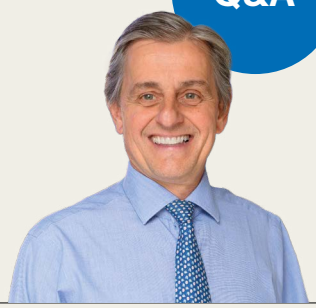
THE FEINSTEIN INSTITUTES FOR MEDICAL RESEARCH

Q&A



Kevin J. Tracey: Electrifying treatment

Excessive inflammation is a key feature of autoimmune diseases such as rheumatoid arthritis. Drugs that block pro-inflammatory molecules are already in use, but electrical stimulation might provide an alternative. Kevin J. Tracey, a neurosurgeon and chief executive of the Feinstein Institutes for Medical Research in Manhasset, New York, spoke to *Nature* about the role of the nervous system in managing inflammation, and his work to treat rheumatoid arthritis by stimulating the vagus nerve.

How does the nervous system affect inflammation?

Inflammation is a normal response to injury and infection, but too much inflammation can damage tissues. You see this in many diseases, including autoimmune conditions such as rheumatoid arthritis. The nervous system of mammals has therefore evolved mechanisms to control inflammation. One of these, which my team discovered, involves signals from the vagus nerve to the brain that draw out anti-inflammatory neurotransmitters.

What is the vagus nerve?

It is one of the longest nerves in the body. It travels from the brainstem, down both sides of the neck and chest to the abdominal cavity, and it touches nearly every organ. About 80% of its fibres are sensory and carry information from the body to the brain. The rest carry signals from the brain back to each organ. So it is similar to a transatlantic cable, conducting massive amounts of information from the organs to the brain and back again.

What evidence is there that this nerve modulates inflammation?

In the late-1990s and early-2000s, we were studying the effects of an anti-inflammatory molecule called CNI-1493 in rats. When we injected the molecule into their brains, we found that not only did inflammation that we had induced in the brain subside — which we expected — but there was also reduced production of the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) in the spleen, liver and heart. We then showed that cutting the vagus nerve in rats blocked the far-flung anti-inflammatory effects of CNI-1493 — and in another study, electrically stimulating the vagus nerve recapitulated the blocking of inflammation in the body.

So our fundamental discovery was that immune responses are under the control of reflex circuits, similar to how heart rate is controlled by nerves. I called this the inflammatory reflex.

Can these circuits be harnessed to treat chronic inflammation?

When we started our work, more than 30,000 people around the world already had vagus nerve stimulators implanted for conditions such as epilepsy, so we wondered if it would be possible to develop an electrical stimulator that would specifically target the inflammatory reflex.

In the mid-2010s, the company I co-founded — SetPoint Medical in Valencia, California — showed that implanting vagus-nerve stimulators in people with rheumatoid arthritis recapitulated the inflammatory reflex. It turned off cytokine responses, and many people got significantly better — one patient went from being unable to hold a pencil to riding her bicycle 20 miles to the Dutch coast every weekend. Some are still in complete remission. But we need to test this in a larger population, so the company is currently enrolling up to 250 people with rheumatoid arthritis at 40 sites in the United States.

How does the device work?

The latest version is about the size of your little fingernail, and is implanted through a small incision in the neck. It delivers an electrical current to the entire vagus nerve, which contains about 100,000 fibres. But some are more sensitive to stimulation than others — a small current will activate only a few thousand fibres. Those that control the inflammatory response are among the most sensitive, so it usually takes only about one milliampere of current for up to five minutes, one to three times a day, to block inflammation for 24–48 hours. There aren't usually any side effects at this low current. My hope is that people won't have to use it forever — with repeated use, people might eventually be able to stop treatment without their symptoms returning.

How does this therapy compare with what is already available?

Autoimmune conditions such as rheumatoid arthritis are typically treated with immunosuppressive drugs that block cytokines such as TNF-α, interleukin-1 and interleukin-6. But these drugs don't work in everyone, and they can also be toxic and expensive. Electricity will never replace all drugs — they will remain a mainstay of therapy. And we expect that there will be people who will not respond to these devices, just as some people do not respond to drugs. But for those with chronic autoimmune diseases who have tried everything without success, or people who don't like the drugs' side effects, electrical therapy could be a welcome alternative.

What are your expectations for the future?

I hope bioelectronic devices will have a place alongside drugs. Understanding the mechanisms involved will be important, as these approaches are developed for use in autoimmune diseases such as rheumatoid arthritis. We already know a lot: we have mapped the neural circuit to the point that we can distinguish signals that travel from the brainstem not just to the abdomen, but also right down to the cytokine-producing cells in the spleen that are turned off by these electrical signals. Once they are approved for clinical use in rheumatoid arthritis, I think such devices will be broadly and quickly adopted for severe autoimmune diseases. Our work might also have relevance to other diseases, such as cancer.

Interview by Julianna Photopoulos

This interview has been edited for length and clarity.

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