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Life Sciences 74 (2004) 2605–2610

**Life Sciences**

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# Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy

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## Abstract

Peripheral neuropathic pain, that clinical pain syndrome associated with lesions to the peripheral nervous system, is characterized by positive and negative symptoms. Positive symptoms include spontaneous pain, paresthesia and dyesthesia, as well as a pain evoked by normally innocuous stimuli (allodynia) and an exaggerated or prolonged pain to noxious stimuli (hyperalgesia/hyperpathia). The negative symptoms essentially reflect loss of sensation due to axon/neuron loss, the positive symptoms reflect abnormal excitability of the nervous system. Diverse disease conditions can result in neuropathic pain but the disease diagnosis by itself is not helpful in selecting the optimal pain therapy. Identification of the neurobiological mechanisms responsible for neuropathic pain is leading to a mechanism-based approach to this condition, which offers the possibility of greater diagnostic sensitivity and a more rational basis for therapy. We are beginning to move from an empirical symptom control approach to the treatment of pain to one targeting the specific mechanisms responsible. This review highlights some of the mechanisms underlying neuropathic pain and the novel targets they reveal for future putative analgesics.

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*Keywords:* Peripheral neuropathic pain; Primary sensory neurons; Ectopic excitability; Phenotypic switch; Sensory neuron loss; Central sensitization; Disinhibition

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## Mechanisms of peripheral neuropathic pain

Multiple mechanisms contribute to the neuropathic pain syndrome. These include changes in the peripheral nervous system, spinal cord brainstem and brain. The temporal profiles of the mechanisms

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differ, some are transient, some require the presence of ongoing peripheral pathology for their maintenance, and others produce persistent or autonomous changes in the operation of the nervous system. In a given patient multiple mechanisms may co-exist, there may be a temporal evolution from one mechanism to another over the course of the natural history of the disease, or a single mechanism may dominate. The etiological factors responsible for driving the mechanisms are not disease specific (Woolf et al., 1998). Patients with postherpetic neuralgia, for example, may have multiple mechanisms and may share mechanisms with patients with painful peripheral diabetic neuropathy (Koltzenburg, 1998; Woolf and Mannion, 1999).

We face three major challenges in studying neuropathic pain mechanisms. The first is, what are the neurobiological mechanisms responsible for the pain (Devor and Seltzer, 1999; Scholz and Woolf, 2002)? The second is, how can we identify which mechanism operates in patients to produce their pain (Galer and Jensen, 1997; Rowbotham and Fields, 1996; Woolf and Decosterd, 1999)? The third is to develop pharmacological tools that are targeted specifically at the mechanisms and enable their disruption (Sindrup and Jensen, 1999; Woolf and Max, 2001).

The unifying feature of peripheral neuropathic pain is pain in the presence of a lesion, damage or disruption to some component of primary sensory neurons. The lesion may be in a peripheral nerve, the dorsal root ganglion or a dorsal root and may be the consequence of trauma, compression, tumor invasion, ischemia, inflammation, metabolic disturbances, nutritional deficits, cytotoxic agents and degenerative disorders (Woolf and Mannion, 1999). These factors act to interfere with or damage some part of a primary sensory neuron, its peripheral axon, cell body or central axon. A change in the function of the somatosensory system with no evidence of a lesion to the PNS, as in fibromyalgia, migraine, irritable bowel syndrome, should not strictly speaking, be considered neuropathic pain. Disruption of the continuity of a primary sensory neuron with its peripheral target or, a loss of the neuron due cell death, will result in a loss of sensory inflow and some detectable sensory impairment. Positive symptoms result from changes in the injured primary sensory neurons but also in neighboring non-injured sensory neurons, as well as transynaptic changes in neurons at multiple levels of the CNS. What are these changes and how do they produce pain? I will briefly survey a few of the key mechanisms to illustrate how identifying these represent a major step forward in our understanding of neuropathic pain.

## **Ectopic excitability**

Injured and neighboring non-injured sensory neurons can develop a change in their excitability sufficient to generate pacemaker-like potentials, which evoke ectopic action potential discharges, a sensory inflow independent of any peripheral stimulus (Devor and Seltzer, 1999; Liu et al., 2002). These changes may manifest at the site of the injury, at the neuroma, and in the DRG. Ectopic input is most prominent in A fibers but also occurs to a more limited extent in cells with unmyelinated axons (Devor and Seltzer, 1999). Three factors appear to be responsible, upregulation of voltage gated sodium channels, including Nav1.3 and Nav1.8, down regulation of potassium channels, and possibly a reduction in threshold of Trp transducer heat sensitive channels so that they can be activated at body temperature (Waxman et al., 1999). The ectopic activity may directly initiate spontaneous sensations; paresthesia, dyesthesia and burning pain. In addition the spontaneous inflow may generate activity-dependent changes in excitability of central neurons (central sensitization). Potential treatment options aimed at ectopic activity include sodium channel blockers (ideally use-dependent blockers targeted at the

specific channels involved), potassium channel openers, Trp channel blockers, and treatment targeted at the mechanisms responsible for the alterations in the density, distribution or kinetics of these channels, blocking the alterations in the transcription, post-translational changes and trafficking of the ion channels after nerve injury.

### **Phenotypic switch**

Differentiated neurons are characterized by expression of a large number of specific genes enabling the cells to carry out their particular functions. For primary sensory neurons these include those genes that enable transduction, conduction, and synaptic transmission as well as many housekeeping and cytoskeletal genes. After peripheral nerve injury there is a surprisingly large change in the levels of transcripts, several hundred genes are either up or down regulated (Costigan et al., 2002; Xiao et al., 2002). These include regeneration-associated genes, survival factors and many genes that determine the function or malfunction of the neurons. A consequence of these changes are alterations in the excitability of the neurons (ectopic excitability, see above), as well as their transduction, and transmitter properties. Some changes include a switch in the phenotype of the neurons. For example, the neuromodulators BDNF and substance P are normally expressed only in C-fibers, but begin after peripheral nerve injury to be expressed in A fiber neurons (Noguchi et al., 1995; Fukuoka et al., 2001). This may mean that these fibers acquire the capacity to produce central changes such as central sensitization, which is normally produced only by C-fibers (Decosterd et al., 2002). The identification of the altered expression profile of sensory neurons after nerve injury is revealing many exciting new putative targets for novel analgesics and helps explain the differential action of some existing analgesics. The  $\alpha 2\delta$  calcium channel subunit, for example, is markedly upregulated after nerve injury (Luo et al., 2001; Costigan et al., 2002), and this may contribute to the analgesic action of gabapentinoids in neuropathic pain.

### **Primary sensory degeneration**

Peripheral nerve injury disrupts the contact of the cell bodies of DRG neurons with their peripheral targets. These targets are a source of growth factors such as NGF or GDNF. Following peripheral axonal injury there are over weeks, atrophic changes in the injured neurons, a reduction in axon caliber, a decrease in the size of the cell body and a loss of the contact that the central terminals of the afferents make with spinal cord neurons. Later, some months after the nerve injury some neurons begin to die, most of which are C-fibers (Tandrup et al., 2000). Although most treatment of neuropathic pain is aimed at reducing the positive symptoms, loss of neurons and the resulting imbalance of sensory inflow may contribute to the abnormal sensations. We need to evaluate what is responsible for nerve-injury induced sensory neuron loss and if preventing this is beneficial.

### **Central sensitization**

Central sensitization represents a state of heightened sensitivity of dorsal horn neurons such that their threshold of activation is reduced, and their responsiveness to synaptic inputs is augmented, essentially

the gain of the system is increased (Woolf and Salter, 2000). There are two forms of central sensitization; an activity-dependent form that is rapidly induced within seconds by afferent activity in nociceptors and which produces changes in synaptic efficacy that last for tens of minutes as a result of the phosphorylation and altered trafficking of voltage- and ligand-gated ion channel receptors, and a transcription-dependent form that takes some hours to be induced but outlasts the initiating stimulus for prolonged periods. Under normal conditions the activity-dependent form of central sensitization is produced only following the activation of small caliber A $\delta$  and C fiber afferents by a noxious or tissue damaging stimulus (Woolf, 1983; Woolf and Wall, 1986). After peripheral nerve injury C-fiber input may arise spontaneously and drive central sensitization. In addition, the phenotypic changes that occur in A fibers after nerve injury (see above) enable them now to drive central sensitization and repeated light touch can after nerve injury begin to produce central sensitization (Decosterd et al., 2002). The activity-dependent form of central sensitization is responsible for generating secondary pinprick hyperalgesia and dynamic tactile allodynia (Campbell et al., 1988; Koltzenburg et al., 1992). It obviously represents a major target for drug intervention, and the NMDA and AMPA receptors have been shown in many preclinical and clinical studies to have a major role, including in patients with neuropathic pain (Felsby et al., 1996). The problem is that these receptors are so widespread that there is insufficient therapeutic index to produce analgesia without significant CNS side effects. There may be other ways direct and indirect to reduce activity-dependent central sensitization. Indirect approaches could include reducing ectopic activity and preventing phenotypic switches. More direct approaches could include reducing transmitter release with calcium channel blockers (N-type) and  $\alpha 2\delta$  binding drugs, reducing post-translational changes with PKA, PKC, src or MAPK inhibitors, potassium channel openers, as well as antagonists for ligand-gated and G protein coupled receptors.

Transcription-dependent central sensitization has been studied in the context of peripheral inflammation where changes in BDNF, TrkB, substance P, NK1, dynorphin and Cox2 are well described (Neumann et al., 1996; Mannion et al., 1999; Ji et al., 2002). Much less is known about when, how and for how long this form of plasticity manifests in the dorsal horn after peripheral nerve injury, and the extent to which it contributes to neuropathic pain, this is an exciting challenge. There is certainly evidence that microglial activation may be involved (Jin et al., 2003; Watkins et al., 2001).

## Disinhibition

The balance of excitatory and inhibitory influences on neurons plays a major role in determining information flow through CNS circuits. Increases in excitation produced by increased inputs (ectopic activity) and increased responsiveness (central sensitization) shift the balance to increased excitability, which can manifest as spontaneous or evoked pain. A reduction in inhibition can have a very similar net result. Pharmacologically, blocking GABA or glycine-mediated inhibition produces a pattern of pain hypersensitivity very similar to that of neuropathic pain with very prominent tactile allodynia (Sivilotti and Woolf, 1994), and GABA blockade recruits previously absent A $\beta$  fiber inputs to lamina II cells, effectively uncovering a previously silent synaptic pathway (Baba et al., 2003). It turns out that partial nerve injury also reduces inhibition in the superficial dorsal horn with a selective loss of GABAergic inhibitory synaptic currents that is due to induction in GABAergic inhibitory interneurons of apoptosis (Moore et al., 2002). Peripheral nerve injury induces then, a transsynaptic neural degeneration that results in a loss of function which contributes to abnormal pain sensitivity. The implications of this are

considerable. It may become possible to prevent after nerve injury, cell death in the dorsal horn and in this way abort some elements of neuropathic pain preventing its chronicity. This would represent a disease modifying approach to the condition rather than just symptom control. There remain many questions to be answered, what is responsible for the nerve injury induced cell death, what is the duration of the therapeutic window of opportunity, what is the best form of therapy to prevent the cell loss.

## Conclusion

Dissecting out the mechanisms responsible for the production of neuropathic pain is helping both to explain how existing drugs produce their analgesic effects and is revealing novel biological and molecular targets which will lead to new drugs. Neuropathic pain constitutes a major clinical problem. Given the pace of recent advances in our understanding it is at last realistic to expect that new and improved therapy will become available to help control the syndrome.

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