



# GLOBAL YEAR AGAINST NEUROPATHIC PAIN

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## Mechanisms of Neuropathic Pain

Understanding the neurophysiological, cellular, and molecular mechanisms that contribute to neuropathic pain is important for the development of new therapeutic strategies. Many preclinical models of neuropathic pain have been developed.

- Most preclinical studies use partial peripheral nerve injury models in rodents. Common models include transection of two of the three distal branches of the sciatic nerve (spared nerve injury); transection or ligation of one or more spinal nerves (spinal nerve ligation); transection of half to two-thirds of the diameter of the sciatic nerve (partial sciatic nerve ligation); and constriction of the sciatic, and more recently the infraorbital, nerve (chronic constriction injury). Variations of these traumatic nerve injuries include models of neuritis and sciatica.
- Other preclinical models that perhaps better mimic the clinical neuropathic pain condition include peripheral neuropathies induced by diabetes, cancer chemotherapy, antiretroviral drugs, alcohol, and varicella zoster virus.
- Less common are preclinical studies of central neuropathic pain. These studies use rodent models of traumatic or neurotoxin-induced spinal cord injury or experimental allergic encephalomyelitis, which models multiple sclerosis.
- The typical testing endpoint is mechanical and thermal (heat or cold) hypersensitivity of the hindpaw or of the cheek. More recently, investigators have used conditioned place preference or conditioned place aversion assays, as well as tests involving other complex behaviors, such as burrowing and predator avoidance behaviors, to assess the behavioral impact of ongoing or spontaneous pain in the setting of nerve injury.
- Peripheral nerve injury induces extensive molecular changes throughout the primary sensory neuron, from the periphery to the cell bodies in the dorsal root, the trigeminal ganglia, the spinal cord, and the trigeminal nucleus. Which of these changes are essential contributors to the neuropathic pain phenotype is under intense study.
- Central sensitization is an important contributor to the persistent pain and allodynia following traumatic nerve injury.
- A wide array of molecular, anatomical, and electrophysiological changes in spinal cord dorsal horn circuits are induced by nerve and tissue injury and contributed to central sensitization. Molecules implicated in central sensitization include receptors, ion channels, second messengers, cytokines, and chemokines. These molecules derive from neurons, glia, blood-borne mediators, and invading immune cells.
- Many of the molecules implicated in central sensitization also contribute to the process of long-term potentiation, which is considered a substrate for memory generation and consolidation. In this respect, the neuropathic pain condition can be considered to result from a maladaptive memory of the injury.
- Coupling between sympathetic efferent and sensory afferent fibers at various sites may also contribute to the development of neuropathic pain. Adrenoceptor-mediated coupling can occur at the site of nerve injury (neuroma) as well as in dorsal root ganglia, where sprouting of sympathetic efferents has been observed after traumatic peripheral nerve injury. This aberrant sprouting may underlie a pathophysiological activation of sensory afferents that engage pain transmission circuits in the dorsal horn.
- Dynamic tactile allodynia, namely the generation of pain by activation of low-threshold mechanoreceptive myelinated afferents, can result from central sensitization of normally nociceptive-specific dorsal horn circuits.
- Loss of descending brainstem inhibitory controls or abnormal descending facilitation of spinal cord pain transmission circuits can also contribute to central sensitization and exacerbate the neuropathic pain condition.
- Loss of GABAergic inhibition at the level of the spinal cord dorsal horn and possibly at higher cortical centers (including the anterior cingulate gyrus) may contribute significantly to the neuropathic pain condition following nerve injury.
- Available data indicate that the decrease in GABAergic inhibition is largely due to a complex sequence of events that involve the ATP-mediated activation of microglia via P2X<sub>4</sub> purinergic receptors. Activated microglia, in turn, synthesize and release brain-derived neurotrophic factor (BDNF), which acts on TrkB receptors on dorsal horn neurons that transmit nociceptive messages. The BDNF-TrkB interaction alters the chloride gradient in the dorsal horn neurons, which reduces the inhibitory control exerted by GABAergic interneurons. The consequence is an increase in the excitability of dorsal horn neurons, enabling even low-threshold input to gain access to nociceptive circuits and thereby providing substrates for ongoing pain and allodynia.



- A major question in the field concerns the predictive validity of any given model, namely the extent to which the model can be used to predict the utility of a treatment modality in the clinical setting.
- Back-validation of the preclinical models is quite strong, in that agents that are effective in the clinic are generally effective in animal models. In fact, the great majority of effective compounds in the clinic are anticonvulsants and antidepressants, which have proven effective in animal models. What is clearly necessary is the successful translation to the clinic of novel therapeutics that are effective in the animal models.