Hitting a Nerve: Ion Channels May Hold the Key for Treating Chronic Pain

Chandra Shekhar
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Modern anesthetics work like a miracle, providing the comprehensive nerve blockade required for millions of surgeries performed every day. Modern analgesics, in contrast, haven't progressed much beyond folk remedies: among the most widely used pain relief drugs are morphine and other compounds derived from the opium poppy. While effective for short-term, acute pain, their long-term use leads to tolerance, dependence, and severe side effects. They offer little help to treat the chronic pain that afflicts nearly one in four Americans and costs the US nearly $100 billion each year. In the quest for a better solution, researchers are developing compounds to modulate the nerve ion channels that help carry pain signals to the brain. One of these new drugs is already in the market for severe, morphine-resistant chronic pain, while many others have shown promise. "Ion channel modulators and other emerging therapeutics could help address the unmet challenge of treating chronic pain," says Andy Dray, Ph.D., chief scientist at AstraZeneca R&D in Montreal.

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This challenge is manifold. Chronic pain often stems from nerve or tissue damage caused by injury, infection, cancer, diabetes, or other conditions. What transforms acute pain from an injury into chronic pain is poorly understood, and the underlying mechanisms change over time. "Chronic pain is a moving target," says Michael Gold, Ph.D., a pain researcher at the University of Pittsburgh. Further, it is hard to tease out the molecules and pathways involved in the pain sensation from those involved in other vital biological processes. "That's why the drugs we have for chronic pain are not consistently effective and can have serious side effects," says Gold. Finally, the maladaptive changes in the nervous system that underlie chronic pain can resist efforts to reverse them. "Pharmacological interventions may provide short term relief," he says. "However, once the nervous system has acquired a new 'state' associated with chronic pain, it can find ways to get back to it."

In the past, as Dray points out, pain relief drugs were typically discovered by "clinical serendipity": compounds developed for other conditions such as depression (e.g. amitriptyline), epilepsy (e.g. gabapentin), and arrhythmia (e.g. mexiletine) were found to relieve pain as well. While these drugs offer an alternative to opioids, they are only moderately effective and come with their own baggage of side effects. Fortunately, newly emerging drugs based on rational design and direct targeting of specific pain processes promise better outcomes. A dramatic early example is ziconotide (Prialt), approved in 2004 for treating severe, morphine-resistant pain due to cancer or AIDS. The drug works by blocking N-type calcium channels, which are critical for the transmission of the pain signal. "It literally works miracles for patients in agony from severe, intractable cancer pain," says Gary Bennett, PhD, a pain researcher at McGill University. "Fifteen minutes after getting it, they smile and say 'the pain is gone!'"

Morphine and other opioids activate μ-opioid receptors in the body, initiating cellular processes that result in the block of N-type calcium channels. Cannabis and the body's own cannabinoids do likewise to create their psychoactive effect. "Mother nature is already blocking the N-type channel as a way to alleviate pain," says Terrance Snutch, Ph.D., a University of British Columbia researcher who was the first to clone this channel. As ziconotide operates directly on N-type channels, which are downstream of and more limited in distribution than opioid receptors, it avoids most opioid side effects. Nor does it create tolerance or dependence even after years of use. Unfortunately, as Snutch points out, ziconotide has its own limitations. Derived from the toxin of a fish-hunting cone snail, it's a large polypeptide molecule that has to be infused into the patient's spine using a surgically implanted pump—a far cry from the oral pill that pain sufferers are hoping for. In 2006, Neuromed Pharmaceuticals, a company founded by Snutch, developed an orally available calcium channel blocker called NMED-160 that it licensed to Merck. Although this compound fared well in safety trials, Merck did not advance it further, citing lack of "ideal pharmaceutical characteristics." However, Neuromed is actively developing other similarly acting compounds that may emerge as a viable alternative to ziconotide.

Further upstream in the pain pathway, and easier to reach, are the voltage-gated sodium channels that help generate the pain signal and tend to become hyperexcitable in chronic pain, epilepsy, and other conditions. "Because sodium channels are involved in the generation of the action potentials, they are very important drug targets," says Manoj Patel, Ph.D., who studies these channels at the University of Virgina. Among the nine voltage-gated sodium channel isoforms identified so far, two ($Na_v1.7$ and $Na_v1.8$) have emerged as important targets in pain, while others have cardiac, motor, and other roles. Broad-spectrum sodium channel blockade with drugs such as the local anesthetic lidocaine and the anticonvulsant carbamazepine has been shown to relieve chronic pain; however, such nonselective blockers can disrupt other vital functions in the body. "That's why toxicity is a big problem when using them to treat pain," says Patel.

Selectively targeting $Na_v1.8$, which is exclusively present in pain-sensing neurons, may be a better option. In 2007, researchers at Abbott discovered a molecule, A-803467, that is a 100-fold more potent at blocking $Na_v1.8$ than other sodium channels. Although Abbott stopped clinical development on the compound due to poor bioavailability, preclinical results were impressive. "That was a good proof-of-concept that it's possible to develop a highly isoform-selective blocker," says Theodore Cummins, Ph.D., who studies the biophysics of ion channels at Indiana University. A number of companies including Merck, AstraZeneca, and GlaxoSmithKline are now in the hunt for a viable $Na_v1.8$ blocker.

The $Na_v1.7$ isoform sprang into prominence in 2006 from a study of certain families in Pakistan whose members are remarkable for their total inability to feel pain. These individuals, who often amaze spectators by walking on burning coals or driving spikes through their bodies, are otherwise fairly normal, although they typically die young due to unattended injuries and infections. It turns out that they owe their unusual trait to a loss-of-function mutation in the $Na_v1.7$ gene. Interestingly, and perhaps logically, it turns out that people with a *gain-of-function* mutation in the same gene suffer from an exaggerated pain response. Taken together, "that's the best validation that $Na_v1.7$ might be an ideal target for pain therapies," says Cummins. However, efforts to find a safe and effective $Na_v1.7$ blocker have failed, in part because this isoform is less structurally distinct and less pain-specialized than $Na_v1.8$. "Modulating and knocking down the channel may be a better approach," says Cummins. In 2008, Merck researchers reported that a tarantula venom peptide, ProTx-II, does precisely that: by binding to the channel's voltage sensor, it increases the membrane voltage needed to activate it. This finding offers hope of finding pain drugs based on selective $Na_v1.7$ inhibition, says Cummins.

Still further upstream in the pain pathway, at nerve terminal membranes, lie the receptors and ion channels that translate noxious stimuli such as heat, cold, pressure, or acidity into nerve signals. A key player among them is the transient receptor potential V1 (TRPV1) channel, a ligand-gated channel activated by noxious heat and acidity. It also responds to capsaicin, the compound that makes chili peppers "hot." Normally responsive only to strong stimuli, this channel, like some sodium channels, tends to become hypersensitive when inflammation or tissue damage is present. Knocking out or inhibiting it improves pain resistance in some animal models. Driven by this rationale, pharmaceutical companies have developed a range of compounds that block the TRPV1 channel. These can typically be taken orally and some have shown therapeutic value. Unfortunately, it so happens that the channel also exists in the hypothalamus, where it helps regulate body temperature. Consequently, TRPV1 antagonists cause persistent fever in many patients. "You particularly don't want that in a postoperative setting, as it would mimic an infection," says Clifford Woolf, M.D., Ph.D., of Harvard Medical School.

While several companies including Eli Lilly, Amgen, and AstraZeneca are exploring ways to improve TRPV1 antagonists, others are taking the opposite approach: exploiting TRPV1 agonists such as capsaicin. By overstimulating the TRPV1 receptor, and causing an initial burning sensation, these compounds can create the inverse effect of desensitizing a target area. This principle underlies folk remedies such as Tiger Balm or Sloan's Liniment as well as more modern preparations such as NeurogesX's skin patch for peripheral neuropathic pain.

In 2007, Woolf's team reported a new twist on this time-tested method. They found that a combined injection of capsaicin and QX-314, a positively charged molecule derived from lidocaine, had a powerful analgesic effect. Because of its size and charge, QX-314 can't penetrate through the neural membrane by itself. But when TRPV1 channels are opened using capsaicin, QX-314 can diffuse through them into the nerve and block its sodium channels. "You can use the TRP channel as a way of getting a large cationic molecule into a specific cell," says Woolf. Since these channels are found predominantly on pain-sensing nerves, other functions will not be disrupted. But the patient will suffer an initial burning sensation due to capsaicin. Fortunately, it now turns out that lidocaine too can open the TRPV1 channel and, unlike capsaicin, it doesn't burn. "If you inject lidocaine in combination with QX-314, you have a transient period of nonselective block of all nerves in the vicinity, followed by many hours of selective block of the pain fibers alone," says Woolf. "The lucky break was that lidocaine turned out to be a TRPV1 agonist." Harvard Medical School has licensed the approach to Endo Pharmaceuticals, who are expected to start Phase I trials late next year.

Besides the ones described above, researchers worldwide are developing a vast array of other molecules targeting nearly every step in the pain pathway. Researchers express cautious optimism that at least a few of these new compounds will eventually bring relief to chronic sufferers. Driving the flurry of new efforts is a changing view of the phenomenon of chronic pain. "We used to think that chronic pain was the symptom of an underlying problem," says Dray. "We now realize that it is a neurological disease process, just like schizophrenia or Alzheimer, with long-lasting changes in nerve biochemistry and connections."

Chandra Shekhar (chandra@nasw.org) is a science writer based in Princeton, NJ.