

Sodium channel expression and the molecular pathophysiology of pain after SCI

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Abstract: The chronic pain that develops as a result of spinal cord injury (SCI) is extremely debilitating and remains largely unmanageable by current therapeutic strategies. Voltage-gated sodium channels regulate the biophysical properties, and thus firing characteristics, of neurons. After SCI the repertoire of sodium channels produced by dorsal horn nociceptive neurons is altered, enabling neurons to fire at higher than normal rates in response to unchanged peripheral stimuli as well as to generate spontaneous discharges in the absence of stimuli, resulting in the genesis of neuropathic pain. Our results have shown increased expression of the Nav1.3 sodium channel in the spinal cord and thalamus. Nav1.3 upregulation allows dorsal horn neurons to generate ramp currents, enhanced persistent currents, and shifts in steady-state activation and inactivation. Further downstream, Nav1.3 causes increased spontaneous and evoked firing of neurons in the ventroposterior lateral (VPL) nucleus of the thalamus. Nav1.3 also underlies changes in burst firing properties of VPL neurons. The combination of spinal and thalamic generation and amplification of pain by Nav1.3 dysregulation contributes to post-SCI chronic pain. If proven to be similar in humans, targeting of this system after SCI may offer hope for treatment of clinical pain.

Keywords: spinal cord injury; pain; sodium channels; thalamus; dorsal horn

Introduction

Although less apparent than paralysis, the prevalence of chronic pain disability after spinal cord injury (SCI) is widespread. Sixty to eighty percent of persons who have sustained SCI, regardless of the level or completeness of lesion or of the type of injury, experience clinically significant pain after injury (Finnerup et al., 2001; Siddall et al., 2003). The pain, which can have a pricking, burning, or aching quality (Cairns et al., 1996), can be so severe as to produce a drastic impairment in daily routines and quality of life (Rintala et al., 1998;

Turner et al., 2001), even to a greater extent than the motor impairment (Mariano, 1992; Stormer et al., 1997). Of patients with low thoracic or lumbosacral lesions, 37% are willing to trade the possibility of recovery for pain relief (Nepomuceno et al., 1979).

Nociceptive signals are transmitted through the dorsal horn of the spinal cord. The spinal cord dorsal horn contains the primary synapses through which afferent somatosensory information, related to touch, pressure, brush, temperature, and noxious stimuli, is received from the periphery. Dorsal horn sensory neurons receive this information primarily from the skin, perform a degree of processing, and transmit signals through distinct tracts within the spinal cord to supraspinal structures

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where pain is interpreted and perceived. Within each level of the nervous system including the spinal cord, nociceptive signals are subject to a degree of modulation by circuitry that it passes through.

Experimental SCI induces electrophysiological changes in dorsal horn and thalamic sensory neurons that contribute to pain-like behaviors in animals. These include shifts in proportions of cells responding to evoked noxious stimulation, increases and irregularity in spontaneous background activity, increased evoked activity to (formerly) innocuous and noxious stimuli, increases in after discharge activity following stimulation, and emergence of abnormal burst firing.

Since the nature of the applied stimuli does not change, other mechanisms must account for the alterations in stimulus processing that lead to central pain after SCI. Central changes in expression of molecules such as ion channels, neurotransmitters, and their receptors, contribute to altered sensory processing by changing the electrophysiologic excitability, and therefore output, of spinal sensory neurons. Specific molecular changes in the expression of voltage-gated sodium channels have recently been shown by our laboratory to contribute to the development and maintenance of central pain following SCI.

Spinal cord sodium channels

Action potential generation and propagation by sensory neurons relies on multiple isoforms of voltage-gated sodium channels (termed Nav). The selective expression of ensembles of sodium channels, unique in different types of neurons, tunes the biophysical properties of each cell. Within the normal nervous system, properties fundamental to neuronal function such as activation threshold, inactivation, refractory period, rates of repriming, and the ability to generate and conduct high-frequency trains of action potentials all depend on the type(s) of sodium channels expressed within a given neuron (Waxman, 2000). As might be expected, dysregulation of channel expression can abnormally reconfigure neuronal function in disease states.

Ten genes encode molecularly distinct voltage-gated sodium channels, at least seven of which are expressed in the rat nervous system. In the adult spinal cord dorsal horn, Nav1.1, Nav1.2, and Nav1.6 are strongly detectable, whereas Nav1.3 expression, while present at early ontogenetic states, decreases with development and is nearly undetectable in adults (Felts et al., 1997).

SCI and dorsal horn ion channel dysregulation

We have studied sodium channel expression at several levels along the pain-signaling pathway in a model of contusive SCI in which, as in humans with non-penetrating SCI, there is central necrosis, surrounded by a rim of surviving ascending and descending axons at the level of the injury (Hains et al., 2004). In this rodent model in situ hybridization and immunocytochemistry with an isoform-specific Nav1.3 antibody show that expression of Nav1.3 is upregulated within dorsal horn neurons caudal to the level of the injury (Hains et al., 2003). These studies show that, 4 weeks after SCI, expression of Nav1.3 is increased, within neurons contained within laminae I–VI in the lumbar dorsal horn (L3–L5) (Fig. 1B). Nav1.3 does not co-localize with OX-42, a marker for activated microglia (which proliferate after SCI and are present in all laminae within the dorsal horn (Hains and Waxman, 2006)), or with GFAP, a marker for astrocytes (which also proliferate in all spinal laminae after SCI). CGRP, restricted to the terminals of primary afferent fibers within laminae I–II, does not co-localize with Nav1.3. The substance-P receptor NK1R, found in second-order nociceptive neurons within laminae I–IV, does however co-localize with Nav1.3, indicating that Nav1.3 is upregulated within nociceptive dorsal horn neurons.

In this model, 88% of sampled lumbar dorsal horn units show increased evoked activity to natural peripheral stimuli (brush, press, pinch, graded von Frey filaments, and 47°C thermal stimuli). In comparison to intact animals in which dorsal horn neurons fire at rates of 5–21 Hz, SCI animals demonstrate increased evoked rates of up to 55–60 Hz (Fig. 1E).

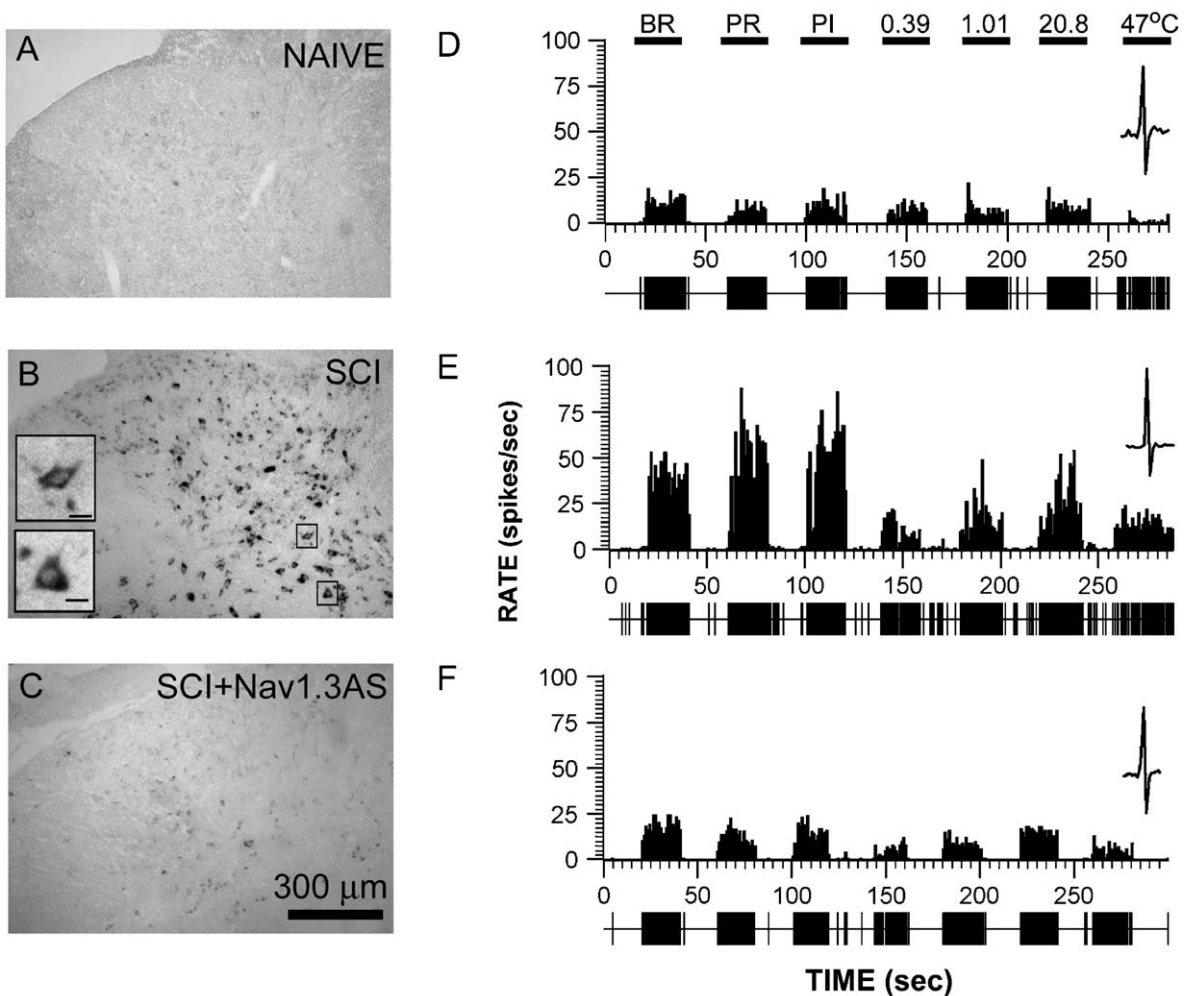


Fig. 1. Nav1.3 mRNA is expressed at low levels in naïve animals (A), but is upregulated in lumbar dorsal horn neurons after spinal cord injury (SCI) (B). Treatment with antisense (AS) oligodeoxynucleotides generated against Nav1.3 reduces Nav1.3 transcripts after SCI (C). Corresponding unit recordings show evoked activity to peripheral stimulation (BR, brush; PR, press; PI, pinch, increasing strength von Frey filament stimulation, and noxious thermal heating (47°C)), after SCI (E) compared with controls (D). After Nav1.3 AS delivery, evoked activity of dorsal horn neurons resembles that found in naïve levels (F). Adapted with permission from Hains et al. (2003).

The Nav1.3 sodium channel plays a role in maintaining neuronal hyperresponsiveness to peripheral stimulation, as well as pain-related behaviors after SCI, as evidenced through selective knock-down of Nav1.3 expression via antisense (AS) oligodeoxynucleotide administration (Hains et al., 2003). Lumbar intrathecal administration of Nav1.3 AS very effectively reduces the expression of Nav1.3 within dorsal horn neurons after SCI (Fig. 1C), and significantly

decreases the evoked hyperresponsiveness of dorsal horn multi-receptive neurons (Fig. 1F), whereas administration of Nav1.3 mismatch (MM) sequence, used as a control, has no effect. Electrophysiological recordings show that 4 days after initiation of Nav1.3 AS, high levels of evoked activity of dorsal horn neurons in SCI animals are markedly decreased in response to all peripheral stimuli, and only 20% of sampled units are hyperexcitable.

Nav1.3 and neuronal hyperresponsiveness

Expression of the Nav1.3 sodium channel after SCI uniquely configures neurons to fire in an abnormal, heightened manner. Nav1.3 produces a rapidly repriming tetrodotoxin-sensitive sodium current that promotes neuronal firing at higher-than-normal frequencies (Cummins et al., 2001). Since stimulus intensity is encoded in the dorsal horn by the rate of firing, this change in neuronal processing of afferent sensory information serves to amplify incoming signals, such that perceived pain thresholds are lowered after SCI.

We recently examined the biophysical properties of sodium currents in acutely dissociated dorsal horn neurons after chronic SCI, and found a number of changes in sodium current characteristics via whole-cell patch-clamp recordings (Fig. 2A) (Lampert et al., 2006). First, we found shifts in the activation and inactivation properties of the voltage-gated sodium currents to more positive potentials after SCI (Fig. 2B). Second, persistent sodium currents in dorsal horn neurons from SCI animals were increased when compared with cells from intact animals (Fig. 2C). Third, the ramp current elicited in response to slow depolarizing potentials

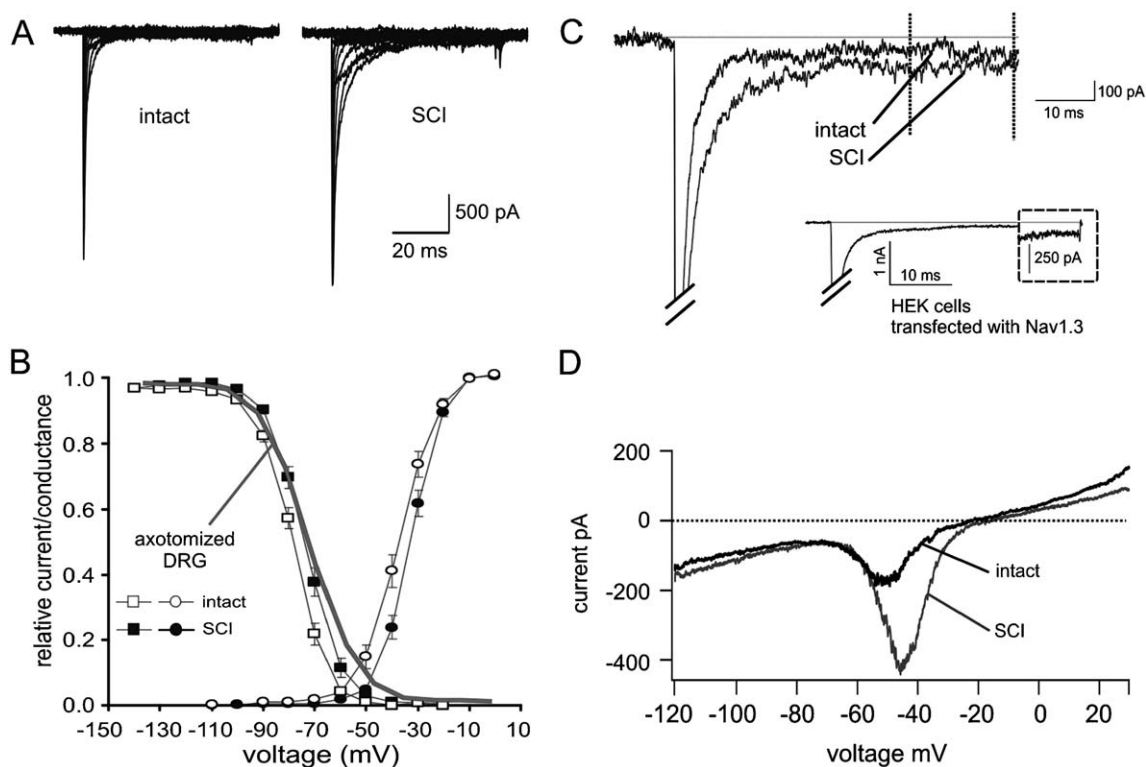


Fig. 2. Whole-cell patch-clamp recordings of acutely dissociated lumbar dorsal horn neurons 28 days after T9 SCI reveal changes in sodium current properties. Representative current traces from intact and SCI animals, elicited by stepwise depolarizations from a holding potential of -120 mV to voltages ranging from -110 to $+40$ mV (A). Steady-state inactivation (open squares: intact, filled squares: SCI) measured as relative available current after a 500 ms prepulse to the indicated potential. Steady-state activation shown as relative conductance (B). Note that SCI shifts steady-state inactivation in dorsal horn neurons toward the curve for axotomized DRG neurons, in which Nav1.3 is upregulated. Representative current traces showing enhancement of persistent current after SCI (C). Vertical lines delimit the region in which the mean persistent current was assessed. Inset: Representative record from a human embryonic kidney cell heterologously transfected with Nav1.3, showing persistent current. Representative current traces in response to a 200 ms voltage ramp from -120 to $+30$ mV showing an increase in ramp currents in SCI but not intact animals (D). Adapted with permission from Lampert et al. (2006).

was increased after SCI (Fig. 2D). The shift in steady-state inactivation and the increase in the persistent and ramp current all would be expected to contribute to dorsal horn neuron hyperresponsiveness, which is observed after SCI. All of these properties, which are consistent with upregulation of Nav1.3, can contribute to hyperresponsiveness of dorsal horn neurons, after SCI.

Thalamic Nav1.3 dysregulation

Dorsal horn neurons project rostrally within the spinothalamic tract to third-order neurons of the

ventroposterior lateral (VPL) nucleus of the thalamus (Jones, 1998). VPL neurons are involved in sensory-discriminative aspects of pain processing. Thalamic changes have been associated with pain following SCI in humans (Lenz et al., 1989; Pattany et al., 2002), primates (Weng et al., 2000), and rodent models (Koyama et al., 1993; Gerke et al., 2003), but the underlying molecular mechanisms are still not fully understood.

After SCI, expression of the Nav1.3 sodium channel is upregulated in VPL neurons (Fig. 3B), and an increase in the spontaneous activity and responses to natural stimuli is observed (Hains et al., 2005). Lumbar administration of Nav1.3 AS

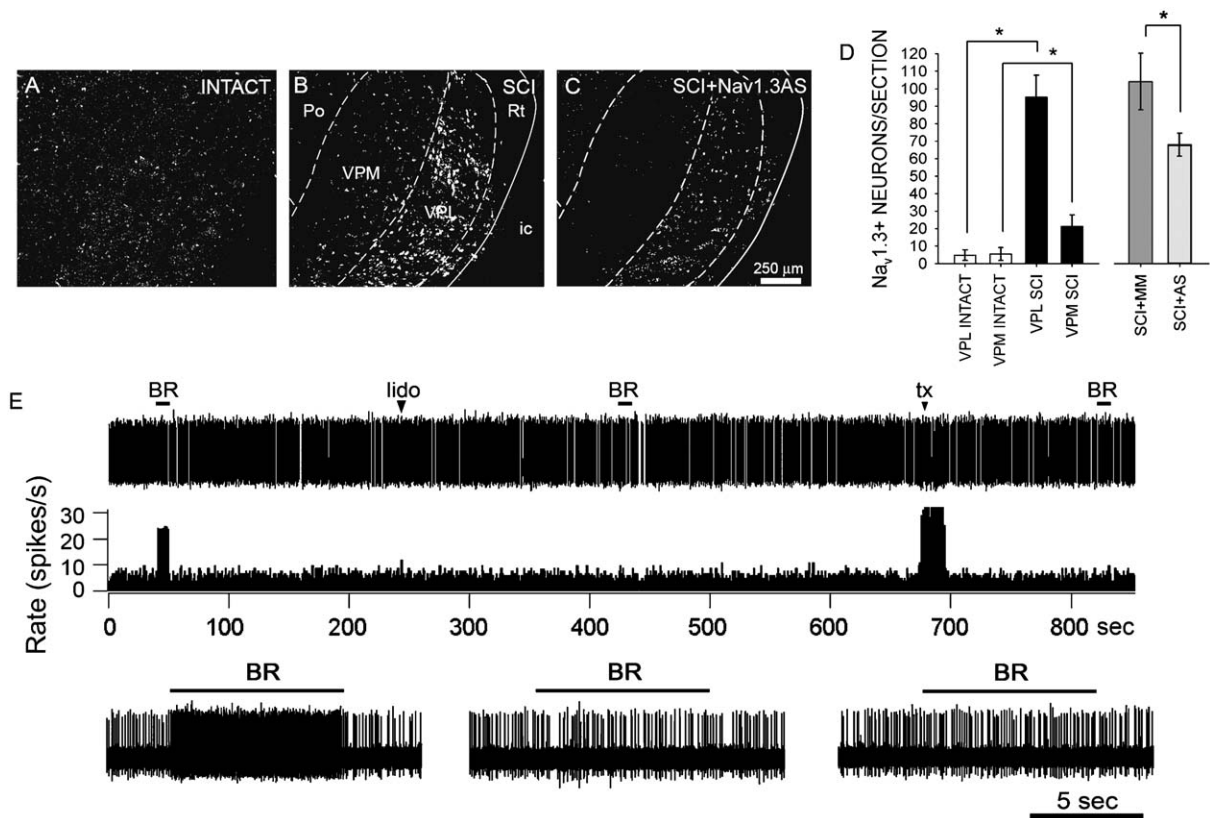


Fig. 3. Expression of Nav1.3 protein within the ventral posterolateral (VPL) nucleus of the thalamus is absent in intact animals (A), but 28 days after SCI Nav1.3 expression is upregulated within VPL and to some degree the ventral posteromedial (VPM) nuclei. Intrathecal Nav1.3 antisense (AS) administration (C) significantly reduced the expression of Nav1.3 within the VPL (D). Long-term recording of a single VPL unit after SCI with a hindpaw receptive field revealed high spontaneous discharge activity and evoked responsiveness to brush (BR) stimulation of the receptive field (E). Following topical application of lidocaine (lido) and cord transection (tx), evoked responses were abolished however high spontaneous activity persisted. Adapted with permission from Hains et al. (2005).

reduced the number of neurons displaying Nav1.3 upregulation within the VPL (Fig. 3C), and reversed thalamic electrophysiologic abnormalities caused by SCI. Importantly, we also observed an increased level of spontaneous background activity in VPL neurons associated with SCI which persists after spinal cord transection (Fig. 3E) that disconnects the site of SCI and ascending projections from the lumbar enlargement from the thalamus, indicating a degree of autonomous hyperexcitability of the thalamus. We cannot exclude the possibility that factors other than Nav1.3 also contribute to the reconfiguration of the firing properties of thalamic units following SCI since the magnitudes of change of Nav1.3 expression levels did not perfectly match the magnitude of the electrophysiologic changes. However, our results demonstrate changes in sodium channel expression within the thalamus that are associated with abnormal sensory processing and chronic neuropathic pain after SCI.

The thalamus also undergoes a change in burst firing properties after SCI. Bursts are involved in normal and pathological perceptual processing; however, rhythmic oscillation of burst firing is observed in pathophysiological conditions, and it has been suggested that abnormal thalamic activity may contribute to the perception of chronic pain (Lenz et al., 1989, 1994; Jeanmonod et al., 1993; McCormick, 1999). Furthermore, the information content of bursts is higher than for single-spikes in the visual system (Reinagel et al., 1999), and the overall probability of generating at least one postsynaptic spike (in the pain-processing sensory cortex) is higher for bursts than for single-spikes (Csicsvari et al., 1998). In neurons of the ventrobasal thalamus, increased gain or transfer ratio induced by burst firing results in increased thalamocortical efficacy, enhancing the postsynaptic response (Swadlow and Gusev, 2001). Thus, it is possible that pathological burst firing after SCI may more potently activate cortical circuits involved in pain perception.

We recently showed that after SCI, burst firing intervals become more regular, spike events are reduced within each burst, acceleration in burst duration occurs in bursts containing higher spike counts, and shifts occur among spike firing modes

(Hains et al., 2006). Furthermore, we observed that Nav1.3 AS returned the number of spikes/burst, burst duration, and interburst interval toward control levels following SCI. Our data are similar to those reported by Lenz et al. (1989, 1994) in humans with post-SCI pain showing that thalamic neurons exhibit oscillatory burst firing characterized by high discharge rates, and deceleration of firing rate throughout the burst period, and suggest that altered sodium channel expression within thalamic neurons contributes to these functional abnormalities.

Multi-tiered alterations in nociceptive processing

Our findings demonstrate changes in excitability and expression of Nav1.3 within dorsal horn and VPL neurons following SCI. We have also observed that hyperexcitability of thalamic neurons following SCI is to at least some degree autonomous, since it persists following spinal cord transection which abolishes ascending barrages from spinal cord neurons near or below the injury site. Together with our earlier results on dorsal root ganglion neurons (Cummins and Waxman, 1997; Cummins et al., 2001), these studies provide evidence for a link between pain after SCI and molecular changes in pain-signaling neurons, suggesting that dysregulation of sodium channel Nav1.3 expression at both spinal and supraspinal levels contribute to altered processing of somatosensory information and chronic neuropathic pain after SCI. Specifically, our results indicate that there is upregulated expression of Nav1.3 in first-, second-, and third-order neurons of the pain pathway after contusive SCI, and suggest that this leads to enhanced neuronal excitability at each of these multiple levels.

As originally proposed by Yeziarski (2001), SCI can trigger the activity of pain generators and amplifiers within the CNS. On the basis of our observations, we propose an integrated model (Fig. 4) in which increased Nav1.3 expression within pain-signaling neurons at multiple levels of the neuraxis causes exaggerated nociceptive signaling by way of spontaneous firing, a lowered threshold for firing in response to synaptic drive,

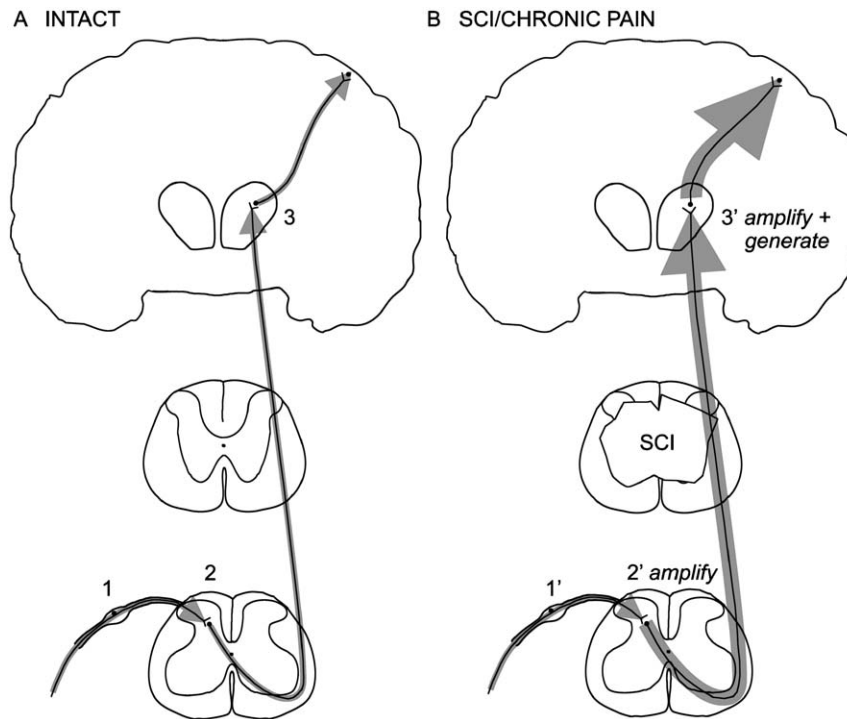


Fig. 4. Model whereby after SCI, multi-tiered dysregulation of sodium channel expression contributes to the pathological amplification and generation of aberrant nociceptive information, and ultimately chronic pain. In comparison to intact animals (A), second-order neurons within the dorsal horn increase the gain with which they respond to innocuous and noxious inputs (1') after SCI (B). The exaggerated responses of these dorsal horn neurons in response to peripheral stimulation poise them to act as an amplifier of normal as well as inappropriate pathological nociceptive signals (2'). After SCI, the thalamus also acts as a pain amplifier by responding in an increased manner to nociceptive information relayed from the dorsal horn, and in addition, thalamic circuitry can act as an autonomous pain signal generator (3'). Treatment strategies that target one or more components of this pathway may be of value in combating chronic pain following SCI.

and increased synaptic drive due to enhanced excitability of presynaptic elements. According to this model, second-order neurons within the dorsal horn increase the gain with which they respond to innocuous and noxious inputs after SCI. The exaggerated responses of these dorsal horn neurons configures them to act as an amplifier of normal as well as inappropriate pathological nociceptive signals.

Because the thalamus is involved not only in relaying, but also processing incoming information from the spinal cord en route to the cortex, injury-induced changes in spinal pain generator circuitry may feed aberrant signals into the injured thalamus which further processes and amplifies the signals before relaying messages that are interpreted as signaling pain to suprathermal structures

(Waxman and Hains, 2006). Abnormal processing at thalamic levels would then be expected to further exaggerate abnormal firing patterns from the spinal cord after SCI. Our observations of increased primary burst firing activity and reduced silence in VPL neurons after SCI leads us to suggest that, following SCI, an increased level of abnormal afferent firing is being forwarded to cortical structures involved in interpreting pain.

Conclusion

SCI induces nervous-system-wide changes in neuronal firing properties which contribute to chronic pain, some of which are governed by the pathological expression of the Nav1.3 sodium channel.

By prevention of the upregulation of Nav1.3, knock-down of Nav1.3 after it is upregulated, or selective pharmacological targeting of Nav1.3 channels deployed after injury, it is possible that the molecular amplifiers and generators of chronic pain associated with SCI may be effectively targeted and muted so that chronic pain can be ameliorated.

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