

## REVIEW ARTICLE

# Emerging concepts and treatment in neuropathic pain

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### Abstract

Knowledge in neuropathic pain has grown rapidly during the past few years. Central and peripheral sensitization is still believed to be the main pathophysiology. New evidence suggests many potential new molecular targets and mechanisms, such as cytokines, lysophosphatidic acid and ion channels. Microglia and astrocyte activation leads to dysregulation of inflammatory cytokines and pain signaling. Many subtypes of the sodium channel have been shown to be the culprit for both congenital and acquired pain syndromes, especially small fiber neuropathy. Lysophosphatidic acid is thought to act as an initiator of neuropathic pain, along with other mediators. Animal models of neurodegenerative diseases and chemotherapy-induced neuropathy reaffirm the role of nociceptor degeneration and cytoskeletal breakdown in peripheral neuropathy. With better understanding of its mechanism, it may lead to new therapeutic targets. Recent trials of new medications, new formulations or new indication of old drugs have shown promising data. We can look forward to better treatment of this debilitating symptom in the near future.

### INTRODUCTION

Neuropathic pain has recently been redefined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. This revised definition emphasizes the importance of pathophysiology in the sensory pathway, which ranges from painful neuropathy to central poststroke pain.<sup>1</sup> Neuropathic pain research has progressed significantly in recent years. In this review, new information in this field is reexamined and summarized; particularly the underlying mechanisms, targeted therapy and new use of known medications.

### NEW DATA ON KNOWN AND ACCEPTED MECHANISMS

#### *Peripheral sensitization*

Ectopic nerve activity after peripheral nerve lesion causes ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus. This is thought to be due to abnormal ectopic impulse generation within the nociceptive pathway after maladaptation of both intact and injured nerves. Voltage-gated sodium channel is thought to play a crucial role

in increased membrane excitability. There are also upregulation of various receptor proteins in the transient receptor potential (TRP) family, such as TRPV1 and TRPM8, induced by nerve injury, resulting in alterations of the threshold of both large and small nerve fibers. All the above mechanisms are also thought to play important roles in primary allodynia and primary hyperalgesia.<sup>2</sup>

#### *Central sensitization*

Concept of central sensitization is well known and plays an important role in many pain conditions, such as fibromyalgia, migraine headache, musculoskeletal pain and other chronic pain disorders. It is essential in pain hypersensitivity, particularly allodynia, hyperalgesia and enhanced temporal summation of pain perception.

Known central sensitization mechanism includes changes in dorsal root ganglia and dorsal horn of spinal cord after nerve injury. Abnormal sensory barrage induces postsynaptic changes and hyperexcitability of second-order nociceptive neurons. It redirects non-painful tactile stimuli signals, which normally synapses at deeper layer of spinal cord, via abnormal wide dynamic range

neurons to the substantia gelatinosa layer, leading to pain perception.

Recent studies suggest that central sensitization is not simply the consequence of a “switching on” of the “pain system” in the periphery, but instead reflects to a substantial extent, the state of excitability of central nociceptive circuits. Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in the central nociceptive pathways. The activity-dependent synaptic function is then increased and maintained by continuous peripheral inputs. The sensitivity of the pain system is increased and misinterprets the non-noxious stimuli as pain, resulting in allodynia. This process may become exaggerated, prolonged and spread to the contralateral side.

In addition, this concept may contribute to post-surgery and post trauma pain. Drugs with known mechanisms to reduce central sensitization such as ketamine, pregabalin, gabapentin and duloxetine may be helpful as pre-emptive analgesia to control postoperative pain.<sup>3</sup>

## EMERGING CONCEPTS AND MECHANISM

### *Role of microglia and astrocytes*

Astrocytes and microglia express various neurotransmitter receptors and are activated by glutamate, ATP and substance P. At synapses, the glutamate transporters (glutamate transporter 1 (GLT1) and glutamate–aspartate transporter (GLAST)), which are crucial for clearing synaptic glutamate, become dysregulated after prolonged exposure to high levels of synaptic glutamate.<sup>4</sup> Ongoing excitation can induce many kinase enzymes, eg. mitogen activated-protein kinase (MAPK)/ extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) activation in microglia and astrocytes. The MAPK/ERK is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell, while JNK mediates pro-inflammatory actions of microglia.<sup>5</sup> Each of these kinases can activate the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B), which induces the synthesis of inflammatory factors. Upregulation of the V1 transient receptor potential channel (TRPV1) after inflammation further contributes to the sensitization to noxious signals. During this time, normally non-nociceptive A $\beta$  fibers can also activate pain-projection neurons.<sup>4</sup>

There is a rapidly growing body of evidence

indicating that microglia, the CNS immune cells, have causal roles in the pathogenesis of pain hypersensitivity following nerve injury. In an animal model, activation of microglia in the dorsal horn of the spinal cord was seen very soon after peripheral nerve injury which is followed by its proliferation. Important microglia-expressed molecules in this mechanism include purines, chemokines, cannabinoids, immune related molecules, mitogen-activated protein kinases, and Src-family kinases.<sup>6</sup>

Removal of glycine inhibition results in tactile stimuli able to activate astrocytes; activated astrocytes may provide d-serine to enable n-methyl-d-aspartate (NMDA) receptor activation and thus allodynia, supporting the important role of astrocytes in pain signaling.<sup>7</sup>

### *Neurodegenerative mechanism of nociceptor*

Neuropathic pain is often underappreciated in neurodegenerative diseases. Mitochondrial and cytoskeletal dysfunction, which has been known to be part of neurodegenerative processes, have been hypothesized to be the key player in neuropathic pain pathophysiology, especially in peripheral sensory nerve fibers. Preclinical animal models of common peripheral neuropathic pain supported the idea that a subset of these cellular mechanisms of neurodegeneration can produce painful hyperactivity in primary afferent nociceptors. This emerging concept may help in identifying novel molecular targets for the treatment of neuropathic pain.<sup>8</sup>

### *Importance of ion channel in neuropathic pain*

Animal models of cancer-chemotherapeutic drug-induced neuropathy (such as paclitaxel, vincristine, oxaliplatin) also give insight to cellular mechanisms of neuropathic pain. These drugs activate plasma membrane localized ion channels on dorsal root ganglia and dorsal horn neurons including sodium, calcium, potassium, glutamate activated NMDA receptors to alter cytosolic ionic milieu particularly intracellular calcium that trigger secondary changes to induce neuropathic pain. These may include opening of mitochondrial permeability transition pore (mPTP) on mitochondria to induce intracellular calcium release; activation of protein kinase C; phosphorylation of TRPV; activation of calpases/calpains; and generation of nitric oxide and free radicals to induce cytotoxicity to axons and neuronal cell bodies. Furthermore, the inflammatory process initiated in glial cells and

macrophages also trigger changes in the sensory neurons to alter nociceptive processing.<sup>9</sup> Altered mitochondrial structure and function in peripheral sensory fibers can also be reversed by agents that enhance mitochondrial function.<sup>10</sup>

A recent study using an animal model suggests that mice in which hyperpolarization-activated cyclic nucleotide-gated (HCN) channel 2 (HCN2) was specifically deleted in nociceptors expressing voltage gated sodium channel (NaV) type 1.8 had normal pain thresholds. When inflammation was induced, it did not cause hyperalgesia to heat stimuli in these mice. After a nerve lesion, they showed no neuropathic pain in response to thermal or mechanical stimuli. It was thus proposed that neuropathic pain is initiated by HCN2-driven action potential firing in NaV1.8-expressing nociceptors.<sup>11</sup>

Voltage-gated sodium channel NaV1.7 is preferentially expressed in dorsal root ganglion and sympathetic ganglion neurons and their axons, and opens in response to small depolarizations close to resting potential. Gain of function mutations in the SCN9A gene encoding NaV1.7 have been found to cause painful disorders such as inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD), which are characterized by increased excitability of dorsal root ganglion neurons, and loss of function mutations of NaV1.7 have been linked to channelopathy-associated insensitivity to pain.<sup>12</sup>

Gain of function mutations in sodium channel NaV1.7, which render dorsal root ganglion neurons hyperexcitable, are present in a substantial proportion (28.6%; 8 of 28) of patients meeting strict criteria for idiopathic small fiber neuropathy. These results point to a broader role of NaV1.7 mutations in neurological disease than previously considered from studies on rare genetic syndromes, and suggest an etiological basis for idiopathic small fiber neuropathy, whereby expression of gain of function mutant sodium channels in small diameter peripheral axons may cause these fibers to degenerate.<sup>13</sup>

#### *Lysophosphatidic acid: the initiator of neuropathic pain*

A recent study suggests the important role of lysophosphatidic acid (LPA) as an initiator of neuropathic pain. The conversion of phosphatidyl choline (PC), which is the component of membrane protein, to lysophosphatidyl choline (LPC) is mediated by cytosolic phospholipase A2 (cPLA2) and calcium-independent PLA2 (iPLA2),

which are activated by receptor-mediated MAPK, protein kinase C (PKC), and Ca<sup>2+</sup>. Autotaxin/lysophospholipase D (ATX/LPLD) subsequently converts LPC to LPA.<sup>14</sup>

LPA also directly activates the transient receptor potential channel TRPV1 by binding to its intracellular C terminus to mediate acute inflammatory pain sensation. Acute pain is mediated via LPA activation of TRPV1 channels present in the sensory nerve endings and some dorsal root ganglion cells. The sources of LPA accessing the C terminus of TRPV1 are unclear. Chronic pain is mediated by the G protein-coupled receptor (GPCR) LPA1 expressed in DRG and Schwann cells. Activation of the latter pool of LPA1 receptors leads to demyelination, whereas LPA1 expressed in the dorsal root ganglion modulates neurotransmitter release, neurite retraction and sprouting.<sup>15</sup>

The intense stimulation of sensory fibers causes biosynthesis of LPA in spinal cord neurons. LPA1 receptor activation causes demyelination and sprouting of dorsal root fibers, leading to an induction of synaptic reorganization underlying allodynia, in which innocuous (tactile) stimuli cause intense pain. The LPA1 signal also initiates the up-regulation of  $\alpha$ -2,  $\delta$ 1 type of calcium channel in dorsal root ganglion and PKC gamma in the dorsal horn, underlying mechanisms for characteristic neuropathic hyperalgesia in myelinated sensory (A-type) fibers. On the other hand, the LPA3 receptor mediates microglia activation at the early stage after nerve injury and LPA-induced LPA biosynthesis. Thus, both the LPA1 and LPA3 receptors play key roles in the initiation step using a feed-forward system for neuropathic pain.<sup>16</sup> These results lead to further hypotheses of physical communication between innocuous A $\beta$ - and noxious C- or A $\delta$ -fibers to influence the molecular mechanisms of neuropathic pain.

#### **NEW DRUGS AND NEW USE OF KNOWN DRUGS**

##### *Dextromethorphan*

NMDA receptor plays an important role in central sensitization process, however, oral medication which targets at this receptor was not available until recently. Dextromethorphan, the common oral cough suppressant in many cough medicinal products, has been used at the dosage of 10-20 mg every 4 hours and maximum dose of 120 mg/day in adult. It is known to

have NMDA antagonistic activity which is an attractive target for neuropathic pain treatment. Additional actions of dextromethorphan include agonist of the sigma-1 receptor, antagonist of the N-type calcium channel, and antagonist at the serotonin reuptake transporter. Therefore, it has been tested in this indication. However, the results were not satisfactory due to inability to achieve the desired drug level. This medication is rapidly and extensively metabolized by hepatic cytochrome P450 2D6. In the absence of P450 2D6 blockade, plasma dextromethorphan levels in some recipients have been undetectably low, even for oral dosage as high as 750 mg/day.

Quinidine is a potent hepatic cytochrome P450 2D6 inhibitor. Therefore, combination of these two drugs will aid in increasing dextromethorphan level to therapeutic level.<sup>17</sup> This combination drug has been approved for pseudobulbar palsy indication by US FDA.<sup>18</sup> The initial trial result in painful diabetic polyneuropathy was promising.<sup>19</sup>

#### *Lacosamide*

Lacosamide is a new antiepileptic drug and was approved for use as an adjunctive treatment for partial-onset seizures. Its dual effects are selective enhancement of slow activation of voltage-gated sodium channels and binding to the collapsin response mediator protein 2 (CRMP2) is involved in the down regulation of a subunit of the NMDA receptor—a key modulator of the transmission of pain. Owing to this potential benefit, it was tested in patients with painful diabetic neuropathy. The initial results showed modest effect<sup>20,21</sup>, but the recent meta-analysis did not support the use for neuropathic pain due to its relatively low efficacy. A higher dosage did not give consistently better efficacy, but was associated with significantly more adverse event and withdrawals.<sup>22</sup> Currently, it is not approved for this indication.

#### *Cannabinoids (CB)*

Endocannabinoid system (ECS) is centrally and peripherally involved in the processing of pain signals. Mammalian tissues express two types of CB receptors. CB<sub>1</sub> receptors are primarily expressed in the central nervous system, where as CB<sub>2</sub> are primarily located in the periphery, especially immune cells.<sup>23</sup> Its action in the central nervous system is mediated through a CB<sub>1</sub> receptor-dependent retrograde mechanism involving the release of

neurotransmitters controlling nociceptive inputs and inflammation.

Recent meta-analysis of smoked cannabis, oromucosal extracts of cannabis based medication, nabilone, dronabinol and tetrahydrocannabinol (THC) analogue in chronic non-cancer pain conditions, ie. neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain showed significant analgesic effects of cannabinoids vs. placebo. Several trials also reported significant improvements in sleep. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and few withdrawals. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.<sup>24</sup>

Due to its abuse potential and current formulation, regulatory approval and clinical usage are currently limited. Since the centrally acting CB<sub>1</sub> agonists are known to produce CNS side effects, many CB<sub>2</sub> agonists are being developed as anti-inflammatory and anti-neuropathic pain medication, based on its proposed action at peripheral sites, such as dorsal root ganglia and spinal cord.<sup>23,25</sup>

#### *Tapentadol*

Tapentadol is a new analgesic with a dual mode of actions which are agonist of the mu opioid receptor and inhibitor of norepinephrine reuptake. It has been studied for treating inflammatory and neuropathic pain, including painful diabetic polyneuropathy and chronic back pain.<sup>26,27</sup> Its potency is two to three folds lower than morphine, but the development of tolerance in animal models is significantly slower than observed with morphine.<sup>28,29</sup> Currently, it has been approved in many countries for the relief of moderate to severe acute pain.<sup>30</sup>

#### *Botulinum toxin*

In addition to the known mechanism of inhibition of acetylcholine release from presynaptic nerve terminal at neuromuscular junction, botulinum toxin also preferentially blocks neurotransmitter release and transient receptor potential vanilloid subfamily, member 1 (TRPV1) receptor signaling in C-fibers. Therefore, it can reduce neurogenic inflammation and increase heat pain threshold. There were some positive studies in painful diabetic neuropathy.<sup>31,32</sup>

### *Capsaicin*

Capsaicin topical preparations have been used in many countries worldwide for various painful conditions, especially musculoskeletal pain. For painful diabetic neuropathy, it is recommended at the concentration of 0.075%.<sup>33</sup> Multiple mechanisms underlie capsaicin-induced defunctionalization of nerve fiber terminals. Inactivation of voltage-gated Na<sup>+</sup> channels and direct pharmacological desensitization of plasma membrane TRPV1 receptors may contribute to an immediate reduction on neuronal excitability and responsiveness. More persistent effects may be due to the overwhelming of intracellular Ca<sup>2+</sup> buffering capacity by extracellular Ca<sup>2+</sup> entering through TRPV1 and being released from intracellular stores, with subsequent activation of calcium-dependent proteases and cytoskeleton breakdown. Microtubule depolymerization may interrupt fast axonal transport. At concentrations far in excess of those required to activate TRPV1, capsaicin can also render mitochondria dysfunctional by directly inhibiting electron chain transport. Thus mitochondria are a key convergence point for defunctionalization.<sup>34</sup>

The site of action of topical capsaicin is in the skin, and pain relief is not mediated by transdermal systemic delivery. Owing to near insolubility in water, capsaicin is not readily absorbed into the microvasculature. When cutaneous nociceptors are hypersensitive and sometimes spontaneously active, localized defunctionalization of capsaicin-responsive nerve fiber terminals in the epidermis and dermis can reduce the afferent barrage which may drive pain syndromes.<sup>34</sup>

New formulation of 8% capsaicin patch was recently approved for post herpetic neuralgia (PHN) indication.<sup>35</sup> With only single one-hour application, it provided up to 12 weeks of pain relief in PHN<sup>35</sup>, as well as in painful HIV-associated polyneuropathy.<sup>36</sup> Recent meta-analysis reported number needed to treat of 6.46 in this particular condition.<sup>37</sup>

### *Pregabalin*

Pregabalin, the alpha2 delta1 calcium channel ligand, has been extensively used for relieving many neuropathic pain conditions for the past several years. However, there was limited data in radiculopathic pain. Recent data from open-label studies and post marketing surveillance were encouraging.<sup>38-40</sup> However, recent randomized controlled clinical trial result was inconclusive.<sup>41</sup> From a small study result, when combining

pregabalin with celecoxib as multimodal pain control in chronic low back pain, the combination is more effective than monotherapy with similar adverse events.<sup>42</sup>

Pre- or peri-operative use of pregabalin or gabapentin has shown benefit in acute post operative pain, especially its opioid sparing effect. Many surgical trials reported both short term and long term benefits in many types of surgery such as cardiac surgery<sup>43</sup>, abdominal hysterectomy and/or salphingo-oophorectomy<sup>44</sup>, lumbar laminectomy and discectomy<sup>45</sup>, lumbar spinal fusion surgery<sup>46</sup>, etc. This finding was confirmed in two meta-analyses.<sup>47,48</sup>

### *Summary*

There are recent advances in neuropathic pain pathophysiology. Emerging key players in central sensitization are microglia/astrocyte, ion channel, and lysophosphatidic acid. The understanding of neurodegenerative process of nociceptor and peripheral nerve fiber will lead to new therapeutic targets. Clinical trials of new medications or new formulations have shown promising data in various pain syndromes. This will add new therapeutic modalities to physicians' future armamentarium to counter pain.

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