Subtype-selective sodium channel blockers promise a new era of pain research

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Chronic pain affects ≈ 1.5 million patients worldwide. Despite several treatment options, successful pain management is difficult to achieve, and this area of therapy remains a major unmet medical need. Chronic pain is thought to originate from aberrant electrical signaling in the nervous system. Pain-sensing neurons of the peripheral nervous system express several sodium channel (Na_v1) subtypes. Their relative contribution to pain signaling is the subject of intense research and debate, and they may vary depending on the cause, anatomical location, and sensory qualities of pain. Knockdown of individual sodium channel subtypes in rodents, either by genetic ablation or through treatment with antisense oligonucleotides, has provided important information on this subject. However, interpretation of the results may be confounded by compensatory mechanisms, in the case of genetic ablation, or residual protein expression and inflammation associated with the oligonucleotide administration, in the case of the antisense technology. Subtype-selective pharmacological agents are needed to identify unambiguously the roles of individual Na_v1 subtypes, but, despite years of efforts, such agents have been difficult to identify. The manuscript by Jarvis *et al.* (1) in this issue of PNAS reveals the first reputed $\text{Na}_v1.8$ -selective small-molecule sodium channel blocker to be publicly disclosed. By providing a much-sought-after exciting new tool, this work represents a seminal contribution to pain research.

One of the most troubling and least well treated forms of chronic pain is neuropathic pain, defined as "chronic pain resulting from a primary lesion or dysfunction of the peripheral nervous system" by the International Association for the Study of Pain (IASP). Sodium channels are thought to play a key role in the pathophysiological hyperexcitability associated with this form of chronic pain because they initiate and propagate the electrical impulses associated with pain signaling (2), and several agents used clinically to treat neuropathic pain block sodium channels (3). A large body of preclinical data and a few small clinical studies suggest that sodium channel blockers may also be efficacious in the treatment of inflammatory pain.

Fig. 1. Effects of tetrodotoxin (TTX) and A-803467 on sodium current in an injured rat. Red traces indicate the current in the presence of the blocker.

Sodium channel blockers currently in clinical use for the treatment of chronic pain were originally developed as anti-convulsants or antiarrhythmics (4). Although clearly beneficial for some patients, the clinical usefulness of these drugs is limited by their narrow therapeutic index. One approach likely to improve the tolerability of sodium channel blockers is to target Na_v1 subtypes that have specialized roles in pain signaling. Pharmacological tools that have been invaluable in delineating the physiological roles of some Na_v1 subtypes are tetrodotoxin and saxitoxin, two potent natural product neurotoxins (5). Indeed, peripheral nervous system sodium currents/channels are classified throughout the literature on the basis of their sensitivity to these toxins. Tetrodotoxin-sensitive channels expressed in the peripheral nervous system are $\text{Na}_v1.1$, $\text{Na}_v1.6$, and $\text{Na}_v1.7$, whereas both $\text{Na}_v1.8$ and $\text{Na}_v1.9$ are tetrodotoxin-resistant. A-803467, characterized by the work of Jarvis and colleagues as a highly selective blocker of $\text{Na}_v1.8$ channels by using electrophysiological protocols (1), is a breakthrough that should allow us to more specifically investigate the role of this particular channel subtype (Fig. 1).

In rodents, the strongest evidence for a role in neuropathic and inflammatory pain signaling exists for the tetrodotoxin-

resistant $\text{Na}_v1.8$ channel. Tetrodotoxin-resistant action potentials have been demonstrated in sensory neurons from human neuropathic pain patients (6) and from nerve-injured rats, and inflammatory mediators, such as prostaglandin E_2 and serotonin, increase tetrodotoxin-resistant sodium currents in rat sensory neurons (7). Knockdown of $\text{Na}_v1.8$ transcript by intrathecal administration of antisense oligonucleotides reversed injury-induced hypersensitivity in a nerve-injury model in rats and inhibited inflammatory responses to prostaglandins (8, 9). $\text{Na}_v1.8$ -null mutant mice also pointed to a role of $\text{Na}_v1.8$ in inflammatory pain signaling, but they were not resistant to neuropathic pain (10).

Jarvis *et al.* (1) tested A-803467 in a wide range of rat pain models. The results are interesting and somewhat puzzling. A-803467, given by i.p. injection, dose-dependently inhibited acute mechanically induced pain but not heat-induced pain. However, after in-

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flammation had been induced, thermal hyperalgesia was inhibited much more potently by A-803467 than was mechanical allodynia. In fact, inflammation-induced thermal hyperalgesia was inhibited much more potently than acute thermally induced pain, whereas inflammation-induced mechanical allodynia was inhibited less than acute mechanically induced pain. A-803467 was quite effective at reversing nerve injury-induced allodynia in two models of neuropathic pain. However, the compound was without effect in the vincristine model of chemotherapy-induced neuropathic pain. Finally, A-803467 had little effect on postoperative or visceral pain.

Interpretation of the *in vivo* efficacy of A-803467 is clouded somewhat by the

very high protein binding (98.7%) exhibited by this compound and by its lack of oral bioavailability. Attenuation of pain behavior was seen at total plasma concentrations in a range that may be expected to block all Na_v1 subtypes; however, free plasma concentrations were 1.5- to 3-fold above the IC_{50} of A-803467 for rat tetrodotoxin-resistant currents and significantly below the IC_{50} values for Na_v1 subtypes other than $\text{Na}_v1.8$. Profiling of A-803467 in $\text{Na}_v1.8$ -null mutant mice would be required to provide definitive proof that blockage of $\text{Na}_v1.8$ is solely responsible for the analgesic efficacy of the compound. Now that $\text{Na}_v1.8$ -selective small-molecule blockers are no longer just wishful thinking, additional selective compounds

are expected to follow quickly. Although it is possible that the accessibility of A-803467 at different sites of action potential generation may vary, the combined profile of several $\text{Na}_v1.8$ -selective compounds should be extremely informative regarding the role of $\text{Na}_v1.8$ in all aspects of pain signaling, at least in rodents.

Recent genetic data (11) suggest that there may be significant species differences between rats and humans and that $\text{Na}_v1.7$ may play a dominant role in human pain signaling. Although clinically challenging, the future development of Na_v1 subtype-selective blockers should be very exciting and will hopefully offer new alternatives for chronic pain sufferers.

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