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Time for new local anaesthetics?

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The aim of this lecture is to answer the question whether there is a need - or the possibility - to develop new local anaesthetics. We suggest any development should be performed for one of three distinct aims:

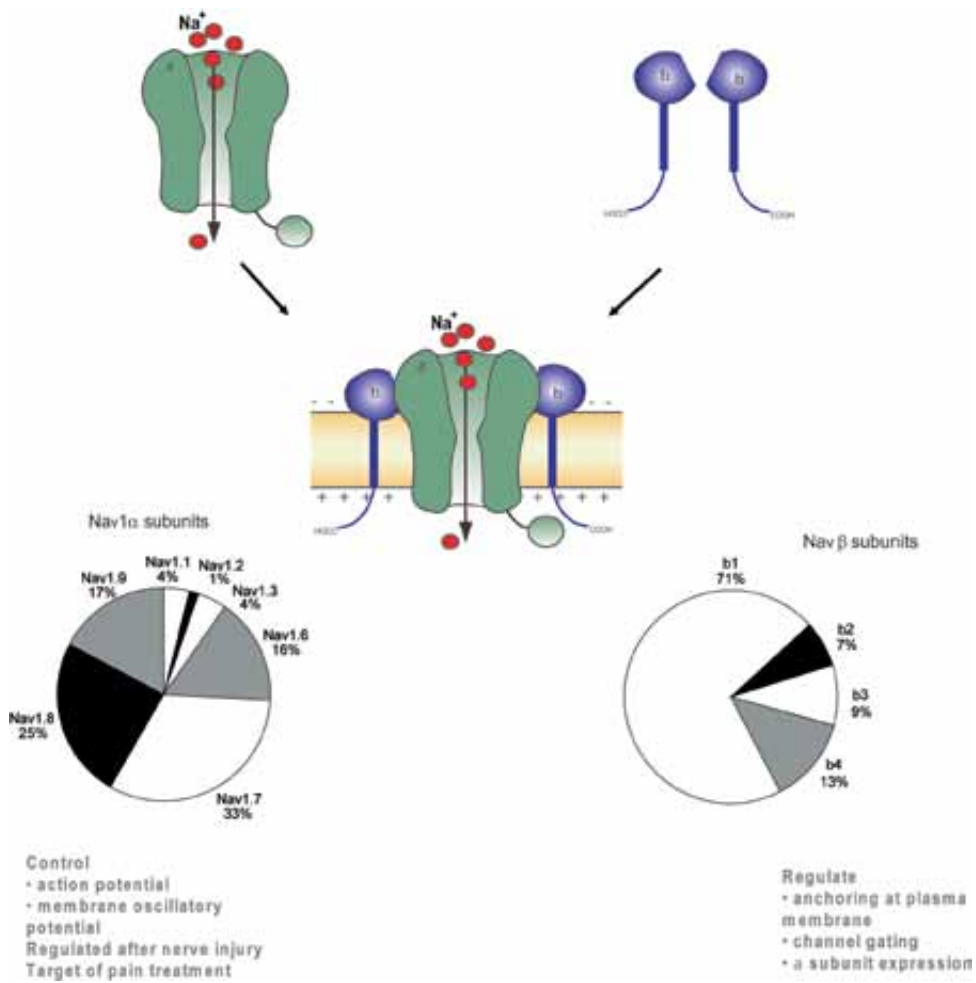
- Peri-operative regional anaesthesia (the patient requires a pain free state (sensory loss) with or without muscular blockade)
- 'Interventional' regional analgesia for acute postoperative pain management (the patient requires a pain free state in the postoperative setting)
- Chronic pain treatment (for pain alleviation, but without alteration of nociception).

The discussion will focus on the new discoveries about voltage-gated sodium channels (VGSCs). These channels are essential for action potential generation and propagation and are the principal pharmacological target of local anaesthetics. During the last 15 years we have learned a lot about the molecular and biophysical functioning of VGSCs that offer future perspectives to manipulate pain sensitivity.

Voltage-gated sodium channels

VGSCs are heteromeric protein complexes consisting of one large Nav1 alpha-subunit and auxiliary beta-subunits. The Nav1 alpha-subunit is the pore forming functional unit, allowing influx of sodium. Nav1 subunits belong to the super-family of voltage-gated ion channel protein and 10 mammalian different isoforms have been reported so far (Nav1.1 to Nav1.9 and Nav) [1]. Table 1 summarises where these different isoforms are expressed and related 'channelopathies'. The identification of Nav1 subunits expressed only in sensory tissues (Nav1.8, Nav1.9, and to some extent Nav1.7) provide a molecular substrate for new specific sensory blockers. On the other hand, sodium channel blockers such as local anaesthetics do not demonstrate targeting of specific isoforms, explaining cardiac and central nervous system toxicities. The auxiliary beta subunits contribute to the anchoring of the channel complex at the plasma membrane, modulate channel gating and participate in adhesion, migration and transcription [2]. Primary sensory neurons, in particular nociceptive neurons, express five tetrodotoxin (TTX)-sensitive Nav1 alpha isoforms (Nav1.7 >> Nav1.6 >> Nav1.1, Nav1.2 and Nav1.3), two sensory neuron-specific TTX-resistant isoforms (Nav1.8 and Nav1.9), and all four beta subunits (Figure 1).

Figure 1



Schematic representation of the alpha and beta subunit of the VGSC complex.

Table 1

Diversities and properties of VGSC subunits

DRG: dorsal root ganglia; PNS: peripheral nervous system; CNS: central nervous system; +++ abundant; + present; - no expression

Adapted from Brackenbury & Isom [2] and Cannon [1].

Subunit	Major tissue locations	Expression in sensory neurons	Disease
Nav1.1	CNS, PNS, heart	+++	Epilepsies Familial hemiplegic migraine Familial autism (?)
Nav1.2	CNS, PNS	+	Epilepsies Familial autism (?)
Nav1.3	CNS Spinal cord and DRG (during development and augmented after nerve injury)	+	
Nav1.4	Skeletal muscle	-	Myotonia, paramyotonia Periodic paralysis Congenital myasthenic syndrome
Nav1.5	Heart, CNS	-	Long QT syndrome, Brugada syndrome Sick sinus syndrome Dilated cardiomyopathy Sudden infant death syndrome
Nav1.6	CNS, PNS, heart, glia, Ranvier nodes	+++	Cerebellar atrophy, ataxia, mental retardation
Nav1.7	PNS, DRG, sympathetic ganglia, Schwann cells	+++	Erythralgia Paroxysmal extreme pain disorder Congenital indifference to pain
Nav1.8	DRG neurons	+++	
Nav1.9	DRG neurons	+++	
Beta1	CNS, PNS, heart, skeletal muscle, adrenal gland	+++	Epilepsies Cardiac block Brugada syndrome
Beta2	CNS, PNS, heart	+	
Beta3	CNS, PNS, adrenal gland, skeletal muscle, kidney	+	
Beta4	CNS, PNS, heart, skeletal muscle	+++	Long QT syndrome (?)

Mutation of VGSC and pain sensitivity

Three families from northern Pakistan were reported to be completely unable to experience pain. After mapping their genome, the authors pointed to a mutation of the gene coding for Nav1.7, which is strongly expressed in nociceptive neurons. This mutation causes a loss of function of Nav1.7 isoform, suggesting Nav1.7 is a crucial requirement for nociception in humans [3]. Conversely, several mutations of Nav1.7 have been linked with primary erythromelalgia or paroxysmal extreme pain disorder [4, 5].

Pain

Pain is defined by the International Association for the Study of Pain (IASP) as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’. It is important to point out that pain is highly subjective to the individual experience, as Margo McCaffery (a pioneer in the field of pain management nursing) defined it: ‘Pain is whatever the experiencing person says it is, existing whenever he says it does’. Nevertheless, pain is based on physiological mechanisms that can be studied, and then, to a certain extent, alleviated.

The modern approach to pain management, based on physiological and pathological mechanisms, proposes four different categories of pain (Table 2). Nociception (that is, the neural processes of encoding and processing noxious stimuli) is a normal process associated with the activation of nociceptive neurons (a highly specialised neuron that is capable of transducing and encoding noxious stimuli) [6]. Nociception is referred to as the physiological alarm system for detection of stimuli which are potentially damaging to normal tissues and is indispensable for the survival of the organism. Mechanical, thermal or chemical noxious stimuli are detected by specific nociceptors such as the transient receptor potential V1 (TRPV1). This channel is either activated by capsaicin (the pungent ingredient of chili pepper) or heat above 43°C. It is expressed only in small-fibre nociceptive neurons and its activation will lead to the entry of calcium in to the nerve fibre terminal. If this current is sufficient, it will open VGSCs and initiate an action potential. The action potentials are conducted along axons to the central terminal of the nociceptor in the dorsal horn of the spinal cord, and the input from the periphery is transmitted via synaptic transmission to the secondary order neurons of the central nervous system. After its penetration through the cell membrane, local anaesthetics interfere with the pore of VGSCs, maintaining it in a state where the sodium influx is impaired, thus blocking the action potential. Local anaesthetics will not selectively block sensory nerves since the expression of multiple Nav1 subunit is present on all sensory fibres (including neurons encoding touch and proprioception) and motor fibres. Anaesthesiologists are used to managing motor and sensory blockade by adjustment of the concentration of the local anaesthetic solution.

Table 2

Pain definitions

Adapted from Loeser et al [6], Woolf [18], and The International Association for the Study of Pain (www.iasp-pain.org).

Pain – an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage
<p>Nociception - the neural processes of encoding and processing noxious stimuli</p> <ul style="list-style-type: none"> • Noxious stimuli: an actually or potentially tissue damaging event • Nociceptor: a sensory receptor that is capable of transducing and encoding noxious stimuli • Nociceptive neuron: a peripheral or central neuron that is capable of encoding noxious stimuli
Inflammatory pain - spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation (previously described as excess of nociception). For example acute postoperative pain, arthritis, etc
Neuropathic pain - pain arising as a direct consequence of a lesion or disease affecting the somatosensory system spontaneous. For example, radiculopathy, post herpetic neuralgia, phantom pain, etc
Dysfunctional pain - hypersensitivity to pain resulting from abnormal central processing of normal input. For example, irritable bowel syndrome, fibromyalgia, etc

In inflammatory pain, neuropathic pain and dysfunctional pain, several mechanisms occur in the nervous system that lead to a peripheral and central sensitisation. Taken together, these mechanisms form the pathological substrate that pushes the pain system toward hyperexcitability and drives pain symptoms.

The role of VGSCs is of particular interest in the context of neuropathic pain. Neuropathic pain is a very disabling disorder, manifesting as spontaneous pain, and the sensitivity to external stimuli is generally augmented in the territory of the non-injured nerves,

with the presence of allodynia and hyperalgesia. Pain treatment is currently unsuccessful in 50-70% of patients and the persistence of pain is the drive for an emotional state of suffering, mood disorders and alteration of cognitive functions leading to significant socio-economical consequences.

Several different experimental models share striking similarities to symptoms described in human allodynia and hyperalgesia-like behaviour, and have already provided information on the underlying mechanisms of neuropathic pain. We will discuss with three examples of activity-dependant mechanisms how VGSCs contribute to an abnormal drive from the periphery that leads to consequences in the central nervous system:

Dysregulation of the VGSC and hyperexcitability

After nerve injury, abnormal accumulations of sodium channels have been observed at the tips of the injured axons as well as modulation of VGSC subunit expression and trafficking in primary sensory neurons [7-9]. Furthermore, Nav1 subunits and currents are modulated by peripheral nerve injury, in the injured nerves, but also in the adjacent non-injured nerves [10]. Nav1 pore-forming channels can be stabilised by the auxiliary beta subunits; in particular the beta2 subunit modulates channel assembly and cell-surface expression where the sodium channel complex is functional. The role of these subunits is not fully understood, but we demonstrated a relationship between the increase and abnormal trafficking of the beta2 subunits and pain symptoms [11]. VGSCs and their auxiliary subunits are probably important for regulating the excitability of the nervous system - thus targeting channel trafficking may provide a promising treatment against neuropathic pain, without affecting normal pain sensitivity.

Activity dependent changes: cell death

The peripheral activity due to injury causes cell death by apoptosis of dorsal horn neurons. In animal models, this loss of more than 20% of GABAergic interneurons leads to a marked decrease in inhibitory postsynaptic currents. This loss of inhibition in the spinal cord is thought to be responsible for the increase of pain [12]. Caspase (cysteinyI-aspartate-cleaving proteases) inhibitor prevents – by impairing apoptosis - the loss of GABAergic interneurons and the reduction of inhibitory currents. Moreover, when a peripheral nerve block with bupivacaine microspheres was applied, the same effect was observed on cell death. Unfortunately, once the block wore off, the abnormal input is restored and the apoptotic process restarts. Taken together these results suggest: that a peripheral nerve block can prevent cell death of central neurons; disinhibition is dependant from an abnormal drive of the peripheral nerve; and a short blockade of peripheral activity (a few days) is not enough and should be combined with other approaches.

Activity dependent changes: spinal microglia

Recent evidence indicates that not only do neurons but also the glia is involved in the generation and maintenance of neuropathic pain. In particular, p38 mitogen-activated protein kinase in spinal microglia contributes to the development of neuropathic pain. The phosphorylation of p38, leading to its activation, occurs in the spinal microglia and not in the other cell types (neurons, astrocytes, oligodendrocytes). The same approach using a peripheral nerve block demonstrates that p38 activation was abolished during the period of the block, and confirms that p38 activation depends on the abnormal peripheral activity.

Future

The ideal properties of new local anaesthetics/sodium channel blockers are listed in Table 3. Three different purposes are distinguished (pre-operative regional anaesthesia, postoperative regional analgesia, and chronic pain management) and each condition has its own requirements. Liposomes or degradable polymers might facilitate the modulation of action duration, but the more challenging issues remain the specificity of channel isoform targeted by the blocker, and the physiopathological mechanisms involved (for instance, channel turnover can be considered as an alternative for chronic pain treatment). New local anaesthetics/sodium blockers should be devoid of effect on the Nav1.5 specific cardiac channel (Nav1.5). We believe that some cardiac and CNS toxicity can be accepted in the context of tight surveillance within the hospital, but are not acceptable for long-term treatment. On the other hand, specific blockade of the Nav1.7 would be very interesting for the postoperative phase, but might not be suitable for chronic pain management, since normal nociception is important for the every day life.

Table 3

The ideal properties for a new sodium channel blockers

	Regional anaesthesia	Regional analgesia	Chronic pain
Cardiac toxicity	low	low	abolished
CNS toxicity	low	low	abolished
Sensory function	abolished/preserved	preserved	preserved
Nociception	abolished	abolished/decreased	preserved
Hypersensitivity	abolished	decreased	decreased/abolished
Motor blockade	abolished/preserved		
Onset	fast	indifferent	indifferent
Duration	various and modifiable	long	> 6 h
Delivery	single injection	single injection no catheter ?!	oral

At the moment, Nav1.8 and Nav1.7 channel blockers have been developed and tested in animal studies: A-803467, a potent and selective Nav1.8 blocker or conotoxins were reported to attenuate neuropathic and inflammatory pain in the rat, without motor blockade [13, 14]; and benzazepinones or venom peptide (from the tarantula) are specific Nav1.7 channel blocker, and were reported to be efficacious in rat model of neuropathic pain [15, 16].

A very smart additional development has been suggested by Woolf's and Bean's groups [17]. Using the TRPV1 nociceptor via capsaicine activation, they were able to allow the penetration through the TRPV1 pore of a charged local anaesthetic (QX-314, which does not usually cross the cell membrane). An exclusively pain block was achieved in the sciatic nerve of rats, without motor or tactile alterations.

Conclusion

The discovery of sensory and cardiac VGSC subunits has opened up the possibility of more selective local anaesthetics for regional anaesthesia and analgesia. Targeting peripheral activity by new specific channel blockers or modifying channel turnover may be new therapeutic alternatives and VGSCs are considered as one of the primary targets for drug development for chronic pain syndromes. Similarly, one might consider preventing PNS and CNS alterations by blocking the activity at the periphery in combination with other therapeutics (preventive analgesia).

Key Learning Points

- Voltage-gated sodium channels are the primary target of local anaesthetics.
- Specific sensory and cardiac sodium channel isoforms have been discovered and offer new perspective for selective channel blockers devoid of cardiac and CNS toxicity.
- Nociceptors channels (for example, the capsaicine receptor TRPV1) can be used as a shuttle for local anaesthetics with the goal to impair nociception and preserve other sensory/motor functions.
- Neuropathic pain is sustained by dysfunction of voltage-gated sodium channels and these channels are one of the major targets for new drug development.

References

1. Cannon SC. Pathomechanisms in channelopathies of skeletal muscle and brain. *Annu Rev Neurosci* 2006; 29: 387-415.
2. Brackenbury WJ, Isom LL. Voltage-gated Na⁺ channels: potential for beta subunits as therapeutic targets. *Expert Opin Ther Targets* 2008; 12: 1191-203.
3. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006; 444: 894-8.
4. Sheets PL, Jackson JO, Waxman SG, Dib-Hajj SD, Cummins TR. A Nav1.7 channel mutation associated with hereditary erythromelalgia contributes to neuronal hyperexcitability and displays reduced lidocaine sensitivity. *J Physiol* 2007; 581: 1019-31.
5. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* 2006; 52: 767-74.
6. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. *Pain* 2008; 137: 473-7.
7. Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na⁺ channels. *J Neurophysiol* 1994; 72: 349-59.
8. Decosterd I, Ji RR, Abdi S, Tate S, Woolf CJ. The pattern of expression of the voltage-gated sodium channels Na(v)1.8 and Na(v)1.9 does not change in uninjured primary sensory neurons in experimental neuropathic pain models. *Pain* 2002; 96: 269-77.
9. Gold MS, Weinreich D, Kim CS, et al. Redistribution of Nav1.8 in uninjured axons enables neuropathic pain. *J Neurosci* 2003; 23: 158-66.
10. Berta T, Poirot O, Pertin M, Ji RR, Kellenberger S, Decosterd I. Transcriptional and functional profiles of voltage-gated Na(+) channels in injured and non-injured DRG neurons in the SNI model of neuropathic pain. *Mol Cell Neurosci* 2008; 37: 196-208.
11. Pertin M, Ji RR, Berta T, et al. Upregulation of the voltage-gated sodium channel beta2 subunit in neuropathic pain models: characterization of expression in injured and non-injured primary sensory neurons. *J Neurosci* 2005; 25: 10970-80.
12. Scholz J, Broom DC, Youn DH, et al. Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. *J Neurosci* 2005; 25: 7317-23.
13. Jarvis MF, Honore P, Shieh CC, et al. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc Natl Acad Sci USA* 2007; 104: 8520-5.
14. Ekberg J, Jayamanne A, Vaughan CW, et al. muO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain behavior without motor deficits. *Proc Natl Acad Sci USA* 2006; 103: 17030-5.
15. Hoyt SB, London C, Ok H, et al. Benzazepinone Nav1.7 blockers: potential treatments for neuropathic pain. *Bioorg Med Chem Lett* 2007; 17: 6172-7.
16. Schmalhofer W, Calhoun J, Burrows R, et al. ProTx-II, a selective inhibitor of Nav1.7 sodium channels, blocks action potential propagation in nociceptors. *Mol Pharmacol* 2008; 74: 1476-84.
17. Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature* 2007; 449: 607-10.
18. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004; 140: 441-51