Sodium channels and nociception – the effects of local anesthetics

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Abstract

Background and Purpose: *Pain is an unpleasant warning sensation of imminent damage of the tissue or organ, and is a very frequent reason for patients to seek the physician's help. The aim of this paper is to give an overview on the role of voltage gated sodium channels in nociception and to highlight the mechanisms of the action of local anesthetics in inhibiting conduction of ion currents, thus affecting the sense of pain.*

Materials and Methods: *A comprehensive search of the literature with key words: voltage gated sodium channels (VGSC), nociception, local anesthetics, α, β- subunit isoforms in Medline was conducted.*

Results: *VGSC isoforms Nav1.7, Nav1.8, Nav1.9 are highly expressed in nociceptive neurons and associated with neuropathic pain syndrome. Human studies demonstrated that point mutations of these isoforms, particularly Nav1.7 underlie insensitivity or hypersensitivity to pain. The sodium channel blockers are anesthetics of choice for local analgesia and anesthesia. However, currently available drugs are not considered selective enough and have relatively narrow therapeutic windows, which can limit their usefulness. Isoform – selective pharmacological blockers or gene therapy approaches targeted at down-regulating specific isoforms could show increased therapeutic efficacy for treating pain.*

Conclusions: *Due to restrictive appearance of isoforms Nav1.7 and Nav1.8 in nociceptive neurons, drugs targeting these isoforms would be of great interest, especially in treatment of neuropathic pain syndrome.*

Pain is an unpleasant warning sensation of imminent damage of the tissue or organ, and is a very frequent reason for patients seeking the physician's help.

Peripheral neurons – nociceptors relay information about noxious stimuli in the periphery to the central nervous system. Activation of both central and peripheral neurons contributes to increased sense of pain. Nociception and altered pain sensitivity occurs due to changing of the activity of ion channels, mainly voltage-gated sodium channels *(1)*. These channels are crucial in clinically relevant analgesics, such as lidocaine *(1)*.

Sodium channels are composed of α-subunit, the primary functional unit of voltage-gated sodium channel, which could be associated with four different β-subunits (β1, β2, β3 and β4)–*(2,3)*. It is likely that β-subunits play a role in stabilization of the α-subunits in the mem-

brane and/or localization of the α-subunits to specific membrane domains *(3)*. In addition several other accessory proteins such as calmodulin *(4)* or annexin II *(5)* that have been identified may be important modulators of voltage-gated sodium channels.

Nine distinct voltage-gated sodium channel α-subunits (Nav1.1-1.9) have been cloned from mammals *(6)*. The predominant sodium channel isoforms in nociceptive neurons are Nav1.7, Nav1.8, and Nav1.9. *(7)*. Additionally, Nav1.1, Nav1.3, and Nav1.6, are the very important voltage-gated sodium channels expressed in peripheral sensory neurons *(1)*. The role of Nav1.3 channels in pain is controversial. Nav1.3 is expressed in developing neurons, and down-regulated in mature neurons *(8)*, but are re-expressed in a condition of neuropathic pain and inflammation *(9)*, contributing to the overall sodium current and the neuronal hyperexcitability observed in dorsal root ganglion (DRG) sensory neurons following nerve injury or inflammation. Nav1.6 is the predominant voltage-gated sodium channel located in the nodes of Ranvier in both peripheral and central nervous system myelinated neurons *(10)*, The role of Nav1.6, if any, in nociception and pain sensations is not clear. Similarly, Nav1.1, although it is expressed in central and peripheral neurons, has no clear place in nociception.

Several recent studies have demonstrated that complete loss of function of one specific voltage gated sodium channel, which expresses Nav1.7 isoform, results in complete insensitivity to pain *(11, 12)*. On the other hand, subtle, but significant changes in gating properties of sodium channels caused by point mutations of Nav1.7, can result in increased pain sensations and contribute to the development of chronic pain syndrome, such as the familiar painful inherited neuropathy, inherited erythromelalgia *(13, 14)*. At least 9 distinct point mutations in SCN9A altering the amino acid sequence of Nav1.7 channels *(13, 14)*. Mutations in the Nav1.7 channels are identified cause significant hyperpolarizing shifts in the channel V1/2 of activation as well as larger ramp currents *(13, 15)*. Other Nav1.7 point mutations underlie a second autosomal dominant chronic pain disorder, paroxysmal extreme pain disorder (PEPD), characterized by severe burning rectal, ocular and submandibular pain sensation *(16)*.

Another isoform of voltage-gated sodium channels, Nav1.8, is almost exclusively expressed in nociceptive neurons, and is important in normal pain function. Nav1.8 is a tetrodotoxin resistant (TTX-R) sodium channel and is highly expressed in small-diameter sensory neurons. Nav1.8 plays a role in inflammatory pain and the onset of neuropathic pain *(1)*. Nav1.8 also plays a role in hyperexcitability in inherited erythromelalgia, together with Nav1.7 isoform *(1)*. More than 50% of C fibers and 10% of A fibers express Nav1.8 channels. The expression and biophysical properties of Nav1.8 channels can be modulated by ongoing nociceptive input *(17)*. Because of the exclusive expression of Nav1.8, a selective Nav1.8 channel inhibitor would be useful in treating inflammatory pain and should be able to provide solid data on the role

of Nav1.8 in human neuropathic pain (CUMMINS 2007). Studies on transgenic mice indicate the Nav1.9 channel, along with Nav1.7 and Nav1.8, may be an important contributor to inflammatory pain, but may not be crucial to neuropathic pain associated with nerve injury *(17, 18)*. The modulation of a tetrodotoxin (TTX) – resistant voltage-gated sodium current (such as via Nav1.8) may underlie inflammation-induced sensitization of nociception of high-threshold primary afferent neurons *(19)*. Modulation of TTX-R currents is an endogenous mechanism used to control neuronal excitability, and therapeutic intervention blocking that current could be effective in treatment of hyperalgesia and pain *(19)*. For example, a study by Gold *et al.* showed that u-opioid receptor agonist blocked PGE2-induced modulation of the current. Furthermore, because of the restricted distribution of TTX-R Na1 currents and the observation that a decrease in the expression of these currents has little impact on low threshold mechanical transduction, targeting these currents may lead to the development of a pharmacotherapy for the treatment of hyperalgesia with fewer side effects than currently available drugs *(19)*.

Several different types of sodium channel isoforms are preferentially expressed in the peripheral sensory neurons, and some of them can be regulated by inflammation or axonal injury *(1)*. For example, Nav1.7 are up-regulated in chronic inflammation *(20, 21)*, suggesting their role in increased pain sensations associated with inflammation. It is known that calmodulin (CaM) can modulate Nav1.4 (skeletal muscle) and Nav1.6 (neuronal) current amplitudes and properties (4). However, a (new) recent study demonstrated that inhibition of sodium current caused by the CaM inhibitor triflouperazine (TFP) is largely independent of the inhibition of CaM interaction with Nav subunit of voltage gated sodium channels, but can be attributed to direct interaction of the drug with the sodium channels in a state-dependent manner. The ability of TFP to block Nav1.7 at low doses could make it a potential therapeutic regimen for regional anesthesia and pain management that would be more potent than traditional local anesthetics *(7)*.

The almost exclusive expression patterns of the voltage – gated sodium channels that are associated with pain makes them very attractive targets for the development of novel analgesics. Sodium channels are subject to extensive modulation in various pathophysiological conditions, such as inflammation or nerve injury as well as pharmacologically induced by drugs. For example, tetrodotoxin (TTX) can block these channels with a high degree of selectivity. TTX and other toxins were invaluable tools in uncovering the functional properties of sodium channels and their roles in electro-excitability. Other substances that interact with sodium channels, such as local anesthetics (LA), class I antiarrhythmic drugs and anticonvulsants, are now commonly used to treat pain, epilepsy, ataxias and other pathophysiological conditions *(22, 23)*. LAs are very effective in preventing the sense of nociception, by blocking sodium currents through voltage-gated sodium channels, thus inhibiting the conduc-

tion of action potentials in excitable tissues, specifically neural tissues. The most commonly used drugs are: bupivacaine, levobupivacaine, ropivacaine and lidocaine *(24)*. Binding of LAs to inactivated Na+-channels at the binding sites inside sodium channels *(25),* inactivates it and prevents the influx of sodium intracellularly. In this way the spreading of a depolarization wave throughout the cell membrane is suppressed *(26)*. LAs are known to produce hyperpolarizing shifts in steady-state inactivation and use-dependent inhibition of sodium currents by binding to a receptor site on the ion channel *(27, 28)*.

It is interesting to note that several phenothiazine neuroleptics structurally related to TFP can also block-sodium currents in a use-dependent manner *(29, 31)*. These studies and a study by Sheets *et al.* *(7)* demonstrating that TFP causes hyperpolarizing shifts in steady-state inactivation, exhibiting a higher apparent affinity for inactivated channels and exhibiting a concentration independent recovery from inhibition indicates that TFP might interact directly with Nav1.7 and Nav1.4 through the LA binding site. Observation that the nerve block by TFP is more potent than lidocaine *(7)* suggests that TFP or TFP analogues might be useful for inducing prolonged nerve block.

Apart from the treatment of neuropathic pain, LAs are clearly useful in many clinical situations for the treatment of pain. Typical LAs (such as lidocaine and carbamazepine) inhibit voltage-gated sodium currents, producing both tonic and phasic (use-dependent) block of sodium currents that often involves negative shifts in the voltage-dependence of steady-state inactivation, indicative of enhanced binding to inactivated channels. Although these drugs are very useful clinically, they do not always show high specificity for sodium channels over other types of ion channels, and in general there are only subtle differences in their effects on the different sodium channel isoforms. Recent studies on peripheral neuronal isoforms indicate Nav1.8 may differ in its sensitivity to some of these compounds. Cardenas *et al.* *(32)* reported that the interaction between carbamazepine and Nav1.8--like currents in DRG neurons was slower than the interaction between TTX-sensitive channels and carbamazepine. Interestingly, it has been proposed that the novel small molecule inhibitor of Nav1.8, A-803467 *(17)* may bind at a distinct site from the local anesthetic binding site.

Although anesthetics of choice for local analgesia and anesthesia, the sodium channel blockers currently available are not considered sufficiently selective and have relatively narrow therapeutic windows, which can limit their usefulness. Isoform – selective pharmacological blockers or gene therapy approaches targeted at down-regulating specific isoforms could show increased therapeutic efficacy for treating pain. In treatment of human neuropathic pain syndrome, drugs targeting Nav1.7 and Nav1.8 would be of the greatest interest, due to the restrictive appearance of these isoforms in nociceptive neurons.

REFERENCES

1. CUMMINS T R, SHEETS P L, WAXMAN S G 2007 The roles of sodium channels in nociception: implications for mechanisms of pain. *Pain 131(3):* 243–257.

2. SHAH B S, STEVENS E B, GONZALEZ M I, BRAMWELL S, PINNOCK R D, LEE K, DIXON A K 2000 Beta3, a novel auxiliary subunit for the voltage-gated sodium channel, is expressed preferentially in sensory neurons and is upregulated in the chronic constriction injury model of neuropathic pain. *Eur J Neurosci 12:* 3985–3990

3. ISOM L L 2001 Sodium channel beta subunits: anything but auxiliary. *Neuroscientist 7:* 42–54

4. HERZOG R I, LIU C, WAXMAN S G, CUMMINS T R 2003 Calmodulin binds to the C terminus of sodium channels Nav1.4 and Nav1.6 and differentially modulates their functional properties. *J Neurosci 23:* 8261–8270

5. OKUSE K, MALIK-HALL M, BAKER M D, POON W Y, KONG H, CHAO M V, WOOD J N 2002 Annexin II light chain regulates sensory neuron-specific sodium channel expression. *Nature 417:* 653–656

6. GOLDIN A L, BARCHI R L, CALDWELL J H, HOFMANN F, HOWE J R, HUNTER J C, KALLEN R G, MANDEL G, MEISLER M H, NETTER Y B, NODA M, TAMKUN M M, WAXMAN S G, WOOD J N, CATTERALL W A 2000 Nomenclature of voltage-gated sodium channels. *Neuron 28:* 365–368

7. SHEETS P L, GERNER J P, WANG C-F, WANG S-Y, WAND G-K, CUMMINS T R 2006 Inhibition of Nav1.7 and Nav1.4 Sodium Channels by Trifluoperazine Involves the Local Anesthetic Receptor. *J Neurophysiol 96:* 1848–1859

8. BECKH S, NODA M, LUBBERT H, NUMA S 1989. Differential regulation of three sodium channel messenger RNAs in the rat central nervous system during development. *EMBO J 8:* 3611–3616

9. BLACK J A, CUMMINS T R, PLUMPTON C, CHEN Y H, HORMUZDIAR W, CLARE J J, WAXMANN S G 1999. Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. *J Neurophysiol 82:* 2776–2785

10. CALDWELL J H, SCHALLER K L, LASHER R S, PELES E, LEVINSON S R 2000 Sodium channel Na(v)1.6 is localized at nodes of ranvier, dendrites, and synapses. *Proc Natl Acad Sci USA 97:* 5616–5620

11. COX J J, REIMANN F, NICHOLAS A K, THORTON G, ROBERTS E, SPRINGELL K, KARBANI G, JAFRI H, MANNAN J, RAASHID Y, AL-GAZALI L, HAMAMY H, VALENTE E M, GORMAN S, WILLIAMS R, McHALE D P, WOOD J N, GRIBLLE F M, WOODS C G 2006 An SCN9A channelopathy causes congenital inability to experience pain. *Nature 444:* 894–898

12. GODLBERG Y, MACFARLANE J, MACDONALD M, THOMPSON J, DUBE M P, MATTICE M, FRASER R, YOUNG C, HOSSAIN S, PAPE T, PAYNE B, RADOMSKI C, DONALDSON G, IVES E, COX J, YOUNGHUSBAND H, GREEN R, DUFF A, BOLTSHAUSER E, GRINSPAN G, DIMON J, SIBLEY B, ANDRIA G, TOSCANO E, KERDRAON J, BOWSHER D, PIMSTONE S, SAMUELS M, SHERRINGTON R, HAYDEN M 2007 Loss-of-function mutations in the Na(v)1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet 71:* 311–319.

13. YANG Y, WANG Y, LI S, XU Z, LI H, MA L, FAN J, BU D, LIU B, FAN Z, WU G, JIN J, DING B, ZHU X, SHEN Y 2004 Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genet 41:* 171–174

14. LEE M J, YU H S, HSIEH S T, STEPHENSON D A, LU C J, YANG C C 2007 Characterization of a familial case with primary erythromelalgia from Taiwan. *J Neurol 254:* 210–214

15. CUMMINS T R, DIB-HAJJ S D, WAXMANN S G 2004 Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. *J Neurosci 24:* 8232–823

16. FERTLEMAN C R, BAKER M D, PARKER K A, MOFFATT S, ELMSLIE F V, ABRAHAMSEN B, OSTMAN J, KLUNGBAUER N, WOOD J N, GARDINER R M, REES M 2006 SCN9 A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron 52:* 767–774

17. JARVIS M F *et al.* 2007 A-803467, a potent and selective Nav 1.8 sodium channel blocker,, attenuates neuropathic and inflammatory pain in the rat. *PNAS 104:* 8520–8525

18. PRIEST B T, MURPHY B A, LINDIA J A, DIAZ C, ABBADIE C, RITTER A M, LIBERATOR P, IYER L M, KASH S F, KOHLER M G, KACZOROWSKI G J, MACINTYRE D E, MARTIN W J 2005 Contribution of the tetrodotoxin-resistant voltage-gated sodium channel NaV1.9 to sensory transmission and nociceptive behavior. *PNAS 102:* 9382–9387

19. GOLD M S 1999 Tetrodotoxin-resistant Na1 currents and inflammatory hyperalgesia. *PNAS 96:* 7645–7649

20. TANAKA M, CUMMINS T R, ISHIKAWA K, DIB-HAJJ S D, BLACK J A, WAXMAN S G 1998 SNS Na+ channel expression increases in dorsal root ganglion neurons in the carrageenan inflammatory pain model. *Neuroreport 9:* 967–972

21. BLACK J A, LIU S, TANAKA M, CUMMINS T R, WAXMAN S G 2004 Changes in the expression of tetrodotoxininsensitive sodium channels within dorsal root ganglia neurons in inflammatory pain. *Pain 108:* 237–247

22. RAGSDALE D S, AVOLI M 1998. Sodium channels as molecular targets for antiepileptic drugs. *Brain Res Rev 26:* 16–28

23. CLARE J J, TATE S N, NOBBS M, ROMANOS M A 2000 Voltage-gated sodium channels as therapeutic targets. *Drug Discov Today 5:* 506–520

24. MORRISON S G, DOMINGUEZ J J, FRASCAROLLO P, REIZ S 2000 A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine and ropivacaine in anesthetized swine. *Anesth 90:* 1308–14

25. LI R A, ENNIS I L, TOMASELLI G F, MARBAN E 2002 Structural basis of differences in isoform-specific gating and lidocaine block between cardiac and skeletal muscle sodium channels. *Mol Pharmacol 60:* 136–141

26. HILLE B 2001 Classical mechanisms of block. *In:* Ion Channels of Excitable Membranes. Sinauer Associate Inc., Sunderland, MA, p 503–536

27. BEAN B P, COHEN C J, TSIEN R W 1983 Lidocaine block of cardiac sodium channels. *J Gen Physiol 81:* 613–642

28. HILLE B 1977 Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. *J Gen Physiol* 69: 497–515

29. AHMMED G U, HISATOME I, KURATA Y, MAKITA N, TANA-KA Y, TANAKA H, OKAMURA T, SONOYAMA K, FURUSE Y, KATO M, YAMAMOTO Y, OGURA K, SHIMOYAMA M, MIAKE J, SASAKI N, OGINO K, IGAWA O, YOSHIDA A, SHIGEMASA C 2002 Analysis of moricizine block of sodium current in isolated guinea-pig atrial myocytes. Atrioventricular difference of moricizine block. *Vascul Pharmacol 38:* 131–141

30. BOLOTINA V, COURTNEY K R, KHODOROV B 1992 Gate-dependent blockade of sodium channels by phenothiazine derivatives: structure-activity relationships. *Mol Pharmacol 42:* 423–431

31. LIU W, CLARKSON C W, YAMASAKI S, CHANG C, STOLFI A, PICKOFF A S 1992 Characterization of the rate-dependent effects of ethmozine on conduction, *in vivo,* and on the sodium current, in vitro, in the newborn heart. *J Pharmacol Exp Ther 263:* 608–616

32. CARDENAS C A, CARDENAS C G, de ARMENDI A J, SCROGGS R S 2006 Carbamazepine interacts with a slow inactivation state of NaV1.8-like sodium channels. *Neurosci Lett 408:* 129–134