MEDICAL ELECTRONICS

SHOCK MEDICINE

Stimulation of the nervous system could replace drugs for inflammatory and autoimmune conditions

By Kevin J. Tracey

IN BRIEF

Exposure to heat, pressure, light or chemicals sets in motion a process to ensure that bodily organs do not overreact to these stresses.

Nerve signals that link the brain and the rest of the body inhibit the making of immune molecules that cause inflammation.

Electrical stimulation of neural pathways with an implanted medical device may assist the body in suppressing inflammation.

Bioelectronic medicine is the name of the new discipline that uses electrical stimulation to treat inflammation and other disorders.

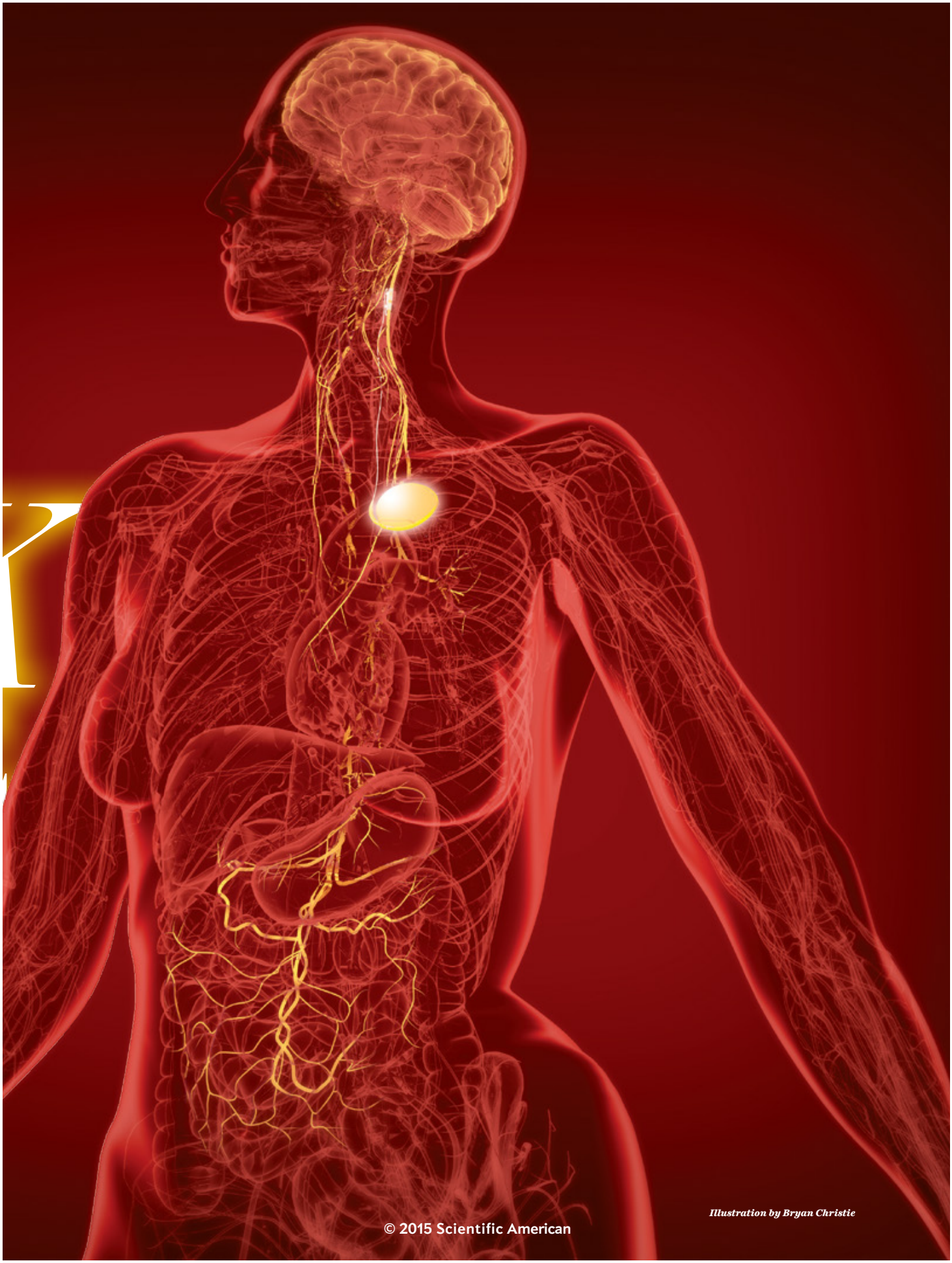

Illustration by Bryan Christie

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I am a brain surgeon who is fascinated by inflammation. Along with my laboratory colleagues, I examine molecules that cause inflammation so that we can discover methods for alleviating the pain, swelling and tissue damage that is a consequence of many diseases.

Some of this work has already benefited patients. In 1987 I published the results of an experiment that targeted an inflammatory molecule called tumor necrosis factor, or TNF, to rescue lab baboons from the consequences of lethal infection—a study that contributed to the discovery of a new class of drugs for inflammatory, autoimmune and other diseases that disrupt the normal functioning of the body's immunological defenses.

As a neurosurgeon, I am also intensely interested in the workings of the brain. A surprising discovery we made in the late 1990s, again involving TNF, merged insights from neuroscience and immunology. We inadvertently discovered that neurological reflexes—predictable responses to certain sensory stimuli—block the production of TNF. This insight culminated in an invention I devised to treat inflammation using small, electrical nerve stimulators implanted in patients.

The use of nerve-stimulating electronic devices to treat inflammation and reverse disability is laying the foundation for a new discipline called bioelectronic medicine. It is being tested in clinical studies of patients with rheumatoid arthritis and other diseases. It is based on a deceptively simple concept of harnessing the body's natural reflexes to develop an array of effective, safe and economical alternatives to many pills and injectable drugs. By precisely targeting the biological processes underlying disease, this nerve-stimulating technology should help avoid the troublesome side effects of many drugs.

THE REFLEX CIRCUIT

HEAT, TOUCH, PRESSURE, LIGHT and the presence of specific molecules generate an electrical signal in nerve cells called sensory neurons. This electrical information is transmitted to "interneurons," another type of nerve cell in the central nervous system that passes the incoming impulse along to motor neurons, which complete the third and final stage in the simple reflex circuit. The subsequent firing of the motor neuron sends electrical signals back to the body's muscles and organs, triggering behaviors ranging from the withdrawal of a finger from a hot plate to the dilation of an airway during a three-mile run.

Simple reflex circuits harmonize the activity of individual organs, so that you do not have to consciously plan the minute actions that keep your body functioning efficiently. When you leap from a chair and run up the stairs to answer the ring of a telephone, you do not have to think about coordinating your respiration, heart rate and blood pressure. Reflexes take care of all the essentials, matching organ function to the body's needs, whether resting comfortably or running at full speed.

Charles Scott Sherrington (1857–1952), the Nobel Prize–winning British physiologist, proposed that simple reflexes made up of neural circuits are the basic building blocks of the nervous system. The combined output of millions of nerve signals that control reflexes directs the functioning of the body's organs. But Sherrington did not address one lingering question: How do the electrical signals that course through motor neurons actually control organ function? The answer is relatively simple. In effect, they produce "drugs." Neurons transmit information along nerve fibers, or axons, the long, wirelike extensions that terminate in the organ being regulated. At the very end of the axon lies the "synapse," a word coined by Sherrington. The motor neuron's axon on one side of the synapse does not physically touch the nerve or organ cells on the opposite side of the narrow gap called the synaptic cleft. Instead the arrival of the electrical signals at the end of the axon stimulates release of neurotransmitters that diffuse across the synaptic cleft and bind to receptors, docking sites on the target nerve or organ cells. Chemical neurotransmitter molecules latch on to receptors at the other side of this cleft to alter the behavior of the targeted cells, changing their function. It turns out that many drugs work in a similar manner.

The pharmaceutical industry invests billions of dollars to design, synthesize and develop new chemicals as experimental drugs that, like neurotransmitters, are nothing more than molecules that interact with receptors. Many blockbuster drugs

selectively bind to specific receptors that modify metabolic activity and turn on genes in selected cells. But drugs can have dangerous side effects. Once swallowed or injected, pharmaceuticals travel throughout the body, where they may produce undesired consequences when interacting with cells that are not their intended targets.

Using a device to send signals down a nerve to stimulate production of druglike neurotransmitters offers a distinct advantage. The body's self-made drugs deliver chemicals to specific tissues in precise, nontoxic amounts at just the right time, diminishing the occurrence of side effects.

AN ACCIDENTAL DISCOVERY

BY THE LATE 1990S a new class of pharmaceutical called monoclonal antibodies were being used to treat patients with rheumatoid arthritis, inflammatory bowel disease and other disorders. Monoclonal antibodies, which my colleagues and I helped to pioneer, can alleviate the pain, swelling, tissue destruction, and other symptoms of inflammation caused by the overproduction of TNF and other molecules. For many patients, it offers their only chance for a normal life. But success has come with soaring costs. Drug bills range from $15,000 to $30,000 annually for a single patient, even though anti-TNF is ineffective in up to 50 percent of patients. Perhaps most worrisome to patients and their caregivers, these drugs can cause dangerous, even lethal, side effects.

In my lab, now at the Feinstein Institute for Medical Research in Manhasset, N.Y., I was working with my colleagues on an alternative approach to block TNF, a molecule we had developed and named CNI-1493. My original hypothesis was that injecting this experimental drug directly into the brain would prevent TNF production during a cerebral infarction, or stroke. Although this proved to be true, I was entirely unprepared to find that administering tiny quantities of CNI-1493 into the brain also blocked TNF production in organs *throughout the body*. At first not believing the results, we repeated the experiments many times. In each instance, we confirmed that vanishingly small quantities of CNI-1493 in the brain, concentrations too low to saturate the body's organs, somehow blocked TNF outside the brain. For months we discussed these findings in weekly lab meetings, never getting any closer to understanding how the drug worked.

Initially we reasoned that perhaps CNI-1493 activated the brain's pituitary gland at the base of the brain to stimulate production of hormones, including steroids—or glucocorticoids—that in turn inhibited TNF production in distant organs. Alas, after surgically removing the pituitary gland in rats and repeating the experiments, we found that CNI-1493 injected into the brain still inhibited TNF. This result meant that the pituitary gland did not convey the signal that turned off TNF production in the body. Searching for another explanation, we began to consider the improbable possibility that motor neurons exiting the brain carried electrical signals to inhibit TNF in the rest of the body.

To test the hypothesis, we relied on the established practice in neuroscience that links a particular brain area to certain behaviors. Much of what is known about neural control of behavior originated in early studies of stroke patients with localized brain damage. Paul Broca (1824–1880) observed that damage to a small region in the left posterior frontal cortex resulted in an inability to speak while preserving language comprehension, a condition called expressive aphasia. Similarly, Carl Wernicke (1848–1905) noted that stroke damage in a nearby area—the left posterior, superior temporal gyrus—produced sensory aphasia, an incapacity to either understand or produce meaningful speech. The insight that discrete brain regions control specific behaviors led us to postulate that cutting the individual circuits connecting the brain and organs could reveal the identity of specific nerves controlling TNF. We were perplexed about where to begin because there are millions of such connections between the brain and the organs.

While contemplating a plan of attack, we came across a seminal paper by Linda Watkins of the University of Colorado Boulder that demonstrated that the vagus nerve has a major role in transmitting sensory information from the body's organs into the base of the brain. In her experiments with rats, Watkins administered a signaling molecule called interleukin-1, or IL-1, that causes inflammation and fever. When injected into the abdomen, IL-1 increased body temperature. But when she cut the vagus nerve and repeated the experiment, no fever occurred. She concluded that the nerve transmitted information to the brain about the presence of IL-1 and that these neural signals controlled the onset of fever.

How do electrical nerve signals control organ function? The answer is relatively simple. They make and deliver drugs.

Working independently at Japan's Niigata University School of Medicine, Akira Niijima also had been injecting IL-1 in rats. He discovered that IL-1 administration to the animals spurred electrical activity in the vagus nerve traveling to the brain. Reviewing these data, I hypothesized that they might hold the key to identifying a reflex circuit for the immune system.

Considering the consequences of vagus nerve signals stimulated by IL-1, I reasoned that there would be a corresponding motor signal returning to organs outside the brain to regulate the inflammatory process. I proposed that a simple reflex control mechanism would shut down inflammation and fever to minimize possible damage to tissues. The process could be carried out if signals from inflammatory molecules in tissues not only traveled up the vagus nerve to the brain but also returned through the nerve to the original tissues, directing them to turn off the production of TNF and other inflammatory molecules, collectively known as cytokines.

Abiding by Sherrington's idea that a simple reflex begins with sensory input traveling along a nerve, I proposed that the TNF "off" signal from the vagus nerve completes a reflex nerve circuit between the brain and the immune system. This idea

had potentially profound implications for understanding the body's defense mechanisms against infection and injury. I theorized that reflex neural circuits controlling immunity would maintain health-promoting processes—as opposed to disease-triggering inflammation—by preventing the toxic release of TNF and other inflammatory signaling molecules. I became immediately concerned, though, that someone else must have already thought of this seemingly obvious biological mechanism.

Searching the published literature turned up evidence that the major organs of the immune system, including the thymus, spleen, liver, lymph nodes and lungs, are all innervated with connections that descend from the brain. But none of this work identified research on reflex circuits controlling immunity. In fact, the antithesis had become medical dogma. Decades of immunology studies had focused on the role of the immune system in protecting the body independent of the nervous system. Immunity, in these accounts, centered on the workings of lymphocytes, monocytes, macrophages and other white blood cells, but not neurons.

The inflammatory reflex, which keeps the immune system from becoming overactive or underactive, is the name I gave the circuit that prevents toxicity and tissue damage. When the inflammatory reflex did not function well, the presence of cytokines would lead to the complications that occur in autoimmune diseases, such as rheumatoid arthritis. It seemed like a good theory, but experimental evidence was needed.

Testing this idea required a painstaking process of surgically dividing the vagus nerve at various points along its route from the brain to the body's organs. The nerve originates in the brain stem (at about the level of the ear in humans) and travels as paired left-and-right bundles of nerve fibers, descending through the neck, crossing the thorax, and coursing throughout the abdomen. Along its wandering path, it connects directly or indirectly to most of the body's organs. Working in anesthetized rats, we cut the vagus nerve in the neck, injected CNI-1493 into the brain, and then measured TNF in the brain, spleen and other organs. Convincing results emerged: an intact vagus nerve was required for CNI-1493 in the brain to switch off TNF production by immune cells in various organs. Mapping farther downstream, we selectively cut the vagus nerve at points along its route from the neck to the abdominal organs. The TNF off switch functioned only when the vagus nerve was intact in its entire trajectory beginning in the brain stem and proceeding through the neck, thorax and abdomen and into the spleen.

Proof that vagus nerve transmission provides the TNF off signal to the spleen came using a handheld nerve-stimulating electrode I acquired from the North Shore University Hospital's neurosurgery operating room. I had often used it to identify the facial nerve while removing a brain tumor to spare damage to the nerve. Resembling a flashlight that doctors carry in their shirt pockets, the battery-operated device has a small wire extending from the tip, near where a lightbulb would be in a flashlight. When placed onto a nerve, the tip delivers an electrical charge that stimulates the nerve to fire action potentials, the transmission of electrical information along the nerve fibers.

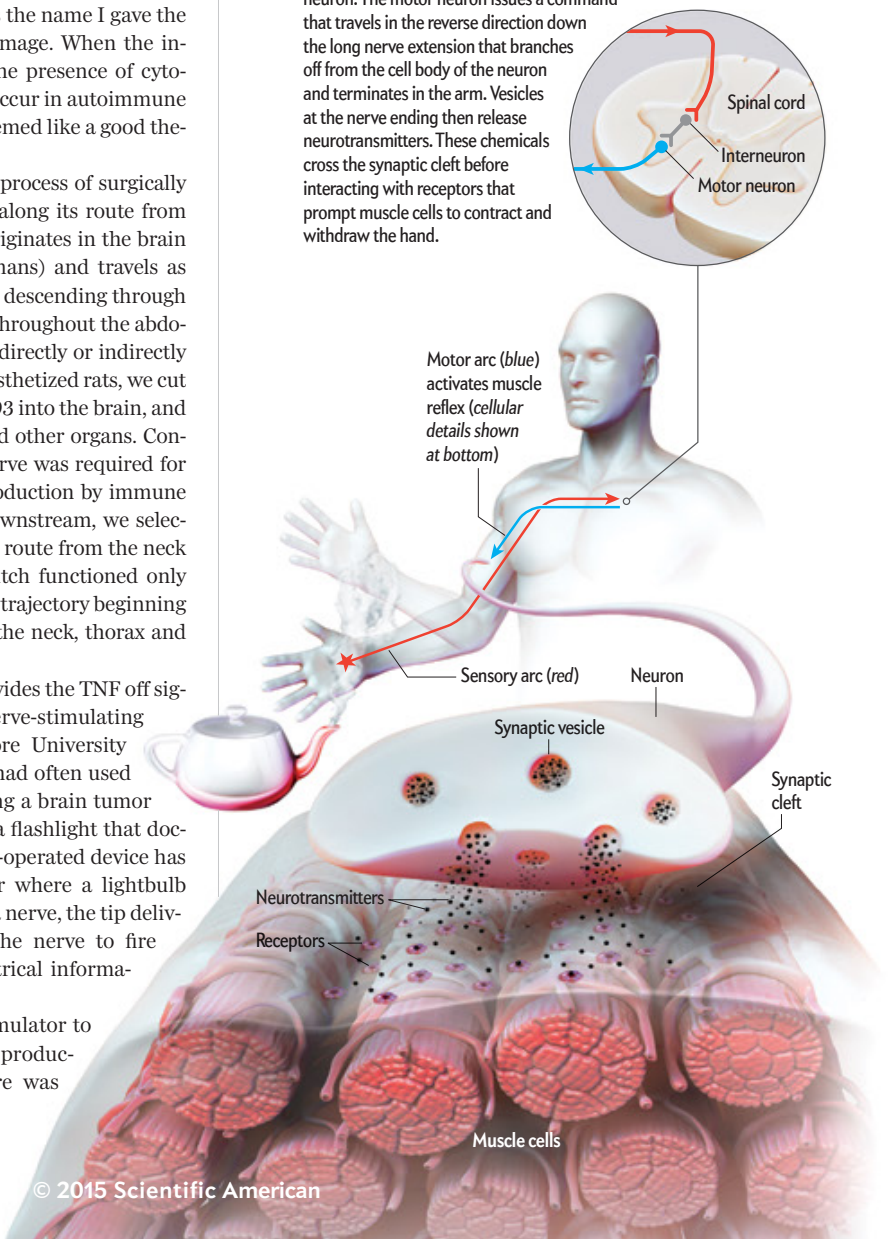
When I applied the tip of the nerve stimulator to the vagus nerve of anesthetized rats, TNF production in various organs was blocked. Here was

Reflexes and Inflammation

The nervous system receives inputs from throughout the body that it processes to enable various organs to function smoothly. Sudden exposure to a flame from a hot stove causes a reflex that makes a hand recoil. Reflexes also quell inflammation, opening the possibility for new therapies that forgo anti-inflammatory drugs.

Basics: Reflexes Ensure That We Don't Kill Ourselves

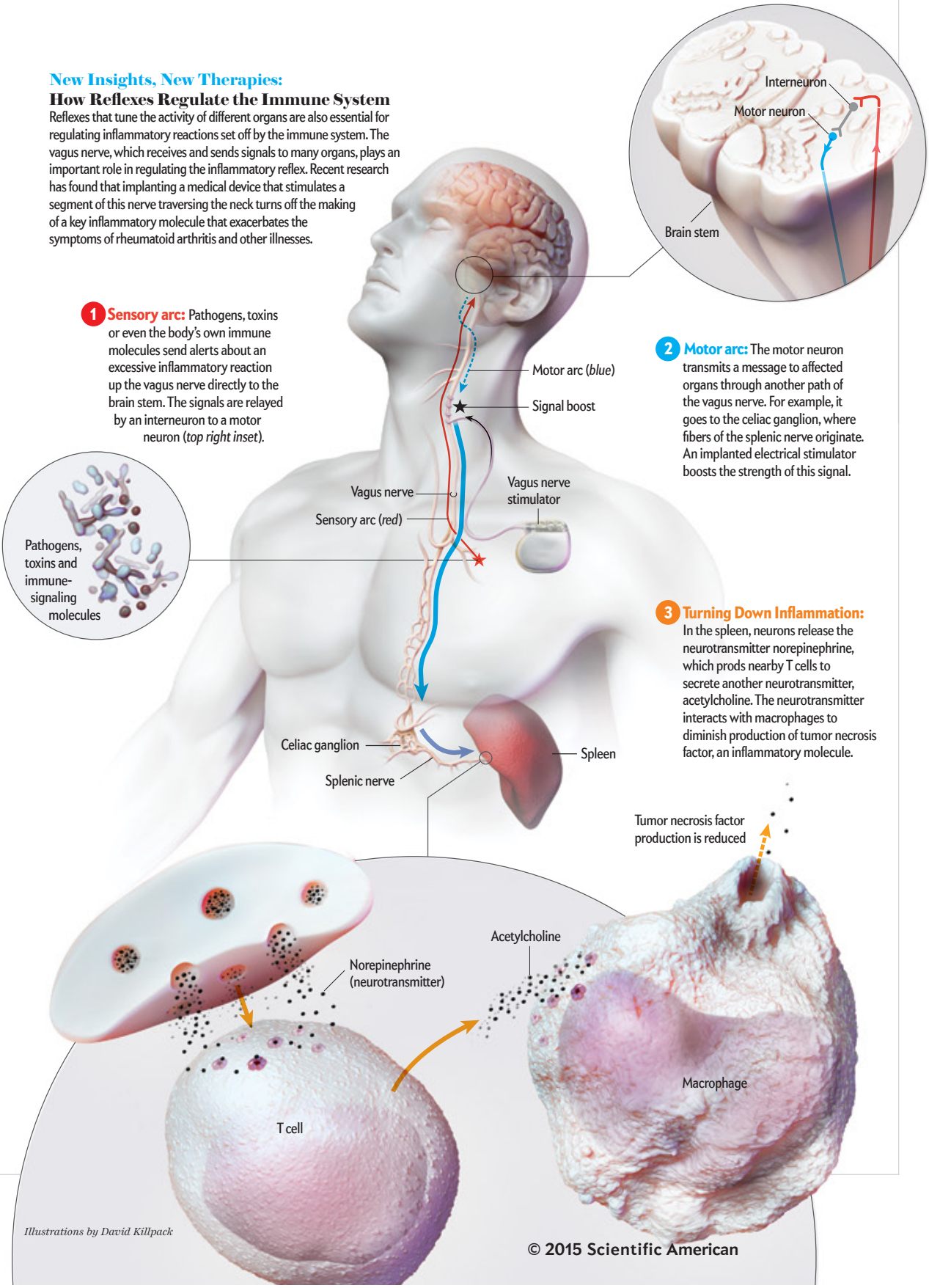
When a hand grazes a cloud of hot steam from a teapot, the inadvertent slip intiates a set of events—a reflex—in nerves and muscles. A nerve cell in the hand sends an electrical signal up a nerve pathway—known as a sensory arc. It goes up the arm to the spinal cord, where an interneuron relays it to a motor neuron. The motor neuron issues a command that travels in the reverse direction down the long nerve extension that branches off from the cell body of the neuron and terminates in the arm. Vesicles at the nerve ending then release neurotransmitters. These chemicals cross the synaptic cleft before interacting with receptors that prompt muscle cells to contract and withdraw the hand.



New Insights, New Therapies:

How Reflexes Regulate the Immune System

Reflexes that tune the activity of different organs are also essential for regulating inflammatory reactions set off by the immune system. The vagus nerve, which receives and sends signals to many organs, plays an important role in regulating the inflammatory reflex. Recent research has found that implanting a medical device that stimulates a segment of this nerve traversing the neck turns off the making of a key inflammatory molecule that exacerbates the symptoms of rheumatoid arthritis and other illnesses.



Illustrations by David Killpack

proof that electrical transmissions carried in the vagus nerve regulated TNF production by the immune system. This experiment inspired us to consider that treating inflammatory diseases using a bioelectronic device might be possible. At lunchtime, on the back of a napkin, I drew a sketch showing a pacemaker connected to an electrode placed on the vagus nerve in the chest of a patient with rheumatoid arthritis or another inflammatory disease. Usually I save things. I have accumulated more old junk than most, dating all the way back to a paper I wrote about Louis Pasteur in eighth grade. But somehow I lost that napkin. Too bad because today it would be a nice memento.

More than a decade of work by dozens of colleagues in my lab and by many others in research institutions around the world has laid out the physiology and molecular biology of the inflammatory reflex. The vagus nerve—the central focus of most of this research—sends signals from the brain to the spleen, liver, gastrointestinal tract, heart and other organs. Many of these studies have examined the spleen as a target because it is a major site for production of TNF. Along this pathway, action potentials descend down the vagus nerve to the upper abdomen, terminating in the celiac ganglion, a group of nerve cells that send their fibers to the spleen. These fibers deep within the spleen release a signaling molecule, norepinephrine, that then binds to immune system cells called T lymphocytes. Norepinephrine attaches to receptors on T cells, which trigger production of another neurotransmitter, acetylcholine, that binds to receptors on immune cells called macrophages, which produce TNF in the spleen. Acetylcholine docking onto the receptor—abbreviated α7 nAChR—causes macrophages to shut down TNF production by inhibiting two molecular pathways.

One pathway controls the activity of a protein, NF-κB, that instructs genes in the nucleus of the macrophage to initiate the making of TNF. The other pathway governs the release of IL-1 and other inflammatory molecules. Future research will examine other organs reached by the vagus nerve and investigate other nerves that interact with the immune system.

Defining the anatomical and molecular basis of these pathways demonstrates that an immune response can be controlled by the nervous system. When infection or injury creates a biochemical imbalance, these changes are relayed to motor neurons in the brain, which return signals to the affected tissues to regulate the release of TNF, IL-1 and other molecules into the tissues and the bloodstream that produce inflammatory reactions throughout the body.

The development of new techniques to observe and control these pathways is proceeding rapidly. Today we measure cytokines to monitor the course of inflammation. In the future, we will decipher the electrical signals carried in the nerves as a method to diagnose, monitor and control inflammatory disease.

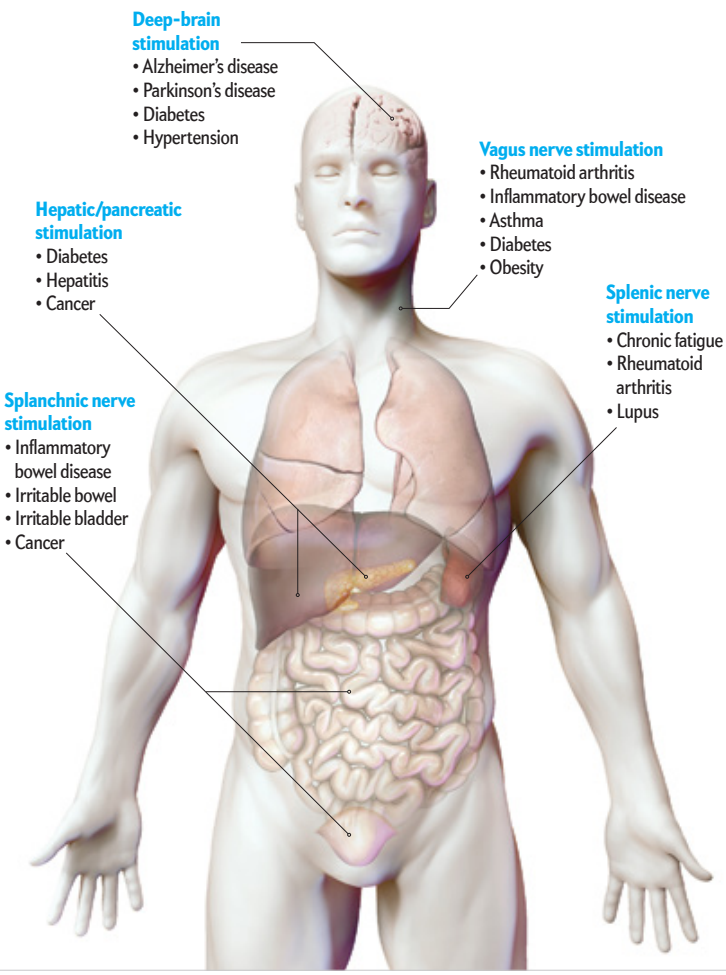
As we have shown, neural circuits that regulate immune responses can be mapped by cutting and stimulating nerves and by looking at pathways that activate genes and immune molecules. Results so far suggest these approaches will help treat disorders that include rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and perhaps even diabetes and cancer.

In 2011 in Mostar, Bosnia and Herzegovina, 13 years after sketching on a nap-

TARGETS AND DISEASES

Where to Zap

Bioelectronic medicine holds promise for using electrical stimulation technologies to treat a variety of diseases—and may become an alternative to some pharmaceuticals. Vagus nerve stimulation—the topic of this article—is only one of these techniques. Deep-brain stimulation is already helping patients with Parkinson's disease. Other therapies, such as splenic nerve stimulation, are being investigated but have not reached clinical trials.



kin, I met the first rheumatoid arthritis patient treated with a vagus nerve stimulator—a more sophisticated version of the simple handheld device that I had used in my lab. A middle-aged father of young children, he told me that his hands, feet and knees hurt so much that he spent days at a time lying on the couch, unable to work, play with his children or enjoy life. Without access to expensive anti-TNF drug therapy in his country, he had tried and failed therapy with steroids, methotrexate and other anti-inflammatory drugs. He consented to participate in a clinical trial led by Paul-Peter Tak, a leading rheumatologist at the Academic Medical Center at the University of Amsterdam and GlaxoSmithKline. Neurosurgeons implanted a vagus nerve stimulator just underneath his collarbone—and the man went home hoping for the best. Within days he was improving. Within weeks he was nearly pain-free. He began playing Ping-Pong, soon advancing his sporting activities to include tennis, at which point he injured his knee. The clinical team cautioned him against further strenuous exertion—this advice to the same person who could barely move a few weeks before. Now, nearly four years after surgery, he remains in remission, free of dangerous medications, which in the case of steroids can include lowered resistance to infection, diabetes and hypertension.

His case was presented at the November 2012 meeting of the American College of Rheumatology in Washington, D.C., by Tak and his colleague Frieda Koopman of the Academic Medical Center, along with Ralph Zitnik of SetPoint Medical, a company I cofounded to develop nerve stimulation to regulate the inflammatory reflex. Of the eight patients with long-standing, disabling, rheumatoid arthritis, he and five others benefited significantly after surgical implantation of a vagus nerve stimulator. As of this writing, additional studies are under way to assess vagus nerve stimulation in inflammatory bowel disease as a supplement to drug therapies. If successful, the potential for bioelectronic medicine to replace some drugs will be realized.

Progress in the field continues. In mid-January the Food and Drug Administration approved a device that stimulates the vagus nerve to induce a feeling of satiety in obese patients. Prospects for bioelectronic medicine were discussed at the first Bioelectronic Medicine Summit in 2013, a meeting hosted by GSK to begin charting a research road map for the field. GSK announced a $1-million innovation prize, beyond the $50 million the company had committed to support research on individual projects. In addition, the National Institutes of Health recently announced a $248-million program over seven years called SPARC—Stimulating Peripheral Activity to Relieve Conditions—to advance biolectronic technologies, and DARPA has launched ElectRx—Electrical Prescriptions—to fund work on techniques to promote health by harnessing the body's nerves.

Our original approach of inspecting the molecular mechanisms underlying the inflammatory reflex is now being widely applied to other diseases of the immune, cardiovascular, respiratory, gastrointestinal, neuroendocrine and renal systems. The broadening knowledge of specific neural circuits enabled by ever finer electrodes and molecular tools will shape our ability to stimulate small nerve fibers or even single axons.

The question might arise about whether the field of bioelectronic medicine presents a threat to the drug industry. I believe that bioelectronic devices will replace some drugs and supplement others. Antibiotics and other anti-infection agents, however, are here to stay. But I expect that drug companies will continue to increase their investments in bioelectronic medicine.

MIND OVER IMMUNITY

MOST PEOPLE DO NOT THINK much about reflexes. But they are everywhere. Primitive animals, such as worms that lack brains or consciousness, rely on reflexes to find food and mates, avoid predators, and develop defensive responses to infection and injury. Consider *Caenorhabditis elegans,* an evolutionarily ancient roundworm that feeds on soil bacteria for sustenance. On occasion, it encounters pathogenic bacteria, a potentially lethal event that activates a series of defensive countermeasures within the worm's immune system. Evolution favors species that present a coordinated, protective response to a threat from infection or injury with minimal collateral damage and side effects, and the worm has evolved an elegant system to do so. Of the 302 neurons that constitute the worm's simple nervous system, a select few are sensitive to the presence of pathogens. These same neurons trigger a reflex circuit that controls the activity of the worm's immune system, preventing the immune response from becoming toxic for the worm itself.

In higher vertebrates, the two biological systems that learn from experience to defend an organism are the nervous and immune systems. Discovery of the inflammatory reflex revealed that these two systems intersect in simple, precise reflex circuits to maintain immunological homeostasis. Like the lowly roundworm, we do not have to be conscious of these mechanisms to be the beneficiaries of their amazingly protective functions.

We have arrived at a unique juncture in the history of medicine. Simple reflexes are distributed across the entire nervous system. Trillions of synapses in the human nervous system connect one neuron with another. Today our research tools are sensitive enough to detect specific circuits that control the immune system and might be harnessed for therapy. In the early 20th century Sherrington ascribed the dominance of the human race as the most successful animal species on earth to the capacity of the higher-order areas of the human brain to master its primitive reflexes, noting that "reflex-arcs are controllable by mechanisms to whose activity consciousness is adjunct." Back then, he could not have envisioned the advent of technologies to control reflexes to keep the inflammatory processes of the immune system in proper balance. But that time has come. SA

DISCLOSURE OF COMMERCIAL TIES: Kevin J. Tracey co-founded and serves as a consultant to SetPoint Medical. The Feinstein Institute for Medical Research has applied for patents related to work summarized here. Tracey has received grants from GSK.

MORE TO EXPLORE

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