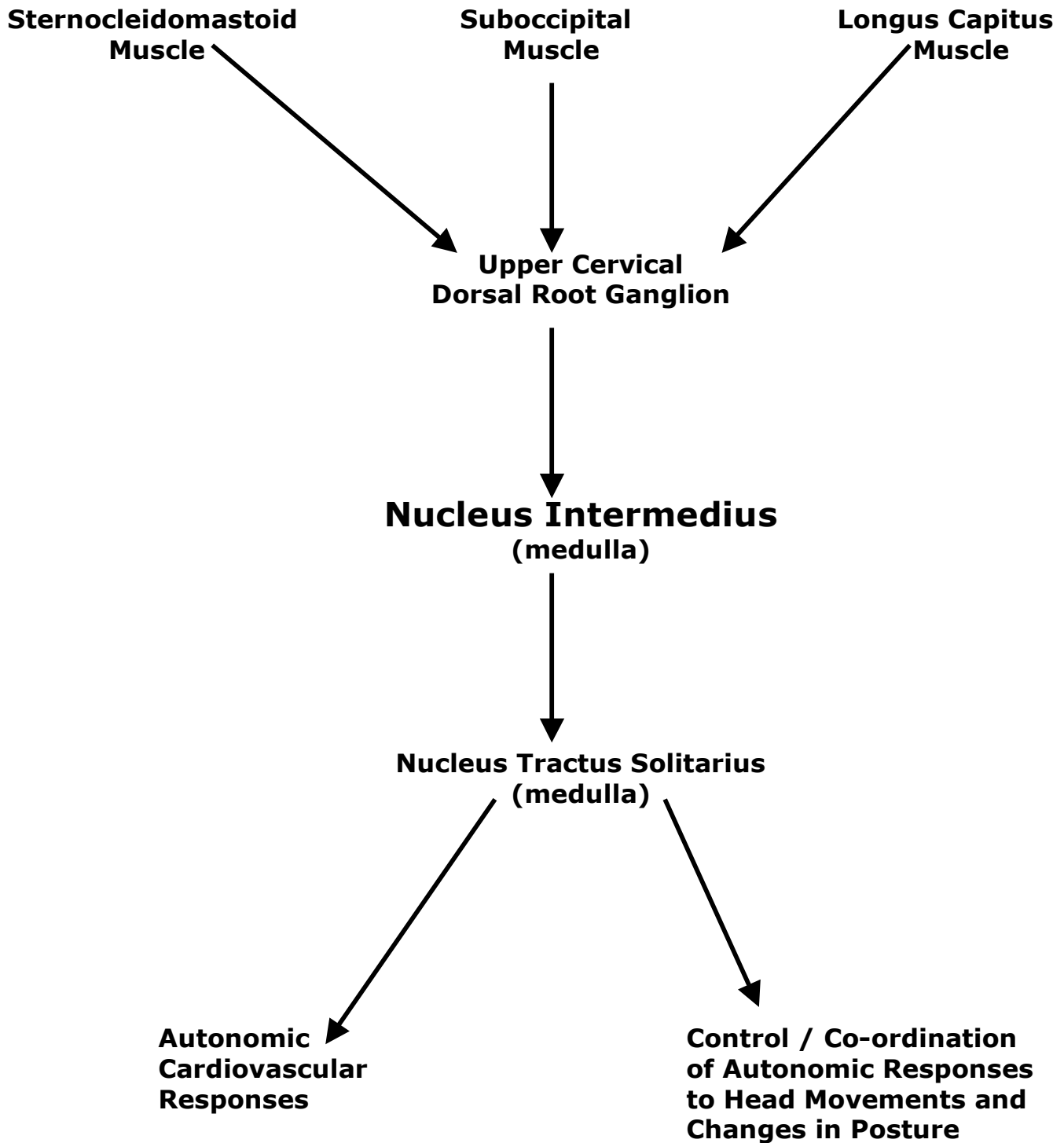
**Upper Cervical
Dorsal Root Ganglion**

**Nucleus Intermedius
(medulla)**

**Nucleus Tractus Solitarius
(medulla)**

**Autonomic
Cardiovascular
Responses**

**Control / Co-ordination
of Autonomic Responses
to Head Movements and
Changes in Posture**



Neck muscle afferents influence oromotor and cardiorespiratory brainstem neural circuits

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Abstract Sensory information arising from the upper neck is important in the reflex control of posture and eye position. It has also been linked to the autonomic control of the cardiovascular and respiratory systems. Whiplash associated disorders (WAD) and cervical dystonia, which involve disturbance to the neck region, can often present with abnormalities to the oromotor, respiratory and cardiovascular systems. We investigated the potential neural pathways underlying such symptoms. Stimulating neck afferent activity by electrical stimulation of the second cervical nerve in a working heart brainstem preparation (WHBP) altered the pattern of central respiratory drive and increased perfusion pressure. Tracing central targets of these sensory afferents revealed projections to the intermedius nucleus of the medulla (InM). These anterogradely

labelled afferents co-localised with parvalbumin and vesicular glutamate transporter 1 indicating that they are proprioceptive. Anterograde tracing from the InM identified projections to brain regions involved in respiratory, cardiovascular, postural and oro-facial behaviours—the neighbouring hypoglossal nucleus, facial and motor trigeminal nuclei, parabrachial nuclei, rostral and caudal ventrolateral medulla and nucleus ambiguus. In brain slices, electrical stimulation of afferent fibre tracts lateral to the cuneate nucleus monosynaptically excited InM neurones. Direct stimulation of the InM in the WHBP mimicked the response of second cervical nerve stimulation. These results provide evidence of pathways linking upper cervical sensory afferents with CNS areas involved in autonomic and oromotor control, via the InM. Disruption of these neuronal pathways could, therefore, explain the dysphagic and cardiorespiratory abnormalities which may accompany cervical dystonia and WAD.

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Immunohistochemistry · Electrophysiology

Introduction

The intermedius nucleus of the medulla (InM) is a neurochemically diverse perihypoglossal nucleus (Edwards et al. 2007, 2009) with no known function. Furthermore, very little is known regarding the anatomical connectivity of the nucleus. We have previously identified a monosynaptic projection from the InM into the neighbouring nucleus of the solitary tract (NTS) using electrophysiology (Edwards et al. 2007), indicating a possible role in autonomic and/or respiratory control. Direct primary afferent input to the InM arises from upper cervical levels in a number of

7) "These results provide evidence of pathways linking upper cervical sensory afferents with CNS areas involved in autonomic and oromotor control, via the InM." **[Key Point]**

8) "Disruption of these neuronal pathways could, therefore, explain the dysphagic and cardiorespiratory abnormalities which may accompany cervical dystonia and whiplash associated disorders."

9) There exists a monosynaptic projection from the InM into the nucleus of the solitary tract (NTS), "indicating a possible role in autonomic and/or respiratory control."

10) There is direct primary afferent input to the InM from upper cervical levels.

11) "Studies are suggestive of a possible role for the InM in mediating autonomic/respiratory responses to sensory afferent signals arising from the upper neck."

12) "Physiological studies are consistent with the notion that cervical sensory afferents influence autonomic function." **[Key Point]**

13) In animal studies, low threshold electrical stimulation of the C2 or C3 nerve evokes activity in the hypoglossal nerve, abdominal nerves, and the splanchnic sympathetic nerves. **[Important]**

14) Experimental stimulation of proprioceptive afferents causes sympathetic cardiovascular and respiratory responses. **[Key Point]**

15) These findings reveal cardiorespiratory responses to neck muscle afferent stimulation.

16) The primary investigations in this study involved rats, antibody phenotype tracings, immunohistochemistry staining, confocal microscopic assessment, electron microscopy, nerve stimulation, and much more. The exact protocols are extremely sophisticated and complex.

17) The experiments showed:

- Cardiovascular and respiratory responses to C2 nerve stimulation.
- "C2 muscle afferents terminate within the intermedius nucleus of the medulla (InM)."
- There is also a direct pathway from the cuneate nucleus to the InM.
- "Neurons in the InM send efferent projections to known CNS areas associated with cardiovascular and oromotor functions."

- The “efferent projections from the InM were bilateral with an ipsilateral predominance.”
- The InM neurons fired to (and significantly bilaterally):
 - Cranial Nerve XII
 - Cranial Nerve VII
 - the ventrolateral medulla, coursing through the intermediate reticular formation with terminals observed within the nucleus ambiguus
 - the nucleus tractus solitarius (NTS)
 - the caudal portion of the spinal vestibular nucleus
 - they showed medullary catecholamine immunoreactivity
 - the ventral horn motoneurons in the cervical spinal cord at levels C4–6, predominantly around the phrenic motoneurons
 - the pontine parabrachial nucleus
 - medullary sympathetic relays
 - “Efferent projections from the InM were observed within cardiovascular, respiratory and oromotor regions of the brainstem.”

18) “This study shows that stimulation of neck muscle afferents can influence behaviour of the cardiovascular and respiratory systems. This is due to unique neuronal pathways which exhibit specialized functions, the first stage of this signaling arising from neck muscles.”

19) “Neurophysiological and neuroanatomical experiments indicate that the [upper cervical] sensory input exerts its influence via the InM, which appears to act as an integratory center.”

20) “Neck muscle afferent input to the intermedius nucleus of the medulla (InM).”

21) “Neuroanatomical studies looking at the central targets of cervical sensory afferents have revealed a direct sensory projection to the InM from upper cervical but not lower cervical levels.”

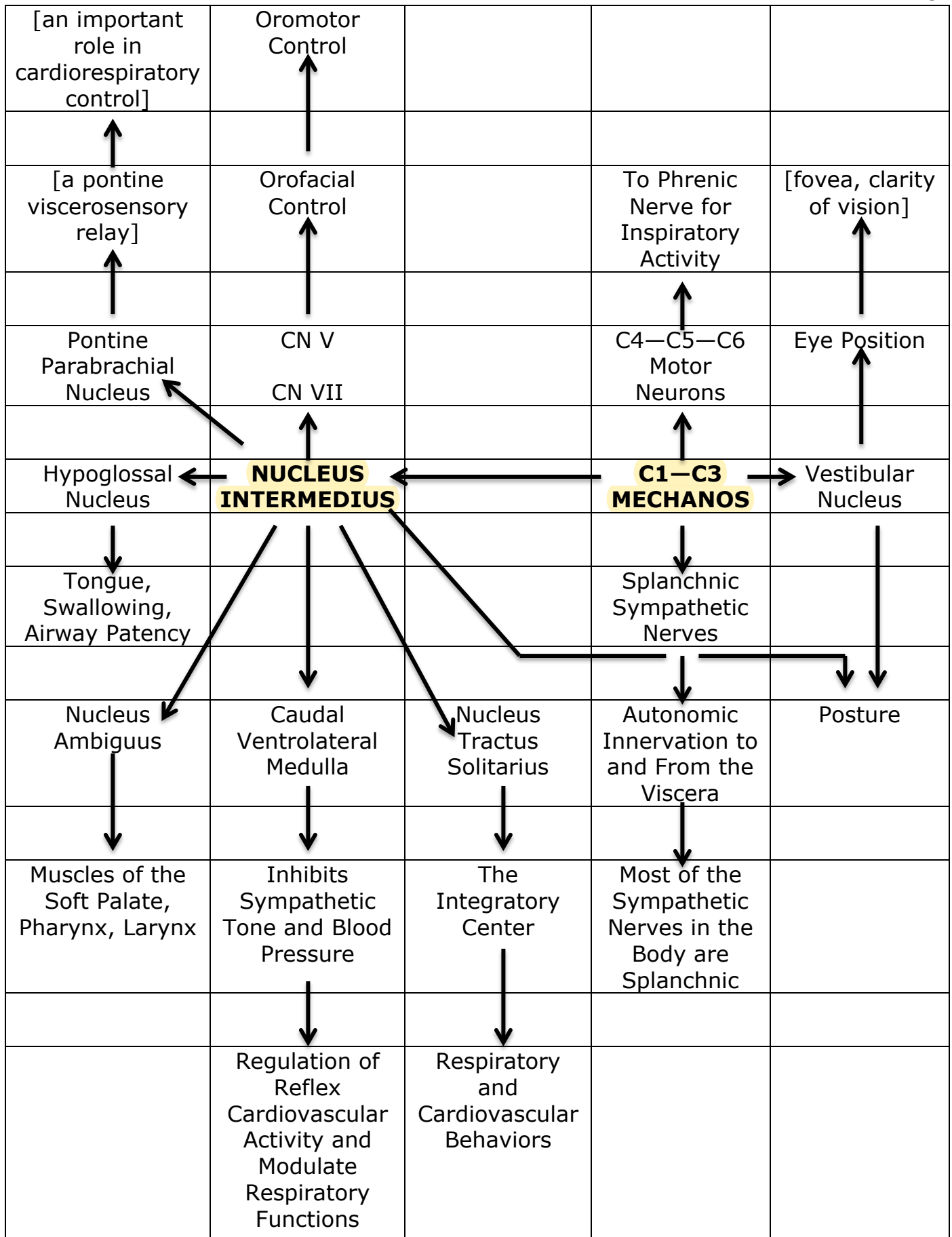
- 22) "The input to the InM is thought to be of a muscle origin [muscle proprioceptors/spindles] as when tracers are applied to the lesser occipital nerve, a pure skin nerve branch of C2, no terminal labeling is observed within the InM."
- 23) "The majority of the traffic to the InM through the C2 nerve is likely to be of a muscle origin." "Many of the primary afferent inputs to the InM arise from the musculature of the neck."
- 24) "The muscles supplying the upper cervical segments are particularly rich in muscle spindles."
- 25) Only afferents arising from C1–4 have been demonstrated to project to the InM. "The InM does not receive inputs from primary afferents caudal to C4."
- 26) There is a strong "role of InM in mediating specific actions of neck muscle afferents on oromotor, respiratory and sympathetic systems."
- 27) The InM may be acting as an upper cervical muscle sensory relay station.
- 28) The InM is a major source of input to the hypoglossal nucleus. "The InM appears to be in a prime position to integrate information from both the periphery and the CNS before influencing airway patency and tongue movements through the hypoglossal nucleus."
- 29) A main unique target of the "upper cervical sensory afferents is the InM."
- 30) The InM plays an integral part to upper cervical peripheral nerve stimulation.

COMMENTS FROM DAN MURPHY

I significantly simplified this article. The authors presented detailed, complex, sophisticated primary research showing the biological plausibility of how the proprioceptors of the upper cervical spine influence a wide variety of visceral responses. This supports more than a century of chiropractic anecdotal and clinical observations.

The basic premise is that upper cervical alignment influences the length and therefore the tone of the suboccipital muscles, thereby influencing the proprioceptive firing through the upper cervical spine nerve roots to the nucleus intermedius (InM).

The nucleus intermedius (InM) in turn influences the function of the lower 7 cranial nerves, including their parasympathetic functions, as well as medullary sympathetic relays. The biological plausibility is that the upper cervical spine mechanosensitive afferents have a major influence in the balance between the parasympathetic and sympathetic nervous systems, influencing whole body homeostasis and health. Please note the following schematic:



Concept Paper

The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health

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Abstract: Global burden of diseases (GBD) includes non-communicable conditions such as cardiovascular diseases, cancer and chronic obstructive pulmonary disease. These share important behavioral risk factors (e.g., smoking, diet) and pathophysiological contributing factors (oxidative stress, inflammation and excessive sympathetic activity). This article wishes to introduce to medicine and public health a new paradigm to predict, understand, prevent and possibly treat such diseases based on the science of neuro-immunology and specifically by focusing on vagal neuro-modulation. Vagal nerve activity is related to frontal brain activity which regulates unhealthy lifestyle behaviors. Epidemiologically, high vagal activity, indexed by greater heart rate variability (HRV), independently predicts reduced risk of GBD and better prognosis in GBD. Biologically, the vagus nerve inhibits oxidative stress, inflammation and sympathetic activity (and associated hypoxia). Finally, current non-invasive methods exist to activate this nerve for neuro-modulation, and have promising clinical effects. Indeed, preliminary evidence exists for the beneficial effects of vagal nerve activation in diabetes, stroke, myocardial infarction and possibly cancer. Thus, we propose to routinely implement measurement of HRV to predict such GBD in populations, and to test in randomized controlled trials effects of non-invasive vagal nerve activation on prevention and treatment of GBD, reflecting possible neuro-modulation of health.

Keywords: global burden of diseases; neuroimmunology; neuromodulation; vagal nerve; prediction; prevention

1. The Problem

Major non-communicable causes of death and of years of life lost today include coronary heart disease (CHD), stroke, cancer and pulmonary diseases [1]. Many risk factors (pollution, smoking, diet-driven cholesterol, insufficient exercise, etc.) explain a large proportion of major global burden of diseases—GBD (e.g., [2]). Furthermore, many of these diseases have common underlying biological causes, as we shall see below.

While modernization has brought many positive developments (e.g., transportation, huge improvements in disease detection and treatment, immense improvements in access to information via

The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health

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BACKGROUND FROM DAN MURPHY:

Heart Rate Variability (HRV) is a measurement of the time intervals between adjacent heartbeats. It may be used to evaluate the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. "It is crucial to measure HRV for at least 5 min, to obtain both time and frequency domain HRV parameters in a reliable manner."

Analysis of beat-to-beat variability is a simple, non-invasive technique to evaluate autonomic neurological dysfunction. Heart rate variability data may be collected using:

- Electrocardiogram
- Plethysmograph

Spinal manipulation may alter heart rate variability.

The sympathetic nervous system uses the neurotransmitter norepinephrine.

- Norepinephrine is a catecholamine.

The vagus nerve is a parasympathetic nerve that uses the neurotransmitter acetylcholine. It descends from the brain stem and innervates most visceral organs. "The vagus nerve is a major branch of the parasympathetic nervous system."

.....

Global burden of diseases (GBD) includes non-communicable conditions such as cardiovascular diseases, cancer, and chronic obstructive pulmonary disease.

Cardiovascular diseases, cancer, and chronic obstructive pulmonary disease share 2 important behavioral risk factors:

- Smoking
- Diet

Cardiovascular diseases, cancer, and chronic obstructive pulmonary disease share 3 important pathophysiological contributing factors:

- Oxidative stress
- Inflammation
- Excessive sympathetic nerve activity **[Important Point]**

This article introduces a new paradigm to predict, understand, prevent, and possibly treat such diseases based on the science of neuro-immunology and specifically by focusing on vagal (parasympathetic/acetylcholine) neuro-modulation.

This study cites 80 references.

KEY POINTS FROM THIS ARTICLE:

- 1) Neuro-immunology is the science that investigates the interplay between the nervous and immune systems.
- 2) High vagal nerve activity alters homeostasis. It is key for neuro-modulation.
 - "HRV, the vagal nerve index, could be used to predict onset and prognosis of major global disease burdens."
 - "Vagal nerve activity predicts the risk of and prognosis in many major GBD."
 - High HRV predicts reduced risk of overall mortality.
 - "Higher HRV significantly predicts longer survival in cancer."
 - "HRV is inversely related to insulin resistance and to levels of HbA1C."
- 3) Vagal nerve activity (parasympathetic/acetylcholine) is related to frontal brain activity.
 - Frontal brain activity also "regulates unhealthy lifestyle behaviors."
- 4) High vagal activity predicts reduced risk of global burden of diseases (GBD) and better prognosis in global burden of diseases. **[Important Point]**
 - High vagal activity is measured by greater heart rate variability (HRV). **[Important]**
- 5) "Biologically, the vagus nerve inhibits oxidative stress, inflammation and sympathetic activity (and associated hypoxia)." **[Key Point]**
- 6) Several non-pharmacological and non-invasive methods exist for activating the vagus nerve for neuro-modulation:

- "Evidence exists for the beneficial effects of vagal nerve activation in diabetes, stroke, myocardial infarction and possibly cancer."
- "Physical activity increases HRV."
- Transcutaneous vagus nerve stimulation devices have been developed.
- "Various forms of meditation and yoga also increase HRV."

7) Modernization has brought heavy deleterious environmental, occupational, and lifestyle consequences, "with vast health implications."

- Modernization leads to more air pollution, to a more sedentary lifestyle with reduced physical activity, and more job stress, "all having immense and adverse health consequences."

8) With the escalation of the global burden of diseases, there is one factor that is epidemiologically related to major causes of death, which is related to behavioral risk factors contributing to these diseases, and which is related to their common underlying pathophysiological causes. It is the "vagus nerve hypothesis for global public health, reflecting a neuro-immunological paradigm." **[Important]**

- These authors focus on three pathophysiological causes of many major health problems:
 - Oxidative stress
 - Inflammation
 - Excessive sympathetic activity **[The Key To Chiropractic]**

9) "Higher vagal activity predicts reduced risk of major chronic diseases." **[Key Point]**

10) Oxidative Stress and Chronic Diseases:

- "Oxidative stress occurs when the body has more pro-oxidants than anti-oxidants." This damages molecules such as DNA.
- Hypoxia can drive oxidative stress.
- "Pollution-induced oxidative stress is linked to cardiovascular diseases and cardiac death." Air pollution is also a risk factor for dementia.
- "Pollution also causes inflammation to induce oxidative stress and subsequent DNA damage, obvious contributing factors in carcinogenesis."
- Stress (psychological stress, job stress) is also associated with higher oxidative stress.

- Chronic stress is related to reduced telomere length, “which predicts diseases and earlier mortality.”

11) Inflammation and Chronic Diseases:

- “Inflammation reflects recruitment of immune cells (mostly innate) due to various danger signals (e.g., injury, infection, cell damage).”
- “Inflammation contributes to all stages of carcinogenesis from escape from apoptosis and tumor onset, to angiogenesis and metastasis.”
- Inflammation contributes to multiple stages of atherogenesis, plaque rupture and thrombosis.
- “Inflammation is also a major contributing factor to insulin resistance, the main factor underlying diabetes.”
- Psychosocial stress is related to elevated pro-inflammatory cytokines and to reduced anti-inflammatory cytokines.
- “Inflammation, the over-reaction of the immune system to danger signals, underlies multiple non-communicable chronic diseases.”

12) Excessive Sympathetic Nervous System Activity and Chronic Diseases:

- “Excessive sympathetic nervous system (SNS) activity is related to cardiovascular diseases by inducing greater oxygen demand from the heart and by inducing vasoconstriction, which can induce ischemia.” **[Key Point]**
- High SNS activity affects the direction to which cancer cells will metastasize.
- “Excessive sympathetic activity was found in diabetic patients to predict increased risk of cerebral and cardiovascular events.”
- “Job stress is associated with higher SNS activity.”
- Driving in peak traffic is associated with elevated *catecholamines* and sympathetic neuro-hormones.
 - Increasing wealth causes the constant global increase in traffic congestions and elevates *catecholamines* and sympathetic neuro-hormones.
- “The prevalence and possible impact of increased SNS activity on health are expected to rise in the future.” **[Critical Point]**

13) Physicians and health policy makers should use HRV “routinely for prediction and possible prevention of major diseases in the population.” **[Key Point]**

14) The Vagus Nerve Inhibits Oxidative Stress, Inflammation, and Sympathetic Activity:

- “Vagus nerve stimulation (VNS) reduces oxidative stress.”
- “The vagus plays a key neuro-immune mediator and modulator between peripheral immune signals and the brain.”
- The vagus inhibits inflammation through two mechanisms:
 - “Via activation of the hypothalamic pituitary adrenal axis which results in systemic cortisol secretion which reduces inflammation.”
 - Via the vagus to the spleen activates splenic T-cells (via adrenergic receptors), “resulting in the inhibition of synthesis of inflammatory cytokines.”

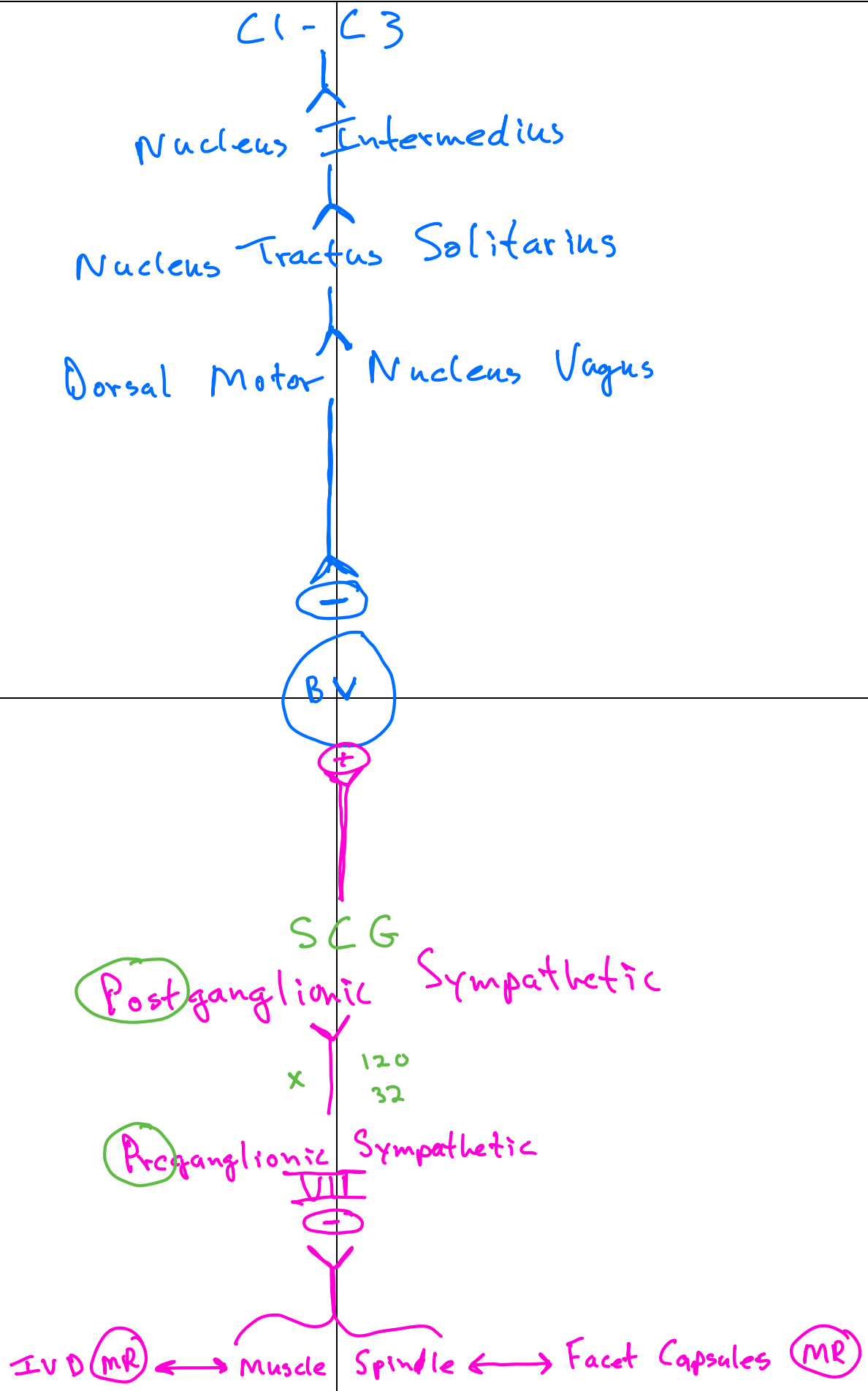
15) “Activity of the vagus nerve, being a major part of the parasympathetic nerve system, inhibits sympathetic activity.” **[Key Point]**

16) “An important parasympathetic role of the vagus is vasodilation.”

- “This anti-hypoxic role is crucial for reducing risk of CHD, stroke and even also cancer since many tumors flourish in hypoxic conditions and hypoxia is prognostic in cancer.”
- “There is evidence that hypoxia (related to excessive sympathetic vasoconstrictive activity), oxidative stress and inflammation are causally related in a vicious circle manner.” **[Key Point]**
- “The vagus nerve inhibits all three promoters of the major chronic diseases mentioned above.” **[Key Point]**

17) “Vagus nerve activity, indexed by HRV, is positively related to executive functioning.”

- Vagal nerve stimulation “increases executive control and emotional regulation, possibly relevant to ‘emotional eating’ and to greater frontal control of GBD behavioral risk factors in general.” **[Important]**
- “The vagus nerve reduces certain behavioral risk factors and inhibits three main pathophysiological factors which contribute to those diseases (oxidative stress, inflammation and excessive SNS activity).”



Nasal Specific → Sphenoid

Upper Cervical → Occiput/Atlas → Cork CSF

- * Calming
- * Vasodilation
 - ↓ B.P.
 - ↓ artery disease
- * Immune Enhancing
- * Longer Telomere

Acetylcholine

HRV

Stress
Fight/Flight

↓
Vasoconstriction
↑ BP
↑ artery disease

Immune Suppression
Shorter Telomeres
Shrink Brain

Norepinephrine

↑
SNS
↑
~~VII~~
⊖
↑

Mechanoreceptors

The New Science of the
Vagus Nerve and How to Harness
Its *Healing Reflexes*

THE
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KEVIN J. TRACEY, MD

The Great Nerve
The New Science of the *Vagus Nerve* and How to
Harness Its *Healing Reflexes*
Kevin Tracey MD
Avery, 2025

“Your vagus nerve is great because it reaches into so many life and health-giving systems in your body and keeps them all in balance.”

“The vagus nerve can regulate your body’s vital systems and heal a wide variety of medical conditions.”

“The vagus nerve is fundamental to our health and vitality...”

“The previously unknown power of the vagus nerve to reverse inflammation, balance the immune system, treat chronic illness...”

“Inflammation has replaced infection as the greatest threat to healthful human longevity.”

“A functioning vagus nerve is truly a life-or-death matter; it is the only nerve we have that when cut on both sides, we die.”

“How do you know if your vagus nerve is being stimulated? A simple answer is that you know it is being stimulated when your pulse goes down?”

Do inflammatory cytokines cause low back pain?

Google AI Overview
February 14, 2026

Inflammatory cytokines, particularly IL-6, IL-8, and TNF-alpha, play a key role in the development and persistence of low back pain (LBP) by promoting inflammation, disk degeneration, and nerve sensitization. These biomarkers are frequently elevated in patients with chronic LBP, disc herniation, and degenerative disc diseases.

Key Cytokines and Their Roles

Interleukin-6 (IL-6):

Persistently increased levels of IL-6 are associated with chronic lumbar radicular pain and disc herniation.

Interleukin-8 (IL-8)

Identified as a crucial cytokine in disc-related pain, IL-8 levels are higher in patients with chronic LBP and correlate with pain severity.

Tumor Necrosis Factor-alpha) (TNF-alpha):

Higher concentrations are found in patients with restricted lumbar mobility and contribute to the inflammatory process in disc degeneration.

Grok AI Overview
February 14, 2026

Yes, inflammatory cytokines contribute to low back pain (LBP) in many cases.

Research shows that pro-inflammatory cytokines play a significant role in both **disc-related** (e.g., herniation, degeneration) and **non-specific** low back pain by:

- Directly sensitizing nociceptors (pain-sensing nerves)
- Promoting inflammation in disc tissue, muscles, facet joints, or surrounding structures
- Contributing to central and peripheral sensitization
- Amplifying pain signaling pathways

Key Cytokines Involved in Low Back Pain

Cytokine Type		Main Findings in LBP Patients
TNF-α	Pro-inflammatory	Frequently elevated in chronic LBP and disc herniation; correlates with pain intensity and radicular symptoms
IL-6	Pro-inflammatory	Commonly increased in both acute and chronic LBP; linked to pain severity and systemic inflammation
IL-1β	Pro-inflammatory	Elevated in many studies; promotes disc degeneration and nociceptor sensitization
IL-8	Pro-inflammatory	Often significantly higher in disc-related LBP; correlates with radicular pain and herniation
IL-10	Anti-inflammatory	Often decreased in LBP patients → imbalance favoring inflammation

Evidence Summary by Pain Type

- **Disc herniation / radicular pain / sciatica** Very strong evidence that inflammatory cytokines (especially **TNF- α** , **IL-1 β** , **IL-6**, and **IL-8**) are major contributors. These are released from the herniated disc material, nucleus pulposus, and surrounding tissues, directly sensitizing nerves and causing chemical radiculitis even when mechanical compression is reduced.
- **Chronic non-specific low back pain** Most systematic reviews and case-control studies show elevated pro-inflammatory cytokines (**TNF- α** , **IL-6**, **IL-1 β**) and reduced anti-inflammatory cytokines (**IL-10**). This imbalance is associated with pain persistence, central sensitization, and higher pain scores. However, findings are more variable than in disc-related pain, and not all patients show the same pattern.

Vagus

Mechanoreceptors
C1-C3

→ Heart
→ Lung
→ GI

Dorsal Motor Nucleus Vagus

Memory

Nucleus Intermedius

Inflammatory Cytokines:
TNF- α
IL-6

IL-8

IL-1

Acetylcholine

Appetite Control
Satiety
[GLP-1]

Nucleus Tractus Solitarius

Cymba

10-40-10-40
Trevor

NTS

Cymba: 10-40-10-40

Violet-Green
Trevor

carotid sheath

ectopic nidus of depolarization

10-10-10-10

Violet-Green

80%-90%

Spleen

(R)

Liver

(R)

GI

(R)

(R)

Tre

1-10-1-10

Violet-Red

27-44-73-727-1800

1-10-1-10 } Tre
Violet-Red

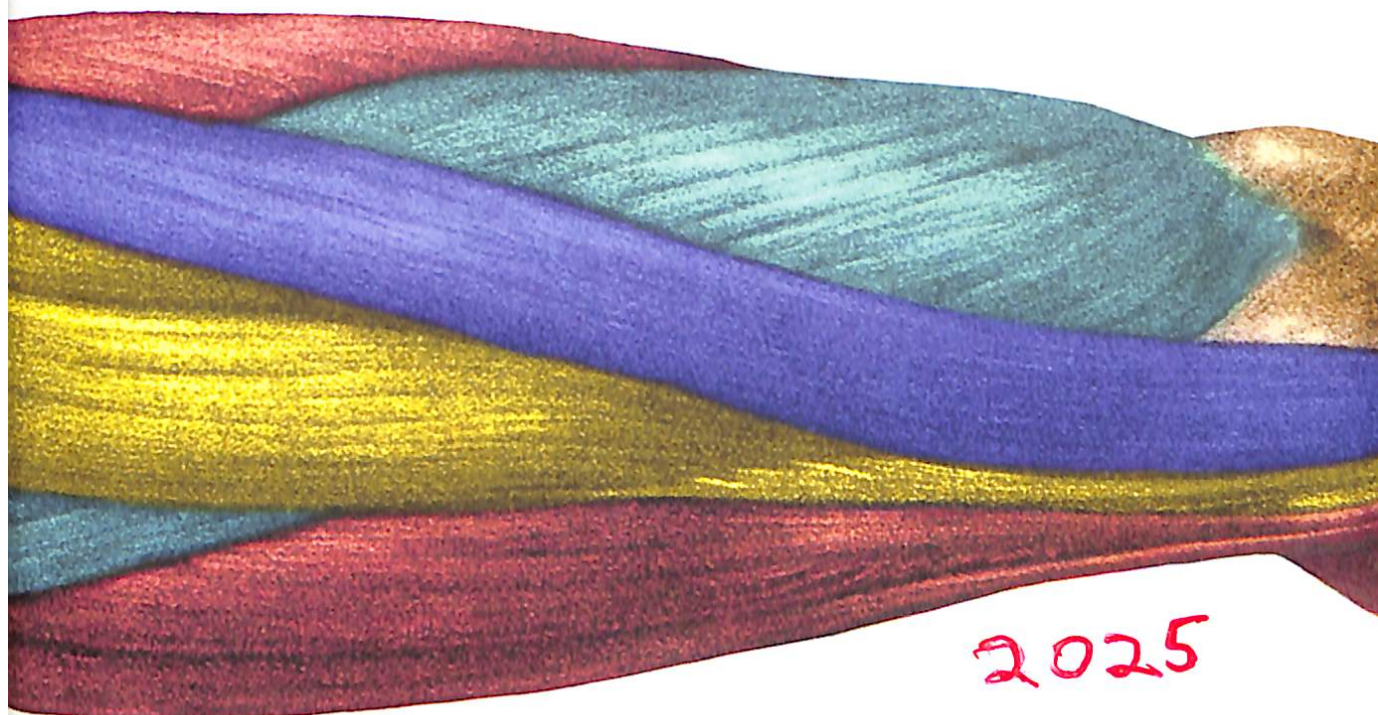
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Health

We may know how exercise fights cancer



CREATIVEPHOTO/ALAMY

EXERCISE can slow tumour growth in mice by shifting the body's metabolism so that muscle cells, rather than cancer cells, take the glucose and grow. A similar process may occur in people.

It is well known that exercise is linked to a lower risk of cancer, but the mechanisms behind this are only partly understood. Some of exercise's influence seems to come via impacts on the community of microbes in our guts and through its effects on the immune system.

To examine another possible route, Rachel Perry at Yale School of Medicine and her colleagues have injected breast cancer cells into 18 mice – 12 of which were fed a diet that caused obesity, which worsens the progression of several types of cancer – and let half the animals run as much or as little as they wanted on an exercise wheel.

They found that after four weeks, tumours in obese mice that chose to exercise were 60 per cent smaller than those in obese mice that didn't have access to a working wheel – and also slightly smaller than those of sedentary mice fed a normal diet (*PNAS*, doi.org/hbdbnz). A 30-minute bout of exercise was tied to increased uptake of oxygen and the key energy source glucose in skeletal and cardiac muscles, and decreased

Being active has long been linked to a lower risk of cancer

glucose uptake in tumours.

"This work reveals that aerobic fitness fundamentally reshapes metabolic competition between muscle and tumours," says Perry. "Importantly, the exercise intervention was voluntary. We're not talking about training for a marathon-type exercise, just what the mice wanted to do."

The researchers analysed gene activity and identified 417 genes in key metabolic pathways in mice that change as a result of exercise, essentially meaning the muscle tissues metabolise glucose more and the tumour tissues metabolise it less.

In particular, the researchers say down-regulation in cancer cells of mTOR, a protein involved in cell growth, may be restricting tumour growth.

Perry says these metabolic pathways are very similar across mammals, so she would expect the same process to happen in people.

"We need a clinical trial in people, but I really can't see any reason why you wouldn't have a similar effect in humans," says Rob Newton at Edith Cowan University in Perth, Australia. ■ CS

Mental health

Exercise may match antidepressants

We're learning more about the benefits of exercise for treating depression, even if the exact reasons why remain unclear, reports **Carissa Wong**

MANY of us experience a mood boost after exercise, and now an updated review has revealed just how powerful it can be. Even light exercise, like walking or gardening, may ease the symptoms of depression as effectively as talking therapies or antidepressants.

"It really reiterates that exercise provides an option for people who have depressive symptoms, and confirms that exercise may be as effective as psychotherapy and antidepressants," says Andrew Clegg at the University of Lancashire in the UK.

Prior studies, including a key review published by the Cochrane Library in 2013, have found exercise may ease symptoms of depression as effectively as standard therapies, including antidepressants and cognitive behavioural therapy (CBT), where a therapist helps people change their thoughts, feelings and behaviour.

This has prompted healthcare organisations to recommend regular exercise for managing depression. For instance, the UK's National Institute for Health and Care Excellence (NICE) recommends weekly aerobic exercise, such as jogging, for 10 weeks – usually in combination with other therapies, which, on their own, don't benefit everyone.

But since the 2013 review, dozens more trials have been conducted, so the Cochrane Library is now publishing an updated review. "This latest review [almost] doubles the evidence base that was in the previous one," says Clegg, one of the authors.

He and his colleagues analysed results from 69 randomised controlled trials involving nearly

5000 adults who were either clinically diagnosed with mild, moderate or severe depression, or who had a score on a depression symptom scale that is generally considered indicative of the condition. First, the researchers focused on 57 of the trials, in which participants were randomly assigned either to a group that exercised regularly or to a control group that was offered no treatment or that was placed on a waiting list for treatment.

Feeling the difference

The trials varied in design, but they usually involved asking participants to exercise on a weekly basis for a few weeks to months, with the style of exercise ranging from low- or moderate-intensity activities such as gardening and brisk walking, respectively, to vigorous activities such as sprinting or playing football. Trials involving yoga or stretching

weren't included as these often involve meditation and breath work, and the team wanted to focus more on the effects of physical activity alone, says Clegg.

The researchers found that exercise seems to moderately reduce the severity of depressive symptoms, such as often feeling sad, or losing interest in other people. "They found a clinically meaningful change – people will feel the difference from that," says Brendon Stubbs at King's College London.

Next, the team focused on 10 trials among the 59 that compared exercise to CBT, and five trials in which some participants took antidepressants but there was no exercise component at all. This revealed that, on average, regular exercise worked as well as the two other therapies (Cochrane Library, doi.org/hbh4x9). "There wasn't a difference between them," says Emily Hird at University College London.

By taking a closer look, the team found that light and moderate exercise seem to be more effective than vigorous kinds, which may simply be because they are easier to stick with, says Stubbs.

How exactly exercise brings its benefits is unclear, but it probably works in several ways, says Stubbs.

"It really reiterates that exercise provides an option for people who have depressive symptoms"

Group exercise, for instance, can boost people's social well-being.

Studies have also shown that, during exercise, chemicals released from muscles called myokines help mop up inflammation that is thought to contribute to depressive symptoms, says Stubbs. One particular myokine called brain-derived neurotrophic factor also spurs the growth of new brain cells, which could help the brain rewire itself and break free of negative thought patterns, says Stubbs. In line with this idea, Clegg and his colleagues found that resistance training – which leads to a greater release of myokines versus other forms of exercise – was more effective than aerobic exercise alone, says Stubbs.

Together, the findings support guidelines that recommend exercise for treating depression. However, in all the studies reviewed, participants knew whether they were in a treatment group or control group. This raises the possibility that at least some of the exercise-related improvements could be down to the placebo effect, says Hird.

Larger studies are needed to better understand which types of exercise – including those not included in the review – are best, for whom, and why, says Hird. ■

TON MOLINA/PHOTO VIA GETTY IMAGES



Jogging has previously been recommended for managing depression

THE LONGEVITY ISSUE

What to expect when you're expecting to live longer *by Alice Park*



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RESOLUTIONS THAT CAN HELP YOU AGE BETTER THIS YEAR

BY ANGELA HAUPT

If you're aging—and who isn't?—even small habits can have a profound impact on your current and future well-being. That's true whether you're 25 or 75.

"For the majority of us, genetics will explain about 20% of our aging," says Nathan LeBrasseur, director of Mayo Clinic's Robert and Arlene Kogod Center on Aging. "Thinking about your trajectory of aging and how you can influence it, starting as early as possible, can make a difference in your year ahead regardless of your age."

Choices in key arenas can determine whether you're thriving or merely surviving as you get older. As you think about what kind of resolutions you want to set for better aging, prioritize those that are both specific and measurable, LeBrasseur advises. (Simply pledging to "be healthier" won't get you very far.) It's also smart to ease in, rather than overhauling your routine overnight.

We asked experts which New Year's resolutions they recommend setting for successful aging.

technically difficult," she says. Push-ups, planks, and squats are great moves to start with on your way to weights.

Mediterranean diet, in particular, is linked to a lower risk of dying from any cause.

If you currently subsist on potato chips and chicken wings, however, don't attempt to go cold turkey overnight. Dr. George Hennawi, founder of the Center for Successful Aging at MedStar Health, suggests resolving to eat processed food and meat two times a week instead of your usual five, for example. "Start there, with just a small bite," he says.

BEGIN EACH DAY BY LISTING WHAT YOU'RE GRATEFUL FOR

Looking on the bright side is one of the best longevity practices. "People who are optimistic have a good social life, a strong sense of purpose, and better health habits—and the opposite is also true," says Dr. Alan Rozanski, a cardiologist at the Icahn School of Medicine at Mount Sinai who studies how mindset influences health.

Fortunately, it's never too late to start cultivating optimism. Start each day by listing 10 things you're grateful for, suggests Dr. Kerry Burnight, a geriatrician and

author of the book *Joyspan: The Art and Science of Thriving in Life's Second Half*. "It enables you to see those things throughout the day," she says. You might even be thankful for getting older: researchers have found that positive attitudes about aging can increase lifespan by up to 7.5 years, while also improving cognitive and physical health.

mobility, and even protect against a host of diseases. That's why Dr. Gabrielle Lyon, author of *Forever Strong: A New, Science-Based Strategy for Aging Well*, coined the term musclespan to describe the length of time someone lives with healthy, strong, capable muscle. She urges people to engage in resistance training three days a week, which could mean using free weights, weight machines, resistance bands, or your own body weight. Aim for at least 15 reps of your chosen activity, and make sure you're working at a level that requires you to really push yourself to finish the last one or two, Lyon advises.

"It doesn't have to be complicated, and it doesn't have to be

Strong social connections can help people live longer in good health. It's important to be proactive about maintaining and strengthening these bonds, Burnight says, and to schedule get-togethers rather than waiting for your phone to buzz. She calls once a week the minimum for reaching out to a friend. "Every human is lonely sometimes, and we can solve that problem together," Burnight says. "It can be coffee, a walk, lunch, or whatever, but we have to be proactive about it."

DO RESISTANCE TRAINING THREE TIMES A WEEK

Muscles play a key role in longevity: they improve metabolic health, support

CUT DOWN ON PROCESSED FOOD AND MEAT

Diet is the No. 1 risk factor for premature death, and research shows that a healthy

TRY ONE NEW THING A MONTH

Novelty is good for your brain; it's linked with a reduced risk of cognitive decline.

Every month, challenge yourself to come up with one new thing you've always wanted to try but haven't gotten around to, whether you didn't have the nerve or the time. Then, finally do it. "Look for something you're curious about and that you can think about and talk about—something that will help you grow and continue to develop as a human," says Burnight, who's currently learning how to play the piano.

PERSONAL JOURNAL.

BY NATASHA DANGOOR

Frailty Is a Hidden Cost Of Weight-Loss Drugs

Doctors warn that GLP-1 can cause rapid and significant muscle loss



▲ Makers of weight-loss drugs say they should be taken as part of a plan that includes exercise.

Chanel Robinson achieved exactly what the gold rush of blockbuster weight-loss drugs promised: She lost nearly 100 pounds, lowered her cholesterol to normal levels and reined in her polycystic ovary syndrome.

Yet, nearly three years into her journey on Mounjaro, the 30-year-old from Atlanta, Ga., is discovering the hidden costs of the slimmed-down life.

Robinson experiences muscle fatigue daily, feeling physically weak, frail and often cold. Robinson said she experiences bursts of sluggishness sporadically during the day, and has trouble with basic tasks like opening a jar. "It shouldn't be this difficult," she said.

GLP-1 drugs like Ozempic, Mounjaro and Zepbound have been a success for public health and the pharmaceutical companies that make them.

But for at least some of the 13 million Americans taking them, losing muscle along with fat is an unexpected downside that isn't broadly discussed or immediately apparent. The drugs can cause rapid and significant loss of lean muscle mass, up to 10%, comparable to a decade or more of aging, according to an analysis published by the American Diabetes Association.

The loss of lean tissue is similar to weight loss from dieting, but the magnitude over a short period can lead to frailty, instability and lack of coordination, doctors and researchers say.

"We are curing obesity by encouraging frailty," said Daniel Green, principal research fellow at the University of Western Australia, who contributed to the analysis. Many taking weight-loss medications initially lose fat and feel great, but quickly start to feel weak and lethargic, he said.

Green's research showed that the rate of muscle loss could be slowed significantly by regular strength workouts. "It should say 'must be taken with resistance training' on the box," he said.

Diet and exercise

Drugmakers say weight-loss drugs should be taken only on the advice of a physician and as part of a long-term plan that includes diet and exercise. A spokesperson for Eli Lilly,

maker of Zepbound, said Food and Drug Administration guidelines say it should be used "with increased physical activity." The spokesperson added: "Sustainable weight loss is about more than a number on a scale."

Both Eli Lilly and Novo Nordisk said clinical trials showed users did lose some lean muscle tissue, though at far lower rates than fat. Liz Skrbkova, a spokeswoman for Novo Nordisk, said that trials for its drug Wegovy showed changes in muscle mass didn't "significantly differ" from patients who took a placebo. Eli Lilly said users lost three times more fat weight than lean tissue.

Rayna Kingston, 30, from Denver, said her injections of Zepbound

left her feeling so tired the following day that she struggled to complete anything other than basic tasks. She said she shifted her dose to a Sunday because Mondays were her least busy day. Her partner

would bring her meals in bed.

She stopped exercising, and said her doctor didn't give her any guidance on strength training or muscle maintenance.

Experts say that losing muscle at such a rate can be especially dangerous for those over 50 or with

osteoporosis or limited mobility as it could lead to an increased risk of injury. "Loss of muscle mass is detrimental to moving around and quality of life, but it is also not safe," said Katsu Funai, associate professor at the University of Utah.

Many taking the medications quickly start to feel weak and lethargic.

A 'quick fix'

There is also pushback from doctors and regulators against using weight-loss drugs as a "quick fix" to lose a bit of weight. People who take GLP-1s regain weight four times faster than those who lose weight through lifestyle interventions, and weight regained is often mostly fat, according to a recent analysis published in the British Medical Journal.

The nurse practitioner who prescribed Robinson the medication didn't warn her that resistance training is essential to maintaining muscle mass, Robinson said. She now does Pilates.

In the haste to disrupt the obesity epidemic, weight loss has been treated as the singular, undisputed metric of success, which experts say is problematic. "People worship body weight as an outcome measure because it's simple, quick and inexpensive," said Green. "But what matters

is fat and muscle mass, which is more expensive to measure as it requires an MRI."

Grace Parkin, 34, a property manager from Sheffield, England, has lost 125 pounds after she started taking Mounjaro in 2024. "I don't care about my muscle mass as long as I'm a healthy weight," she said.

The doctor who prescribed the drug didn't tell her to exercise, though the pharmacy that sold the medication gave her information on exercise and protein intake, she said. She didn't exercise and said she soon felt side effects: a "deathly cold, from the inside" likely because of the drug.

In response to some of the side effects, drug companies are hoping to develop weight-loss treatments aimed at preserving or even building lean muscle mass. German drugmaker Boehringer Ingelheim recently said it had promising results from one such drug. Eli Lilly last September halted a trial of a similar drug.

Risks for women

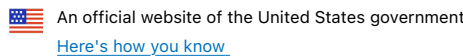
While weight-loss medications are designed as lifelong treatments for chronic diseases, namely obesity and Type 2 diabetes, they are increasingly marketed as lifestyle fixes.

Women may be particularly vulnerable to the drugs's side effects, which can also include nausea, diarrhea, migraines and rarer cases of pancreatitis. A study last year from a university hospital in Turin, Italy, showed women are more prone to adverse reactions to weight-loss drugs than men, including muscle loss.

Green, the researcher, said the issue is of particular concern to those taking GLP-1s recreationally and who don't have much muscle mass to begin with. Others say a lack of oversight is compounding the issue.

An analysis by the FDA from 2023 found that more than half of new Ozempic and Mounjaro users didn't have Type 2 diabetes.

Scientists are calling for more clinical trials to pin down the full effects on muscle loss in different demographics. "The only studies that have been done have looked at people living with obesity or Type 2 diabetes," said Green. "That makes it all the more concerning for those using weight-loss drugs in an ad hoc or unregistered way."



FULL TEXT LINKS



Review [Diabetes Care](#). 2024 Oct 1;47(10):1718-1730. doi: 10.2337/dci23-0100.

Incretin-Based Weight Loss Pharmacotherapy: Can Resistance Exercise Optimize Changes in Body Composition?

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PMID: 38687506 DOI: [10.2337/dci23-0100](#)

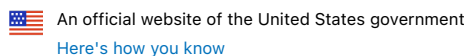
Abstract

This narrative review highlights the degree to which [new antiobesity medications](#) based on gut-derived nutrient-stimulated hormones (incretins) [cause loss of lean mass](#), and the importance of [resistance exercise to preserve muscle](#). [Glucagon-like peptide 1 receptor agonists \(GLP-1RA\)](#) induce substantial weight loss in randomized trials, effects that may be enhanced in combination with glucose-dependent insulinotropic polypeptide (GIP) receptor agonists. Liraglutide and semaglutide (GLP-1RA), tirzepatide (GLP-1 and GIP receptor dual agonist), and retatrutide (GLP-1, GIP, and glucagon receptor triple agonist) are peptides with incretin agonist activity that induce ~15-24% weight loss in adults with overweight and obesity, alongside beneficial impacts on blood pressure, cholesterol, blood glucose, and insulin. However, [these agents also cause rapid and significant loss of lean mass \(~10% or ~6 kg\)](#), [comparable to a decade or more of aging](#). [Maintaining muscle mass and function as humans age is crucial to avoiding sarcopenia and frailty](#), which are strongly linked to morbidity and mortality. Studies indicate that supervised resistance exercise training interventions with a duration >10 weeks can elicit large increases in lean mass (~3 kg) and strength (~25%) in men and women. After a low-calorie diet, combining aerobic exercise with liraglutide improved weight loss maintenance compared with either alone. Retaining lean mass during incretin therapy could blunt body weight (and fat) regain on cessation of weight loss pharmacotherapy. We propose that [tailored resistance exercise training be recommended](#) as an adjunct to incretin therapy to optimize changes in body composition by preserving lean mass while achieving fat loss.

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FULL TEXT LINKS



Review [Biomedicines](#). 2025 May 2;13(5):1108. doi: 10.3390/biomedicines13051108.

Navigating Sarcopenia Risks in GLP-1RA Therapy for Advanced Heart Failure

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PMID: 40426935 PMCID: [PMC12109496](#) DOI: [10.3390/biomedicines13051108](#)

Abstract

Cardiac cachexia (CC) is a severe complication of advanced heart failure (HF), characterized by involuntary weight loss and muscle wasting, leading to poor outcomes and higher mortality. Despite its severity, CC remains under-recognized and undertreated, lacking targeted therapies specifically addressing its pathophysiology. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), though beneficial in reducing cardiovascular risk in patients with HF, may exacerbate muscle wasting in cachectic patients, necessitating further investigation. Non-pharmacological strategies, including tailored nutritional support and exercise programs, have shown positive effects on body composition and quality of life in patients with CC. However, there remains a gap in recommendations tailored to preventive strategies and pharmacologic therapies for patients with CC and concomitant GLP-1RA use. This review highlights the multifactorial mechanisms underlying CC and current and emerging therapeutic approaches for mitigating HF-related sarcopenia while on GLP-1RAs.

Keywords: GLP-1RA; frailty; heart failure; sarcopenia.

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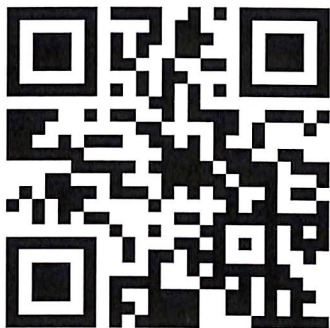
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