Rational Drug Design for Pain Medicine

A New Nav1.7 Inhibitor

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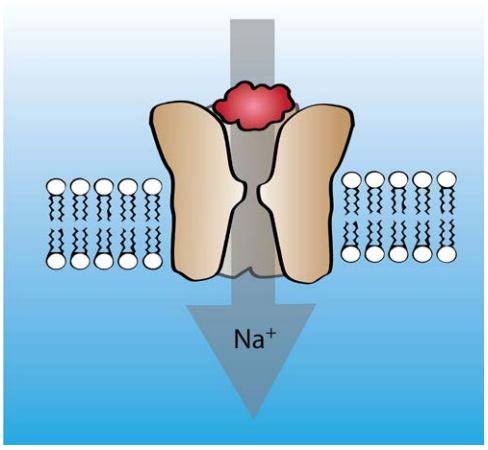
The ability to silence pain messages at their source in the periphery, without dampening neuronal activity elsewhere within the nervous system, is a holy grail of pain research that has focused interest on "peripheral" ion channels as potential therapeutic targets. Sodium channel Nav1.7 has emerged as a key target in this search, due to its preferential expression in pain-signaling neurons within dorsal root, trigeminal, and other sensory ganglia, and its role as a threshold channel that sets the gain and regulates the excitability of these cells.[1] Molecular genetic validation has further propelled interest in Nav1.7 as a pain target: gain-of-function mutations of Nav1.7 produce nociceptor hyperexcitability that underlies severe pain in disorders such as inherited erythromelalgia, which is now regarded as a human genetic model of neuropathic pain[2] while loss-of-function mutations produce a syndrome of profound insensitivity to pain.[3,4] It is no surprise, then, that Nav1.7 has attracted substantial interest as a molecular target for pain and itch. However, while studies within the academic and biopharmaceutical sector have begun to identify subtype-selective inhibitors that block the activity of Nav1.7 while leaving other Nav channel subtypes intact and have yielded positive results in studies in animal models of pain and in some early human studies, Nav1.7 blockers have not yet entered the clinical arena. This reflects, in part, general challenges inherent in clinical studies on pain (subjective readouts such as Numerical Ratings Scores that can vary, for example, depending on level of stress or expectancy; lack of biomarkers; large placebo response) and the fact that, for at least some clinical trials, the patient population studied was, at least at a molecular level, heterogeneous.



"…by targeting [sodium channel] Nav1.7, it may be possible to develop an entirely new class of analgesic medications."

In this issue of Anesthesiology, Chandra *et al.*[5] provide an exciting example of progress in this search. Starting with several compounds known to inhibit Nav1.7 in a relatively selective manner, these investigators adopted a powerful computer-aided strategy to virtually assess about 1.5 million compounds, and followed with molecular docking and molecular dynamic studies. They used patch-clamp to assess the effects of compounds on Nav1.7-expressing HEK-293 cells and in mouse and human dorsal root ganglia. The first stage of analysis yielded four compounds that inhibited sodium currents in Nav1.7-expressing HEK-293 cells by 29% or more. One of these reduced sodium current by 80%, but had no effects on Nav1.5-expressing HEK293 cells. The compound also inhibited sodium channels in mouse and human dorsal root ganglia neurons. *In vivo* effects were examined in multiple rodent models including an inflammatory pain model, a paclitaxel-induced neuropathic pain model, a histamine induced itch model, and a mouse lymphoma model of chronic itch. Intraperitoneal and intrathecal administration of the compound reduced formalin-induced inflammatory pain behavior in mice while intrathecal administration reduced paclitaxel-induced mechanical allodynia, and inhibited histamine-induced acute itch and lymphoma-induced chronic itch.

This study does not reach into the clinic, but even at this early stage it illustrates the power of rational drug design; it also underscores the fact that development of molecules that can effectively inhibit Nav1.7 while sparing other Nav channel subtypes, which was initially considered to be an immense challenge, may be tractable. Thus, in a general sense as well as with regard to the specific inhibitor that

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was identified, it reinforces the concept that, by targeting Nav1.7, it may be possible to develop an entirely new class of analgesic medications.

A next step would be to translate these results into the clinical arena. In that regard, challenges remain, and there are also opportunities. Here we comment on just a few of them:

- The predictive value of preclinical *in vitro* studies may depend on the cell platform used. It is now well established that the biophysical and pharmacologic properties of ion channels can be different in heterologous expression systems such as HEK and CHO cells, as compared to cell types where the channels are normally expressed such as dorsal root ganglia neurons. Even suppression of activity in dorsal root ganglia neurons does not guarantee clinical success. Here, stem cell research may provide a new tool. Induced pluripotent stem cell-derived sensory neurons may provide a platform in which it is possible not only to predict drug efficacy, but also to assess the response of specific subjects to the compound under study.[6] Moreover, high (atomic)–level molecular modeling may provide a basis for predicting, on the basis of analysis of gene variants, the effect of specific Nav1.7 inhibitors on particular patients,[7] a step toward "precision," genomically-guided pain pharmacotherapy.
- Human studies on pain are inherently challenging. Rodent models of pain have taught us important lessons about mechanism, but have not always predicted human therapeutic response. Biomarkers for pain have have not yet been validated. The commonly used Numerical Rating Scale is notoriously noisy, and can vary day-to-day with strong effects of multiple factors such as emotional tone, stress level, and other psychologic elements including expectancy. The placebo effect can be strong, further confounding results. In paroxysmal pain disorders such as inherited erythromelalgia[7] and trigeminal neuralgia where pain occurs in discrete attacks,[8] temporal aspects of pain such as attack duration and frequency can be measured, but in the majority of pain syndromes discomfort is not paroxysmal.
- Further confounding clinical studies, there can interindividual differences in the pain profile, even for different members of the same kindred sharing the same pain-producing mutations.[9,10] In some cases it has been possible to pinpoint specific modifier genes that account for intrafamilial differences in pain.[11] But in many kindreds, the genetic or epigenetic bases for interindividual variability remain enigmatic, and these differences can confound clinical studies.
- We still need to learn more about the degree of receptor occupancy or inhibition needed for a real-world clinical effect. It is known that human subjects who are heterozygous for null mutations of Nav1.7 (and who presumably produce about 50% of the normal complement of these channels) are phenotypically normal,[3,4] and dynamic-clamp studies[12] reinforce the notion that 50% inhibition may not be sufficient. But we do not want to induce a state of total insensitivity to pain where unintended self-injury would occur. We still need to determine the degree of inhibition that is needed.
- What pharmacokinetic and pharmacodynamic properties are needed to optimize clinical effectiveness and minimize unwanted effects in the clinical domain. Protein binding may represent an impediment to clinical effect.[13] And, we need to understand whether central nervous system penetration is necessary, so that the channel can be inhibited along the central terminals of sensory neurons within the dorsal horn.[14] There is much work to do here.
- Finally, while inhibition or block of the channel itself remains an attractive target, partner molecules or mechanisms responsible for channel expression might also be targeted, providing additional therapeutic opportunities. It is known, for example, that trafficking of Nav1.7 is enhanced by inflammation[15] raising the possibility that it might be possible to therapeutically alter the trafficking pathways.

As outlined in the preceding points, there is a lot of work to do, and the search for new pain medications must overcome some unique hurdles. The article by Chandra *et al.*, however, reminds us of the powerful methodologies at our command. As noted previously, new methodologies for molecular modeling and stem-cell based platforms are providing new and powerful tools. More effective, nonaddictive treatment for pain remains a substantial, unmet need. And Nav1.7 continues to be an opportune molecular target.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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