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Translating Basic Research on Sodium Channels in Human Neuropathic Pain

Nadine Attal and Didier Bouhassira

Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, AP-HP and Université Versailles-Saint-Quentin, France.

Abstract: A number of experimental studies in animals have suggested that voltage-gated sodium channels may play a crucial role in neuropathic pain. However, it is still difficult to translate the pathophysiological mechanisms identified in animal studies to the clinic and several questions regarding the role of sodium channels in neuropathic pain must therefore be addressed primarily in the clinical setting. Despite providing indirect information, pharmacologic challenge using sodium channel blockers, such as some antiepileptics, local anesthetics and derivatives, is the best way to investigate the role of sodium channels in the various clinical symptoms of neuropathies (eg, spontaneous pain, mechanical or thermal allodynia, and hyperalgesia). Randomized controlled trials have demonstrated the efficacy of these compounds for various neuropathic pain conditions. Recent psychophysical studies in which symptoms and signs are more accurately assessed indicate that these compounds act as antihyperalgesic agents rather than as simple analgesics. They also show that the sensitivity to these drugs is not affected by the aetiology of pain and the peripheral or central location of the nerve lesion. These data emphasize the role of peripheral and central sodium channels in neuropathic pain. Studies using more selective sodium channel blockers are required to gain further insight into the role of the various subtypes of sodium channel in these pain conditions.

***Perspective:** Pharmacological challenge using sodium channel blockers is the best way to translate basic research on sodium channels in human neuropathic pain. To date, the role of sodium channels in neuropathic pain symptoms/signs is mostly documented for mechanical static and dynamic allodynia, and either peripheral or central sodium channels may be involved.*

***Key words:** Sodium channels, systemic lidocaine, topical lidocaine, antiepileptics, pharmacologic studies.*

A number of experimental studies in animals have suggested that voltage-gated sodium channels may play a crucial role in neuropathic pain. Abnormal accumulation and spatial redistribution of sodium channels have been evidenced after peripheral nerve injury in animals, particularly in the dorsal root ganglia, and may be responsible for spontaneous and/or evoked ectopic neuronal discharges that are a hallmark of injured nerves, and the resulting abnormal nociceptive behavior.[19] Both abnormal nociceptive behavior and ectopic neuronal discharges are reduced by the administration of sodium channel antagonists at plasma concentrations that do not block afferent conduction.[1,14,15,20,45,55] Recently, 9 subtypes of sodium channels classified into tetrodotoxin (TTX)-sensitive or TTX-resistant channels (the latter being preferentially expressed in nociceptors) have been identified in the nervous system: some of these channels may be particularly involved in neuropathic pain.[7,18,31,53]

Unfortunately, it is still difficult to translate the pathophysiological mechanisms identified in animal studies to the clinic.[10,29] Several questions regarding the role of sodium channels in neuropathic pain must therefore be addressed primarily in the clinical setting. Electrophysiologic recordings of ectopic discharges can help to assess the direct relationship between ectopic neuronal discharges, which are considered to be highly dependent on abnormal accumulation of sodium channels,[19] and neuropathic pain. However, the information provided by

Address reprint requests to Nadine Attal, MD, PhD, INSERM E -332, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré 9, avenue Charles de Gaulle, 92 100 Boulogne-Billancourt, France. E-mail: nadine.attal@apr.ap-hop-paris.fr

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these experiments is based essentially on healthy volunteers (see references in Attal and Bouhassira[3]) and concerns very few patients.[3,9,13,39]

In our view, pharmacologic challenge using sodium channel blockers, despite providing only indirect information, is the best way to investigate the role of sodium channels in neuropathic pain.[29] Based on their mode of action and their different molecular targets, pharmacologic drugs may help to determine whether a particular symptom in humans is modulated by a specific pharmacologic agent. It is possible to compare different agents, but also to use different modes of administration of the same agent (for instance topical, systemic administration) in order to gain insight into the site of action of the drugs. However, none of the sodium channel blockers now clinically available targets specific populations of sodium channels and selective sodium channel blockers have not been released. Therefore, it is still impossible to determine which specific type of sodium channel is associated with neuropathic pain symptoms in humans. Furthermore, most of the available compounds are not "pure" sodium channels antagonists and also act on additional targets.[2,21,44] Despite these caveats, pharmacologic studies have provided relevant information with regard to the role of sodium channels in human neuropathic pain. These studies have shown in particular that sodium channel blockers act as antihyperalgesic effects rather than as simple analgesics and that their effect is not impacted by the peripheral or central location of the injury. Thus, a large variety of drugs producing a use-dependent blockade of voltage-gated sodium channels,[7,12,18,47,52] such as some antiepileptics (particularly carbamazepine, oxcarbazepine, phenytoin, and lamotrigine) and local anesthetics and their derivatives (topical or systemic lidocaine and to a lesser extent mexiletine) have been shown to be effective against neuropathic pain.[22,27,33,40,42] This effect does not seem to depend primarily on the aetiology of pain, as controlled studies have found no significant difference in the response to sodium channel blockers between neuropathic pains of different etiologies.[22,42] Recent trials in which pain symptoms and signs were more accurately assessed, particularly through the use of quantitative sensory testing, have provided a more precise analysis of the relationship between sodium channels and particular neuropathic pain symptoms in humans (ongoing pain, paroxysmal pain, mechanical and thermal allodynia and hyperalgesia).[4,5, 6, 26,27,48,49,50,51]

Sodium Channels and Ongoing Neuropathic Pain

Althouth sodium channel blockers have been shown to be effective against spontaneous ongoing pain in most studies, they may have distinct effects in different patients. For example, we recently showed that systemic lidocaine was more effective against ongoing pain due to peripheral nerve lesions (postherpetic neuralgia and nerve trauma) in patients presenting concomitant mechanical allodynia than in patients with "pure" spontaneous pain without allodynia.[5] Previous studies of local lidocaine blockade in postherpetic neuralgia[25] and of the antiepileptic drug lamotrigine in spinal cord injury[26] also reported differences in the effects of these drugs on spontaneous pain depending on the presence or absence of mechanical allodynia (but see Finnerup et al[27]). These data suggest that sodium channels are involved preferentially in some, but not all, types of ongoing neuropathic pain or that different subtypes of sodium channels are involved in these conditions. Clinically, these results suggest that patients presenting spontaneous pain combined with allodynia are good candidates for treatments with the currently available sodium channel blockers. However, further studies of larger samples of patients are required to confirm these data.

Sodium Channels and Pain Paroxysms

Carbamazepine and oxcarbazepine are well known to be particularly effective against spontaneous and evoked pain paroxysms in trigeminal neuralgia.[43] Carbamazepine and phenytoin may also reduce paroxysmal pain associated with other types of nerve lesions,[46] although only 1 controlled trial of intravenous phenytoin has confirmed this observation in patients with various types of neuropathic pain.[35] Similarly, systemic or topical local anesthetics appear to alleviate paroxysmal pain, as suggested for tocainide and intravenous lidocaine in trigeminal neuralgia,[43] for EMLA® anesthetic cream in postherpetic neuralgia.[6] These data suggest that voltage-gated sodium channels are involved in pain paroxysms due to various types of nerve lesions.

More contrasting data have been obtained with the antiepileptic drug lamotrigine, possibly due to the different actions of the drug on sodium channels. Lamotrigine was shown to be moderately effective against pain paroxysms in trigeminal neuralgia in a placebo-controlled cross-over trial in 14 patients. However, the effects of the drug were significant only during the first treatment period due to a major placebo effect or carryover effect in the second period.[56] In another placebo-controlled study performed in a large sample of patients with various types of neuropathic pain, the drug was found to have no effect on paroxysmal pain.[36]

Sodium Channels and Mechanical Allodynia and Hyperalgesia

Psychophysical studies have demonstrated that systemic lidocaine alleviates dynamic mechanical (ie, brush-induced) allodynia due to both peripheral or central nerve lesions.[4,5,8,33,50] Effects on brush-induced allodynia due to peripheral nerve lesions have also been reported with the oral analog mexiletine,[49] with local anesthetic blockade or lidocaine patches[37,41] and with intravenous phenytoin.[35] Intravenous lidocaine treatment has also been reported to alleviate static punctate mechanical allodynia and hyperalgesia (induced by von Frey filaments) due to peripheral or central lesions (Figs 1, 2).[4,5] Mechanical allodynia and hyperalgesia appear to