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An Approach to Identify Nerve Injury-Evoked Changes that Contribute to the Development or Protect Against the Development of Sustained Neuropathic Pain

Esperanza Recio-Pinto^{1,2}, Monica Norcini¹ and Thomas J.J. Blanck^{1,3}

¹*Department of Anesthesiology,*

²*Department of Pharmacology,*

³*Department of Neuroscience and Physiology,*

^{1,2,3}*New York University Langone Medical Center
USA*

1. Introduction

Chronic neuropathic pain is a huge public health problem that compromises the quality of life of millions of individuals. There are many causes for chronic neuropathic pain, one of them being peripheral nerve injury occurring during surgery or trauma. Even when considering only those cases resulting from surgery about 2-10% of patients undergoing various surgeries (amputation, breast surgery, thoracotomy, inguinal hernia, coronary artery bypass surgery, caesarean section) develop chronic severe (disabling) pain (Kehlet et al., 2006). In the USA alone, there are approximately 80 million surgeries performed each year (Apfelbaum et al., 2003); if only 5% of those patients went on to develop severe chronic pain, ~4 million people would be added to the list of chronic pain patients each year. Of the patients attending chronic pain clinics, 20% have implicated surgery as one of the causes of their chronic pain and, in about half of these, it was the sole cause (Macrae, 2001). The intensity of acute postoperative pain is a good predictor of long-term pain; however, adequate control of acute postoperative pain does not always lead to a decrease in the incidence of developing long term pain (Perkins and Kehlet, 2000). To reduce the level of tissue injury during surgery, surgical procedures have been modified including those used for joint repair (Kehlet et al., 2006); mastectomy and breast reconstruction (Gahm et al.; 2010; Vadivelu et al., 2008) and herniorrhaphy (Nathan and Pappas, 2003; Pokorny et al., 2008); however, a significant percentage of patients still develop chronic pain. Hence, there is a need to develop treatments that can be used before and during the early phases following nerve injury (as a result of surgery or trauma) to prevent the development of chronic pain. The development of chronic pain following surgery correlates with the presence of peripheral nerve injury (Macrae, 2001). Studies using various peripheral nerve injury models have shown that these models share some, but not all, of the injury-induced molecular changes that may be contributing to chronic neuropathic pain (Berger et al., 2011; Xu and Yaksh, 2011). Moreover, whether changes in a given molecule contribute to

neuropathic pain also appears to depend in their anatomical location (neuroma at the site of the peripheral nerve injury, dorsal root ganglia somata, spinal cord etc). Hence there is a need to not only identify the molecules but their relevant location with respect to their contribution to neuropathic pain. Those studies have also shown that not all of the underlying causes for neuropathic pain are shared between the various peripheral nerve injury models, for example in the "sciatic nerve ligation" model blocking the excitability of the nerve prior to its ligation (injury) and for a period following the injury (~week) eliminates the development of sustained neuropathic pain (mechanical allodynia)(Kim and Nabekura, 2011). On the other hand in the "sural spared nerve injury model", in which the common peroneal and the tibial branches of the sciatic nerve are cut, blocking the nerve impulses before and during one week after the nerve injury does not eliminate the development of sustained neuropathic pain (Suter et al., 2003). The latter picture more closely resembles the clinical outcome of many surgical patients that endure peripheral nerve injuries (Perkins and Kehlet, 2000). Since dorsal root ganglia sensory neurons are the first sensory neurons that are affected following a peripheral nerve injury; then another approach for treatment could be to modulate (rather than block) their activity. Pharmacological modulation should be directed to either prevent or compensate for the injury-evoked functional alterations that contribute to the initiation and probably maintenance (at least at early stages) of chronic pain and in this way prevent/limit central sensitization and in turn the level of sustained neuropathic pain.

Studies directed towards detecting injury-evoked changes that correlate with the presence of neuropathic pain have identified changes in the expression of a large number of molecules that appear to contribute to neuropathic pain states (Berger et al., 2011; Xu and Yaksh, 2011). This information has provided many insights for possible treatments; sadly, for the most part effective sustained neuropathic pain treatment still remains evasive. Hence studies identifying not only the changes that contribute to neuropathic pain but also those that limit the magnitude of neuropathic pain following a nerve injury should provide additional information that could improve treatment. In this chapter we will touch on two points: first why the dorsal root ganglia is an attractive pharmacological target to prevent as well as reverse neuropathic pain states (at least at the early stages) resulting from peripheral nerve injury. Second, we will describe an approach (using two modalities of an already established animal model, the spared nerve injury (Decosterd and Woolf, 2000)) to distinguish peripheral nerve injury-induced changes within the dorsal root ganglia (or at any level of the sensory pathway) that contribute to the development of chronic neuropathic pain from those that represent a protective response and hence limit the development and the level of chronic neuropathic pain.

2. The dorsal root ganglia provides an interesting pharmacological target for treating neuropathic pain resulting from peripheral nerve injury

2.1 Dorsal root ganglia morphology

The arrangement of the dendrites, cell body and axon in dorsal root ganglia sensory neurons is different from that of most neurons. In early embryonic stages these neurons are bipolar (Matsuda et al., 1996) (Figure 1). During late embryonic development the proximal regions of the two processes coalesce into a T-shaped process and these neurons progressively

become pseudounipolar such that by birth most of them are pseudounipolar (Matsuda et al., 1996). The pseudounipolar conformation appears to ensure as well as allow for modulation of the impulses being transmitted from the periphery to the central terminals of dorsal root ganglia sensory neurons (Amir and Devor, 2003a; Amir and Devor, 2003b; Devor, 1999). Within the dorsal root ganglia there are no synaptic contacts between neurons however, the somata have microvilli that appear to contribute to the observed interactions between the neuronal somata and between neuronal somata and their surrounding satellite glia cells (Pannese, 2002; Takeda et al., 2009). Moreover, the lack of a nerve-blood barrier also exposes the somata within the dorsal root ganglia to plasma molecules that can modulate their function (Abram et al., 2006; Hirakawa et al., 2004). Each soma is completely surrounded by a layer of satellite glia cells (Figure 1); and together the soma and satellite glia cells form a single anatomical and functional unit (Hanani, 2005; Pannese, 1981). These individual units can have one to three neuronal somata, and occasionally some of the somata within a unit are not surrounded by satellite glia cells (Pannese et al., 1991). The units are in turn separated by areas of connective tissue (Pannese et al., 1991). Following nerve injury satellite glial cells, as their glia counterparts in the CNS, undergo functional changes (release of cytokines and neurotrophins, changes in neurotransmitter-scavenging capacity) and hence they may also contribute to the initiation and maintenance of chronic pain (Gosselin et al., 2010; McMahon and Malcangio, 2009; Milligan and Watkins, 2009; Romero-Sandoval et al., 2008; Scholz and Woolf, 2007; Takeda et al., 2009; Watkins et al., 2001; Watkins and Maier, 2002).

DRG: dorsal root ganglia

SGC: satellite glia cell

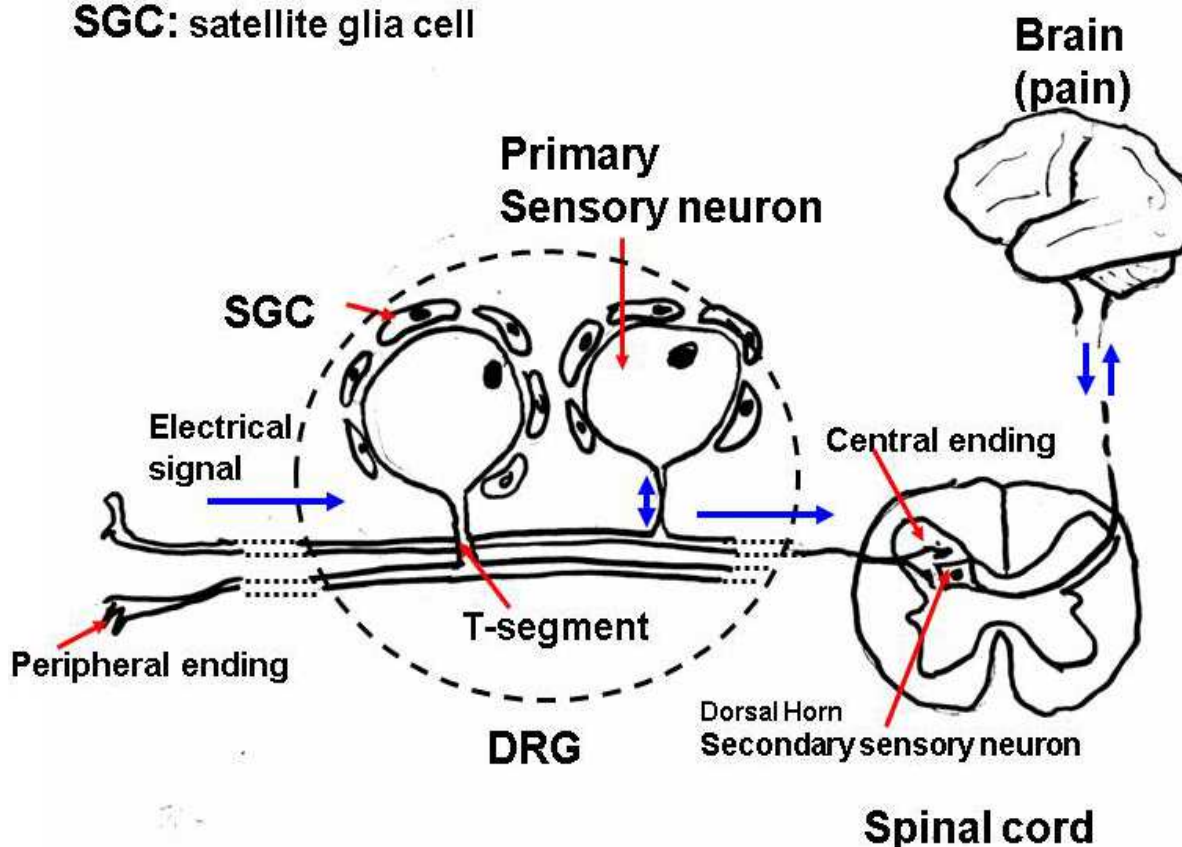


Fig. 1.

2.2 Dorsal root ganglia as a pharmacological target to avoid the development of chronic pain following peripheral nerve injury

The dorsal root ganglia is a good pharmacological target for preventing the initiation and limiting the level of chronic neuropathic pain following peripheral nerve injury because: First, the dorsal root ganglia sensory neurons are the first neurons in the sensory pathway that are affected following a peripheral nerve injury. It is known that within the dorsal root ganglia there is crosstalk between the sensory neurons and signals from the injured sensory neurons can modulate the activity of the uninjured neurons within the same ganglia (Ali et al., 1999; Wu et al., 2002). Even during peripheral nerve injuries that do not directly affect the dorsal root ganglia sensory neurons; for example when the injury solely involves motor axons (e.g. during ventral L5 transection) (He et al., 2010; Li et al., 2002); the dorsal root ganglia sensory neurons still undergo functional changes that have been found to correlate with the development of neuropathic pain (He et al., 2010; Wu et al., 2002; Xu et al., 2006). Some of the peripheral nerve injury-induced functional changes in the dorsal root ganglia sensory neurons are believed to be important for the initiation and sustained alteration of the activity of the spinal cord neurons and in turn of the brain neurons (central sensitization) that underly chronic neuropathic pain (Harris et al., 1996; Jang et al., 2007; Lee et al., 2003; Liu and Salter, 2010; Obata et al., 2003; Ringkamp and Meyer, 2005). Second, although the dorsal root ganglia is surrounded by a thick connective tissue capsule, the dorsal root ganglia is not protected by a “blood-nerve barrier”, as it is the rest of the peripheral nervous system (Abram et al., 2006; Hirakawa et al., 2004). Hence the somata of dorsal root ganglia sensory neurons as well as their surrounding satellite glia cells can be specifically targeted (with respect to the rest of the nervous system including the central nervous system that is also protected by the “blood-brain barrier”) with pharmacological agents. Third, the excitability of dorsal root ganglia somata and their T segments (both located within the dorsal root ganglia) facilitate and regulate the transmission of the electrical signal from the periphery to the central dorsal root ganglia sensory terminals (Amir and Devor, 2003a; Amir and Devor, 2003b; Devor, 1999); hence one could also pharmacologically and locally alter the electrical activity of the somata and their T segments in order to compensate for the injury-evoked changes in sensory activity (from periphery to central endings) that contribute to the initiation and establishment of chronic pain.

2.3 Peripheral nerve injury alters the dorsal root ganglia environment and function

Following peripheral nerve injury, the properties for generating afferent impulses (action potentials) are modified and such modifications are believed to contribute to the initiation of central sensitization which includes several components including activation of the NMDAR and increased AMPA subunit expression (at the spinal cord) (Harris et al., 1996; Liu and Salter, 2010). Peripheral nerve injury-evoked changes in impulse generation include the appearance of ectopic afferent impulses and the modification of the stimuli-evoked impulses. Following sciatic nerve injury (constriction or cutting), ectopic discharges (firing of action potentials) from the injured site (Tal and Eliav, 1996; Wall and Gutnick, 1974a; Wall and Gutnick, 1974b; Wall and Devor, 1983) and the dorsal root ganglia (Amir et al., 2002; Liu et al., 2000a; Liu et al., 1999; Liu et al., 2000b) correlate with the development of neuropathic pain. The frequency of ectopic discharges shows a transient increase within the first 24 hrs

following spinal nerve ligation (Sun et al., 2005). Based on this it was concluded that ectopic discharges may only contribute to the initiation of mechanical allodynia (Sun et al., 2005). In that same study, however, the pattern of the discharges was altered throughout the observation period (14 days) (from tonic and bursting to irregular). This suggests that not only the presence but also the pattern of ectopic discharges could be important to the development and/or maintenance of neuropathic pain. In addition to “ectopic” discharges, changes in the “stimuli-evoked” discharges have also been found to be altered following spinal nerve ligation (Sun et al., 2005). Therefore, both ectopic discharges and alterations of stimuli-evoked discharges appear to contribute to the initiation and maintenance of neuropathic pain.

Studies characterizing the expression of various ion channel proteins that underlie the electrical excitability of dorsal root ganglia neurons show that many of them undergo changes following a peripheral nerve injury, including various sodium channels (Dib-Hajj et al., 2010), potassium channels (Abdulla and Smith, 2001; Chien et al., 2007; Kim et al., 2002) and calcium channels (Abdulla and Smith, 2001;).

Since excitability of sensory neurons involve activation of voltage-dependent sodium channels, many studies have been directed to understand whether their changes (if any) following injury contribute to neuropathic pain. Those studies have been recently reviewed (Amir et al., 2006; Dib-Hajj et al., 2010; Liu and Wood, 2011). Here we will just describe some of the results mostly to indicate the complexity of the problem. There are nine isoforms of voltage-dependent sodium channels and some of the isoforms are expressed by dorsal root ganglia sensory neurons but not by muscle tissue, which make them potential pharmacological targets (Amir et al., 2006). What it has been found is that their role in neuropathic pain following peripheral nerve injury is a complex one (Dib-Hajj et al., 2010; Liu and Wood, 2011). The Nav1.3 is increased in dorsal root ganglia somata following various peripheral nerve injuries, however a decrease of their expression (with antisense) has been reported to either decrease (Hains et al., 2003; Hains et al., 2004) or have no effect in the development of chronic pain (Lindia et al., 2005). Nav1.8 and Nav1.7 accumulate within injured axons in painful human neuromas (Kretschmer et al. 2002, Bird et al. 2007, Black et al. 2008). Nav1.8 is upregulated in the uninjured L4 and L5 dorsal root ganglia after L5 ventral root transection (Chen et al., 2011; He et al., 2010). Moreover, the increased membrane expression of Nav1.8 leads to spontaneous repetitive discharge. However, the increase in Nav1.8 (Amir et al., 2006; Nassar et al., 2005), and of Nav1.7 (Nassar et al., 2004; Nassar et al., 2005) appears to underlie purely inflammatory pain but not neuropathic pain. Finally, Nav1.8 (as well as Nav1.9), is downregulated in axotomized neurons (Dib-Hajj et al. 1998b, Sleeper et al. 2000, Decosterd et al. 2002) and within the injured human dorsal root ganglia neurons (Coward et al. 2000, 2001). Similarly to sodium channels, there are also reported changes in potassium channels (Chien et al., 2007; Kim et al., 2002;) and calcium channels (Abdulla and Smith, 2001; Luo et al., 2001; Newton et al., 2001) that have been postulated to contribute to the excitability changes of sensory neurons and to contribute to neuropathic pain. Hence, although injury-induced changes in excitability of dorsal root ganglia neurons is believed to contribute to the development of chronic pain; the players involved as well as their role are less clear and they may not be the same in different types of injury.

Another approach has been to identify soluble factors that are altered following injury and are responsible for evoking the excitability changes of dorsal root ganglia neurons. Following nerve injury there is an invasion of immune cells into the nervous system that is promoted largely by the Wallerian degeneration of the injured nerve as well as by damage of the tissue surrounding the nerve (Chung et al., 2007; Dubovy et al., 2007; Hu and McLachlan, 2002). The immune cells alter the neuronal environment in part by changing the level of various cytokines/chemokines produced by the immune cells and by the neurons and glial cells in response to those released by the immune cells (Austin and Moalem-Taylor; Brazda et al., 2009; Dubovy et al., 2006; Dubovy et al., 2010a; Dubovy et al., 2010b). Since some of the immune mediators have been shown to contribute to neuropathic pain by altering the excitability of both primary and secondary sensory neurons one approach that has been investigated to treat/prevent chronic pain is to pharmacologically alter their production. This approach however, has been limited because some of these factors also have been found to be involved in axonal regeneration or neuroprotection (e.g. IL-6) (Murphy et al., 1999; Osamura et al., 2005; Wang et al., 2007; Wang et al., 2009) or in muscle regeneration (e.g. CCL2) (Lu et al., 2011; Van Steenwinckel et al., 2011; Wang et al., 2010). The contribution of immune mediators to neuropathic pain appears to involve alterations of excitability of primary and secondary sensory neurons; therefore, a more targeted approach such as decreasing their level (and/or production by) at the dorsal root ganglia, and in this way blocking their effects on excitability of primary sensory dorsal root ganglia neurons, could improve their use for treating neuropathic pain.

In addition to changes in cytokines/chemokines, there are many other genes/proteins that have been found to be upregulated or downregulated in the dorsal root ganglia sensory neurons following nerve injury but in many cases their contribution to chronic pain is also complex (Birder and Perl, 1999; Krekoski et al., 1996; Lee et al., 2002; Schafers et al., 2003; Seijffers et al., 2006; Xiao et al., 2002; Zhou et al., 1999). For example, following sciatic nerve injury there is an increase in the BDNF expression in large dorsal root ganglia sensory neurons and in satellite glia cells, while its expression is decreased in small dorsal root ganglia sensory neurons (Zhou et al., 1999), moreover the magnitude of the change in BDNF expression in dorsal root ganglia neurons depends on the site of the peripheral nerve injury (proximal vs distal) (Obata et al., 2006). These studies suggested that increases in BDNF expression in the large dorsal root ganglia sensory neurons contribute to neuropathic pain following peripheral nerve injury (Obata et al., 2006; Zhou et al., 1999). However, blocking production of BDNF by dorsal root ganglia sensory neurons, showed that BDNF in dorsal root ganglia sensory neurons, while it contributed to inflammatory pain (induced by injections of either Carrageenan, NGF or Formalin), it did not contribute to the development of neuropathic pain (following L5 spinal nerve ligation) (Zhao et al., 2006). Moreover, intrathecal application of BDNF has been shown to have both pronociceptive (Yajima et al., 2002; Yajima et al., 2005) and antinociceptive (Cejas et al., 2000; Eaton et al., 2002) effects following a peripheral nerve injury. These studies indicate that in order to establish that a molecular change within the dorsal root ganglia contribute to neuropathic pain requires more than a simple correlation between the observed molecular change and the presence of neuropathic pain.

As stated above peripheral nerve injuries result in alterations of the properties for generating afferent impulses (action potentials) in primary sensory neurons which in turn

are believed to contribute to the initiation of central sensitization which underlies the development of chronic pain. Therefore, one approach to prevent the development of chronic pain has been to block excitability of primary sensory neurons. Interestingly, blocking the excitability of the nerve prior to its injury and for a period following the injury (~week) eliminates the development of sustained neuropathic pain when the injury involves sciatic nerve ligation (Kim and Nabekura, 2011) but not when it involves cutting branches of the sciatic nerve (Suter et al., 2003). This suggests that the injury-evoked alterations of nerve discharges (ectopic and stimuli-evoked) differ whether the nerve is cut or not. The outcome observed in the model involving partial cut of the sciatic nerve (Suter et al., 2003) closely resembles the clinical outcome of many surgical patients that endure peripheral nerve injuries (Perkins and Kehlet, 2000). For these patients, another approach for treatment could be to pharmacologically modulate (rather than block) the activity of dorsal root ganglia sensory neurons even at the early stages following nerve injury. Such pharmacological modulation should be designed to prevent or compensate for their functional alterations evoked by the nerve injury and in this way prevent/limit central sensitization and in turn the level of sustained neuropathic pain. Such modulation could be potentially mediated by altering the excitability of the dorsal root ganglia neuronal somata. The apparent complexity of the role in neuropathic pain of various molecules in part may reflect our lack of understanding in their overall role in chronic pain. Some of the expression changes (and/or their magnitude) could actually reflect a protective response that would limit the level of sustained pain rather than promote the level of sustained pain. Hence, there is a need to use experimental approaches to distinguish between the peripheral nerve injury-induced changes (within the dorsal root ganglia or at any level of the sensory pathway) that contribute to the development of chronic neuropathic pain from those that represent a protective response and hence limit the development and the level of chronic neuropathic pain.

3. An approach to distinguish injury-induced changes that contribute to the development of chronic pain from those that limit the development of neuropathic pain

As summarized above, multiple studies have identified either increases or decreases in a large number of parameters at the molecular level (protein expression/function) and at the cellular level (morphological/function) in neuropathic pain states. Some of those changes have also been shown to contribute to neuropathic pain. However, the contribution of many of the observed changes is less clear. In fact not all the changes that take place in conditions leading to neuropathic pain are necessarily contributing to neuropathic pain. Most likely some of them could actually represent protective responses that decrease the level of sustained neuropathic pain. One approach to facilitate the distinction between whether a change contributes to or limits the level of neuropathic pain will be use a model in which two levels of neuropathic pain can be induced, and in one of the modalities there is a partial reversal of the level of neuropathic pain. We have found that one such model is the Spared Nerve Injury (SNI). This model has been extensively used but usually by using only one of the modalities. Here we describe the advantage of the simultaneous use of two modalities of the SNI. One modality the Tibial-SNI, displays a transient-strong (low threshold) mechanical allodynia followed by sustained-mild allodynia (Figure 2A green line); while the other modality the Sural-SNI displays sustained strong mechanical allodynia (higher

threshold) (Figure 2A blue line). We have used these two modalities of the SNI to help identify the role of injury-evoked changes at the dorsal root ganglia that contribute to the initiation and maintenance of strong mechanical allodynia (transition from acute to chronic pain), compared to injury-evoked changes that could limit the level of sustained mechanical allodynia (compensatory/protective responses). Basically, changes that are found to be proportional to the level of sustained mechanical allodynia would be identified as contributing to long term mechanical allodynia (to the transition from acute to chronic pain) and changes that are inversely proportional to the level of sustained mechanical allodynia would be identified as limiting the sustained level of mechanical allodynia (protective responses) (Figure 2B). The simultaneous use of these two SNI modalities would allow one to more easily identify changes that could help limit the level of sustained neuropathic pain.

By using this approach we have analyzed changes in mRNA in L4 DRG at about 3 months post injury, by doing so we have identified four groups of mRNA: (1) A group of mRNAs that showed the same expression level in Tibial-SNI, Sural-SNI and Sham; (2) A group of mRNAs that showed changes in expression only in Tibial-SNI as compared to Sham and Sural-SNI; (3) A group of mRNAs that showed changes in expression only in Sural-SNI as compared to Sham and Tibial-SNI; and (4) A group of mRNAs that displayed changes in expression in both Sural- and Tibial-SNI, but not always in the same magnitude or direction (\uparrow or \downarrow) (not shown). As expected when comparisons were done only between one of the SNI groups (Sural-SNI or Tibial-SNI) and Sham it resulted in a large number of genes that displayed changes in their expression in that SNI group; however, when comparisons were done by selecting the genes that their expression changed in one of the SNI groups but not in the Sham and in the other SNI group; the number of genes that changed was highly reduced. Some genes of interest that changed only in the dorsal root ganglia from Tibial-SNI (presumably genes that could be involved in limiting the level of sustained mechanical allodynia) include a reduction in *Hcn2* which encodes a hyperpolarization activated cyclic nucleotide-gated K channel 2 that has been shown to contribute to spontaneous rhythmic activity in both heart and brain (Dibbens et al., 2010; Lin et al., 2009); an increase in *Map3k10* a kinase that functions preferentially on the JNK signaling pathway, and that has been reported to be involved in nerve growth factor (NGF) induced neuronal apoptosis (NGF is increased following nerve injury) (see ref in (Castillo et al., 2011)). A decrease in *Rbm9*, a gene that encodes an RNA binding protein that is believed to be a key regulator of alternative exon splicing in the nervous system. Using this approach will facilitate the identification of additional molecules that are involved in nerve-injured evoked neuropathic pain. Including genes/proteins whose alterations correlate with the initiation and/or maintenance of mechanical allodynia (hence correlating with the transition from acute to chronic pain); as well as with the recuperation from mechanical allodynia (correlating with recuperation from acute pain).

It is well accepted that chronic pain, ultimately reflects functional changes in the brain, in particular in the thalamocortical connections/interactions (Cauda et al., 2009; Cheong et al., 2011; Walton et al., 2010). With respect to structural cortical changes, most of those that have been found to be associated with neuropathic pain have been observed in animals and patients that have been experiencing neuropathic pain for a long period. Such structural changes are believed to underlie the changes in cortical activity observed in patients with long term neuropathic pain (Peyron et al., 2004; Walton et al., 2010). And it has been

concluded that such cortical structural changes take place at latter phases of neuropathic pain, and are believed to be a consequence (rather than a cause), of chronic pain. However, a couple of observations support the involvement of early cortical alterations in synaptic plasticity in brain following peripheral nerve injury. One week after Sural-SNI, pyramidal neurons in the contralateral medial prefrontal cortex display an increase in the number of branches and length of basal dendrites, an increase in the spine density and an increase in the NMDA component of synaptic currents (Metz et al., 2009). And recently it was shown that remodeling of cortical connections in the primary sensory cortex is transiently affected early on following sciatic nerve ligation and those changes correlated with the presence of mechanical allodynia (Kim and Nabekura, 2011). The simultaneous use of both SNI models could also help clarify the role of those early cortical structural changes in the initiation of chronic pain.

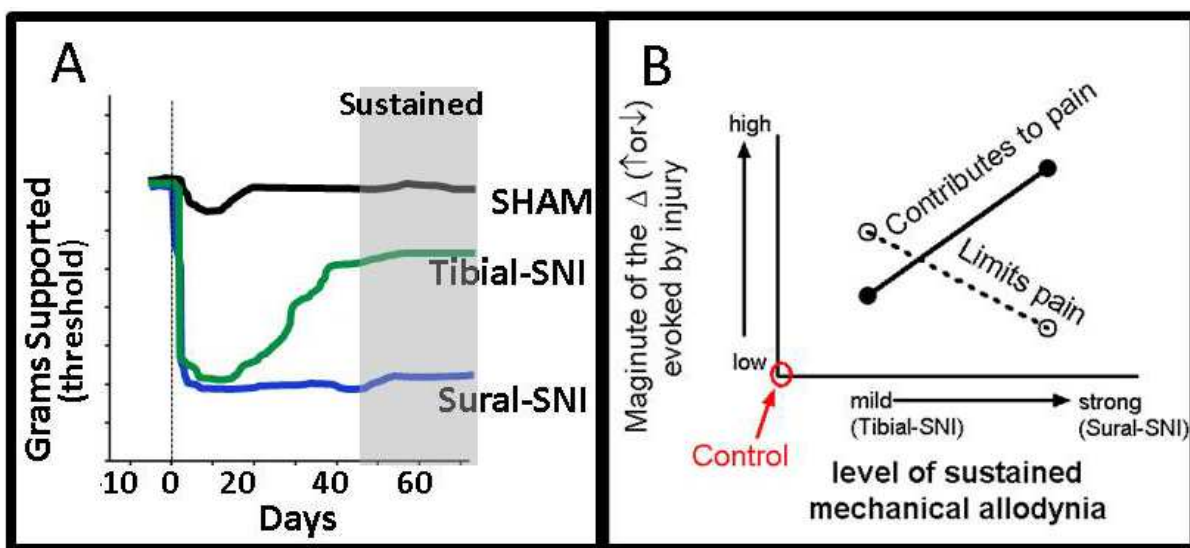


Fig. 2.

4. Conclusion

In summary, peripheral nerve injuries including those occurring during surgery correlate with the development of chronic pain states. Moreover, blocking the nerve impulses during the injury and for a short period following the injury does not prevent the development of chronic pain states in a large number of patients. Hence, there is a need to develop treatments that can be used before and during the early phases of nerve injury (resulting from either surgery or trauma) that will prevent the development of chronic pain in these patients. Most studies have been directed towards the understanding of the changes in the sensory pathway that contribute to the initiation and development of central sensitization. However, equally important but much less studied, are the protective injury-induced functional changes in the sensory pathway in general, and in the dorsal root ganglia in particular that could limit the development of neuropathic pain. Here we describe that the simultaneous use of two of the SNI modalities of the sciatic nerve could facilitate the identification of changes that contribute to the transition from acute to chronic pain as well as those involved in the recovery from acute pain (less than 3 weeks) and that would limit the level of sustained chronic pain; that are involved following a peripheral nerve injury.

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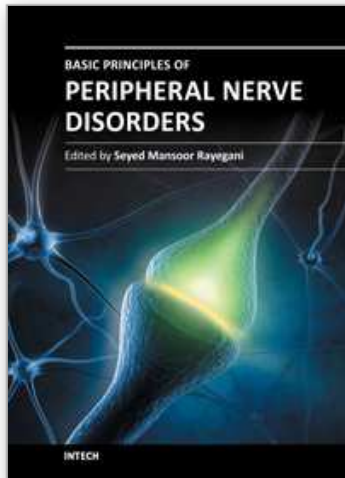
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Peripheral nerve disorders are comprising one of the major clinical topics in neuromusculoskeletal disorders. Sharp nerve injuries, chronic entrapment syndromes, and peripheral neuropathic processes can be classified in this common medical topic. Different aspects of these disorders including anatomy, physiology, pathophysiology, injury mechanisms, and different diagnostic and management methods need to be addressed when discussing this topic. The goal of preparing this book was to gather such pertinent chapters to cover these aspects.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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