WHERE DOES IT HURT?

Researchers are getting to the molecular details of pain’s circuitry to answer the question with real specificity.

BY MARC WORTMAN | ILLUSTRATION BY SAM GREEN
Neuroscientists often use natural ingredients—like menthol, capsaicin, and wasabi extracts—that stimulate nerve cells to react just as they would in response to painful cold and heat, for example, or to inflammation and chemical irritants. Drawing on electrical recordings, imaging, molecular techniques, mouse models, and genetic studies, scientists can explore the nervous system as it reacts to “pain” at the subcellular level. Their studies have revealed many molecular pathways that regulate pain perception, including specialized ion channels that open and close to send pain signals along nerves to the spinal cord and brain. They have also begun to explain the systemic changes in response to pain sensation that can cause chronic disorders.

HHMI scientific officer Ed McCleskey, who spent much of his research career studying pain, believes such progress will translate into health care benefits. “We have been using more or less the same aspirin and morphine variants for centuries now. But a wave of recent basic science discoveries has begun to transform the pain field, and they are already yielding insights for finding new ways to treat pain.”

THE MANY TYPES OF PAIN

Aspirin and opiates work just fine for most of us most of the time. But plenty of people don’t benefit from either drug or can’t handle their serious drawbacks, which range from stomach irritation and excessive bleeding to addiction and respiratory suppression. The devastating daily reality of uncontrolled chronic pain far exceeds the ability of today’s medicines to help. Every year, at least 116 million adult Americans experience severe chronic pain—more than the number affected by heart disease, diabetes, and cancer combined—at a cost of $560 billion annually in direct medical expenses and $635 billion in lost productivity, according to a June 2011 report from the Institute of Medicine.

Researchers today recognize several pain subtypes, which develop via electrical signals running along a complex, interconnected neural perception system genetically encoded to detect and respond to painful stimuli.

The body detects and converts pain stimuli into electrical signals at the fine nerve endings of “nociceptors,” sensory neurons specialized to respond to pain. Their axons, which conduct electrical signals, are only a millionth of a meter in diameter but can be more than a meter long, with one end located where a stimulus is detected—at a fingertip, for example—and the other end in the spinal cord, where it forms a synapse, or communication junction, with a second cell that sends the signal to the brain. The nociceptor’s spinal synapse is highly sensitive to opiates and other agents that can alter pain perception. The cell bodies of nociceptors and other sensory neurons sit just outside the spinal cord in clumps called dorsal root ganglia; action potentials—short-term changes in electrical charge—pass through the ganglia on the way to the spinal cord.

To convey signals from a peripheral organ to the spinal cord, the axon depends on a variety of molecules. Some convert a physical or chemical event into a small electrical signal at the peripheral nerve ending; others amplify the signal and send it along the length of the axon. Molecules at the synapse convert the electrical signal into a chemical signal, triggering release of a neurotransmitter that activates the postsynaptic neuron. Other molecules tune transmission of pain signals. Various types of ion channels—proteins that create pores in cell membranes—serve as detectors, amplifiers, and electrical-to-chemical translators, while receptors for hormone-like molecules modulate the activity of the channels.

When everything works, the pain system triggers behaviors that lead us to flee danger or to rest and recover from an injury. But it doesn’t always work right. In chronic pain, for instance, messaging can become hyperactive so that even the
lightest touch hurts or, in extreme cases, electrical signals fire for no apparent reason. Researchers have recently begun to describe how this malfunction, known as central sensitization, makes nociceptor synapses dangerously hyperactive, as occurs in some mysterious and hard-to-treat pain disorders, such as neuropathy, chronic inflammatory pain, and fibromyalgia.

CHANNELING PAIN
Nerve cell ion channels selectively allow the passage of four types of charged atoms: positive ions of sodium, potassium, and calcium, and a negative ion, chloride. The movement of these ions across a membrane creates an electric current that transiently alters the cell’s membrane voltage. The past two decades have seen an avalanche of discoveries of ion channels related to pain sensation.

In the 1990s, Gail Mandel, now an HHMI investigator at the Oregon Health and Science University, and her colleagues Simon Halegoua and Paul Brehm at New York’s Stony Brook University were exploring the variety of sodium-selective channels in mammals. Sodium channels act as molecular amplifiers, turning small electrical signals into action potentials that can conduct for long distances along an axon. In 1997, Mandel discovered a sodium channel, now called Nav1.7, which is abundant on sensory neurons. From the channel’s location and density, the researchers theorized that it plays a role in pain perception.

Human genetic studies strongly support the idea. Erythromelalgia, a rare disease in which patients periodically feel severe burning pain without any sensory stimulus, is caused by a mutation that increases Nav1.7 activity, rendering nociceptors hyperexcitable. Another mutation that diminishes Nav1.7 activity causes a rare disease in which patients are profoundly insensitive to burns and some other kinds of tissue damage. A few pharmaceutical companies are testing compounds to control Nav1.7 as a way to suppress pain (see Web Extra, “Pain Medicines From Under the Sea”).

The same year that Mandel’s group found the sodium channel, Julius and colleagues published findings about pain perception emanating from one among a subfamily of ion channels called transient receptor-potential vanilloid (TRPV, called “trip-vee”) channels. Julius used capsaicin to demonstrate that burning heat specifically activates the TRPV channel in peripheral nociceptors. That discovery also provided a model for future pain studies using natural ingredients to simulate painful stimuli, opening the door to a host of other findings.

Since then, Julius and others have characterized several TRP channels and their interconnected roles in sensory perception. HHMI investigator David Clapham, an ion channel expert at Children’s Hospital Boston and Harvard Medical School, also studies the channels, looking at their roles in a variety of sensations. He characterized a member of the human vanilloid TRP subfamily, TRPV3, found in the skin and other major organs, and showed its involvement in controlling some aspects of temperature sensitivity. His lab also identified common plant compounds used as spices and insecticides that activate TRPV3, TRPV1, TRPA1, and other TRP channels, leading to irritations and allergies.

RECEPTORS TO DULL PAIN
A major new direction in pain research began with the discovery of the family of Mas-related gene (Mrg) receptors by HHMI investigator David Anderson and his colleagues, including Xinzhong Dong, at the California Institute of Technology. Mrg receptors are found exclusively in sensory neurons. Dong, now an HHMI early career scientist at Johns Hopkins School of Medicine, has shown that while certain Mrg receptors function in itch sensation, one appears to function like the body’s naturally occurring opioid receptors, which help to dull pain. Dong is testing compounds that target this Mrg (continued on page 48)

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(FORCE FACTOR)

And Bustamante is now using similar techniques to probe the basics of numerous biological processes, including protein folding. He’s using optical traps and fluorescent tags to see what happens when a protein strand is stretched and then released, allowing it to fold into its preferred conformation.

He’s also applying the method to nucleosomes—clumps of proteins that control the structure of DNA within a chromosome and influence when genes are expressed. He’s already looked at the interaction between polymerases—enzymes that move along DNA strands—and nucleotides. His team discovered that when polymerases encounter a nucleosome, they pause, not having enough force to unravel the DNA from the nucleosome. Instead, the protein waits for the clump to spontaneously unravel. If he can use optical traps to pull apart a fluorescent chromosome, Bustamante says, he can observe its higher-order structure and the forces that proteins within the nucleosomes exert on the nucleotides.

“It’s natural that as optical trapping starts to mature, we now want to combine these techniques with others,” says Bustamante. “I think in the future we will see even more hybrid experiments that combine optical trapping with other methods.”

He’s happy to see his technique mature and change, he says, if it means applying it to more biological questions.

“There are so many unknowns inside the cell,” he says. Optical trapping lets researchers get a physical handle on those unknowns. While scientists can’t reach inside cells and feel for themselves the forces at work, optical trapping has become their hands that work to sense and manipulate these forces.

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(RAISING THEIR GAME)

Trainers to train up to 8,500 K–12 science and math teachers each year, offering them subject-specific, grade-specific mentoring. Since 1999 they’ve trained half the STEM teachers in the state, Ricks says. Teachers come for two-week workshops for two consecutive summers. AMSTI also employs 500 master science or master math teachers who advise and mentor teachers and even co-teach if the mentees need a hand. AMSTI operates 11 regional 35,000-square-foot warehouses, where workers run forklifts to help sort bins of laboratory materials and equipment designated for math and science teachers.

The state’s investment is paying off in better student performance, according to eight years of external evaluations. For example, Alabama students improved more in math than those in all but one other state, as judged by an internationally recognized test called the National Assessment of Educational Progress. “The state has seen that if you really want students to compete, they need top-notch math and science skills,” says Ricks.

Wendy Bramlett, who used AMSTI to raise her game, is a fan. “My whole way of teaching changed,” she says. “I went from a lecture class to no lecture and all hands on,” she says. Her students’ performance has improved—92 percent scored at the top level on the state science exam last year. And she hears something else she never heard in her first years of teaching. “I have children tell me, ‘Science is my favorite subject.’”

WEB EXTRA: Read more about STEM teacher training online. Go to www.hhmi.org/bulletin/feb2012.

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receptor, looking for ways to avoid narcotic and other side effects from opiates, which would benefit people with chronic pain (see Web Extra, “Boosting the Body’s Natural Painkilling Power”).

The initial discovery that abnormal central sensitization can lead to pain hypersensitivity came from Clifford Woolf at Children’s Hospital Boston and Harvard Medical School. Woolf is now generating hypersensitive and normal human pain neurons in his laboratory from fibroblasts using stem cell techniques to characterize their differences and, perhaps, find ways to regulate their firing without harming other necessary physiological functions. He is also looking at ways to deliver pain relievers directly to hyperactive nociceptors while leaving normal ones untouched.

Undoubtedly, other molecules of normal and pathological pain signaling await discovery, thereby offering additional possibilities for improving pain treatment. “I tell my medical students,” says Woolf, “that pain will be treated completely differently 10 years from now.” Physicians may one day treat pain based on both the source of pain within the patient’s nervous system and the individual’s genetic predisposition for responding to a specific therapy. Perhaps the day isn’t too far off when a physician will ask where it hurts and nearly all patients will respond, nowhere.

WEB EXTRA: For more of the latest research on understanding and controlling pain, go to www.hhmi.org/bulletin/feb2012.