What Happens in Vagus Doesn't Stay in Vagus

The Vagus Nerve's Role in Well-Being

Dr. Kevin J. Tracey must feel conflicted about the press that's been generated by his recent book, *The Great Nerve: The New Science of the Vagus Nerve and How to Harness Its Healing Reflexes*.

On one hand, this amazing structure, which Dr. Tracey has been studying for decades, and its role in moderating the harmful inflammation that occurs in diseases ranging from Crohn's to depression and Alzheimer's, is attracting widespread attention.

And a new form of non-drug treatment for rheumatoid arthritis based on Dr. Tracey's research is being considered for approval by the U.S. Food and Drug Administration. (A neurosurgeon-scientist, Dr. Tracey is the president and CEO of the Feinstein Institutes for Health Research at Northwell Health in Manhasset, N.Y.)

THIS DEVELOPMENT DOESN'T JUST OFFER HOPE FOR PATIENTS WITH RHEUMATOID ARTHRITIS (RA) WHO DON'T RESPOND TO CURRENTLY AVAILABLE THERAPIES LIKE THE NEWER-GENERATION DRUGS THAT APPEAR TO REDUCE THE INCREASED RISK OF DEMENTIA THAT'S ASSOCIATED WITH RA AND OTHER AUTOIMMUNE DISEASES.

The treatment approach, which Dr. Tracey calls bioelectronic medicine, is showing promise in a range of other conditions involving inflammation, and preliminary studies suggest it could even improve some types of brain function.

On the other hand, many news stories sparked by Dr. Tracey's book parrot claims that have become embedded in the public consciousness, but are outdated or otherwise not supported by solid, up-to-date scientific evidence. For example, social media influencers and even some hospital websites promote the idea that activities such as cold-water immersion or gargling induce calm or produce certain health benefits because they supposedly stimulate the vagus nerve.

"That was one of the reasons I wrote the book," said Dr. Tracey. "Because we've learned a great deal where the science has gone deep, but that gets diluted by people making claims that have not been proven to be cause and effect, and are extrapolations or wishes. That cheapens the science and confuses people, and confusion leads to polarization of opinions." This in turn, can arguably lead to the kind of mistrust in science that contributes to problems like decreased uptake of vaccines and the resurgence of measles.

Here's what you need to know about the vagus nerve, the exciting potential of treatments that act on it, and what the science says about non-medical interventions that purportedly influence vagal nerve activity.

ANATOMY & FUNCTION

Our nervous system is made up of two main components: one that we can control (somatic) and one that runs automatically or reflexively in the background (autonomic). The autonomic "half" is further subdivided into parts, including the sympathetic ("fight or flight") and parasympathetic ("rest and digest") systems. The vagus nerve is a major part of the latter.

"The vagus nerve is the longest nerve in the body, which comes out from your brain stem, and interacts with most of the organs in your abdomen," said Dr. Simon Cork, physiology lead at the Anglia Ruskin University School of Medicine in Chelmsford, U.K. Before exiting the skull, the vagus splits into two branches that run down each side of the neck.

Another thing that is important to understand about the vagus is that "it's not one thing," said Dr. James Heathers, Director of the Medical Evidence Project at the Center for Scientific Integrity and an affiliated researcher at Linnaeus University in Sweden. While nerves are sometimes described as a sort of wire, the vagus, "is more like a trunk line from an old phone system – it's a bundle of fibres with many projections that do all sorts of different things."

In fact, according to Dr. Tracey, the vagus comprises more than 200,000 total fibres, or roughly 100,000 on each side. And as with an old-fashioned phone line, information flows through these fibres in both directions.

The various projections are a monitoring system that sends messages to the brain, which responds with instructions to carry out any changes necessary to maintain a stable internal environment in the body (homeostasis).

The vagus modulates or adjusts a host of routine processes, from digestion to heart rate.

> ***"The vagus nerve is really a way of your brain sensing what's going on in the body and modulating it up or down depending on what's required.***

For example, Dr. Cork continued, "the vagus nerve is involved in sending information to your brain about how stretched

your lungs are, and about your rate of breathing to modulate the diameter of your airways," he added.

And relatively small handfuls of these fibres carry out such specific functions. "Individual fibres have specific origins, destinations, anatomy, and function, and they're distinct," Dr. Tracey explained. For example, "We estimate that a few hundred are enough to slow the heart."

The fact that very discrete parts of the vagus nerve have discrete functions is important because "trying to influence the vagus nerve through breathing, for example, does not mean that it is necessarily going to do anything to influence the activity of the vagus nerve involved in inflammation," noted Dr. Cork.

ROLE OF ELECTRICAL STIMULATION

Because of its incredible degree of complexity, there's a lot we still don't understand about how the vagus nerve works. Much of what we have learned comes from studies in which a specific segment of the vagus nerve is stimulated with electricity to either activate or interrupt signals along it.

For instance, delivering certain patterns of electrical signals directly to the vagus nerve near the collarbone reduces the frequency of seizures by more than 50% in roughly half of people with epilepsy. And since 1997, a surgically-implanted pacemaker-like device has been approved in Canada for treatment-resistant epilepsy. Yet we still don't quite know exactly why this works.

"The mechanism of action is not fully understood," explained Dr. Paul Yoo, an affiliated scientist at University Health Network's KITE Research Institute and an associate professor at the Institute of Biomedical Engineering at the University of Toronto.

The clinical use of such implantable devices, commonly referred to as vagus nerve stimulation (VNS) therapy, is the most reliable and accurate method currently available for electrically stimulating the vagus nerve. Trying to stimulate the nerve externally is less reliable since it's very difficult to selectively activate only the vagus nerve – and not others in the area – through the skin.

Stimulating nearby nerves could cause unwanted side effects, for instance.

As well, depending on the patient, the vagus nerve could be several centimetres below the skin surface. Dr. Yoo's lab is developing a less invasive approach of targeting the vagus nerve, combining a millimetre-scale implant with an enhanced version of the over-the-counter TENS nerve stimulating units that are used for treating some types of pain.

Some discoveries about vagal nerve function indirectly stem from the use of VNS for epilepsy. For instance, some of Dr. Cork's research on the role of the vagal nerve in obesity, "came about because patients who had these vagus nerve implants for epilepsy lost weight," he explained. It turns out that "lots of hormones are released from your intestines that signal the vagus nerve to tell your brain that you are full, and should stop eating," Dr. Cork said.

Similarly, in studies of VNS for epilepsy, some people whose seizures did not lessen declined removal of the device because they believed it had improved their mood. Further studies "found that VNS could be effective for patients with depression or mild depression," noted Dr. Yoo.

TODAY, VNS IS APPROVED FOR TREATMENT-RESISTANT DEPRESSION IN CANADA, ALTHOUGH ACCESS TO IT IS VERY LIMITED.

IMMUNE SYSTEM CONNECTION

Many years ago, Dr. Tracey led a research team that was studying an overwhelming and potentially fatal immune system reaction to an infection called sepsis. This work ultimately paved the way for the development of the first class of the powerful biologic drugs that are now used to treat diseases such as rheumatoid arthritis (RA) and Crohn's – so-called TNF (tumour necrosis factor) inhibitors.

Dr. Tracey and some colleagues were doing animal studies with an experimental prototype of such a drug where a very small dose of it and a bacterial toxin were injected into the brain. The idea was to find out whether this would prevent the brain from stimulating the overwhelming flood of TNF that would normally occur in response to the local presence of the toxin.

However, due to a miscommunication, in one group of animals, the toxin was administered into the abdomen. Even though the dose of medication was far too low to enter the bloodstream, somehow, animals that had received it did not produce high levels of TNF. Eventually, Dr. Tracey and his colleagues discovered why: a signal sent from the brain down the vagus nerve was acting like a sort of brake on the immune system.

TNF belongs to a group of immune system proteins called cytokines that are important for healing wounds and fighting infection. However, when produced in large amounts – as they are in autoimmune diseases like RA – inflammation-promoting cytokines such as TNF cause harm.

NEW THERAPY FRONTIER

This discovery eventually led Dr. Tracey and his team to create a surgically-implanted vagal nerve stimulation device that has been tested in clinical trials and submitted to the U.S. Food and Drug Administration for approval. This is a significant development because even powerful biological drugs don't work for a percentage of people with RA.

Recently, Dr. Tracey's research group also tested a similar technique in an animal model of multiple sclerosis (MS), a disease that in addition to damaging nerves, attacks myelin – the fatty, protective sheath surrounding nerve cells. "We showed that not only did vagal nerve stimulation stop the inflammation that causes the damage, it accelerated remyelination," or repair to the myelin, Dr. Tracey said.

> *"That's been the holy grail in the MS world – to try to find things that accelerate remyelination.*

Some companies market devices that are intended to be a non-invasive alternative to VNS, though these don't require the same level of evidence to receive approval as the implantable versions. Worn like an earbud, these gadgets deliver pulses to a part of the ear that overlies a branch of the vagus nerve. According to Dr. Tracey, one limitation of this approach is that anatomy varies from one person to the next, so the electrical pulse may miss the vagus.

THE DOWN-LOW ON DIY STRATEGIES

That brings us to the question of whether we can actually stimulate our vagus nerve via activities like meditation and thereby produce specific health benefits.

> *The strategy with the most evidence to support it is deep, slow breathing for inducing calm and lowering heart rate.*

In Dr. Tracey's words, the expansion of the lungs during a deep breath, "activates signals travelling up the sensory vagus nerve (input). When they arrive in your brain, they activate an outflow of parasympathetic responses returning to the body via other vagus motor fibres (output) to produce a co-ordinated behaviour response, including lower heart rate and lower blood pressure."

It's worth noting that while the parasympathetic nervous system does control the body's ability to relax, it's not "switched off" during activities like exercise. Vagal nerve activity actually rises during intense physical activity, increasing the interval between heartbeats, giving the heart more time to fill with blood.

And there are studies that suggest such techniques can help reduce anxiety, depression, and stress, prolonged or frequent bouts of which appear to increase the risk of dementia and a host of other diseases.

While there is evidence that meditation practices can help manage stress, and some studies suggest it may lower markers of inflammation in the blood, there's no proof of any connection between the vagus and any of these potential benefits. For instance, "we don't know that meditation stimulates the vagus nerve fibres which are responsible for inflammation," Dr. Tracey said.

So are there any activities that are known to improve how well our vagus nerve functions?

In addition to its plethora of other benefits, regular exercise may do so. Regular physical activity that's intense enough to increase your heart and breathing rate, but not so intense as to interfere with your ability to hold a conversation, has been linked to reductions in heart rate variability (HRV) or the variations between individual heartbeats. HRV is sometimes used as an indirect method of measuring "vagal tone" or activity. (There is, however, some disagreement about whether HRV is a valid reflection of vagal activity).

High HRV is typically an indication that the body can efficiently shift between states of stress and relaxation, and it has been tied to lower rates of problems such as cardiovascular disease. Regular exercise also tends to lower resting heart rate, which is also linked to reduced rates of such conditions.

Overall, much more research is needed to learn if strategies like meditation act via the vagus nerve, and whether bioelectronic medicine might one day play a role in reducing dementia risk. In the meantime, it's safe to say some of these practices align with the lifestyle habits that have been shown to be linked to lower dementia risk, including exercise and stress management.