

Neuropathic pain and Kv7 voltage-gated potassium channels: The potential role of Kv7 activators in the treatment of neuropathic pain

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Abstract

Neuropathic pain conditions severely and chronically affect the quality of life in a large human population, but the pain conditions are not adequately managed due to poor understanding of their underlying mechanisms. There is a pressing need for further research into this field to help develop effective and nonaddictive medications to treat neuropathic pain. This article first describes general clinical classification of pain, types and symptoms of neuropathic pain, and current practices of clinical management for neuropathic pain. This is followed by a discussion of various cellular and molecular mechanisms responsible for the development and maintenance of neuropathic pain. In this review, we highlight the loss of function of Kv7 voltage-gated potassium as a mechanism of neuropathic pain and the potential use of Kv7 channel activator as subsequent treatment.

Keywords

Neuropathic pain, voltage-gated K⁺ channels, hyperalgesia, allodynia, retigabine, flupirtine

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Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is classically subdivided into acute pain and chronic pain. Acute pain is a physiologic response to an adverse chemical, thermal, or mechanical stimulus.¹ Typically, short-lived, acute pain usually resolves within one month. However, certain acute pain pathologies as well as acute pain that is untreated, undertreated, or treated inappropriately can progress to chronic pain. Chronic pain is pain without apparent biologic value that has persisted beyond the normal tissue healing time. Chronic pain is multifaceted and composed of numerous pain syndromes and disorders; some of the more common types being neuropathic pain, radicular pain, and cancer pain.² Chronic pain is extremely difficult to manage and even harder to cure. Unfortunately, chronic pain is extremely common in the United States with a prevalence of 11.2% or over 25 million adults with an annual cost estimated at \$560–\$635 billion dollars.^{3–5} Of the various chronic pain syndromes, neuropathic pain deserves special attention

for several reasons: neuropathic pain is generally more severe than other types of chronic pain, it is associated with worse health outcomes compared to nonneuropathic pain, individuals with neuropathic pain have health-related quality of life ratings as low as individuals with clinical depression, and neuropathic pain is pervasive with a reported prevalence of 7%–8%.^{6–10}

Neuropathic pain is typically characterized as a burning or stabbing sensation and is often associated with

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allodynia or hyperalgesia. Hyperalgesia refers to a heightened response to normally painful stimuli. Allodynia refers to the experience of pain induced by innocuous stimulus. Some important types of allodynia are mechanical allodynia (static or dynamic), thermal allodynia (hot or cold), and movement allodynia. Allodynia is associated with severe pain induced by stimuli that are not normally painful, and it is associated with several disease conditions including complex regional pain syndrome (CRPS), chronic low back pain, and fibromyalgia.^{11–15}

There are several types of neuropathic pain conditions including sympathetic neuropathic pain, peripheral neuropathic pain, and central neuropathic pain based on nervous systems that are involved. Sympathetic neuropathic pain is pain arising from a peripheral nerve lesion and associated with autonomic changes. Complex regional pain syndrome is a common example of sympathetic neuropathic pain. Peripheral neuropathic pain is pain caused by damage to peripheral nerves but without autonomic changes. Examples of peripheral neuropathic pain include postherpetic neuralgia, trigeminal

neuropathic pain, chemotherapy-induced peripheral neuropathy, diabetic peripheral neuropathy, and neuro-oma formation.¹⁶ Central neuropathic pain is caused by abnormal central nervous system (CNS) activity. Examples include phantom limb pain, poststroke pain, and pain from spinal cord injuries.^{16,17} Table 1 lists some examples of neuropathic pain conditions and some treatment modalities. It must be stated that the treatment of neuropathic pain should be multimodal and the most effective treatment will depend on the type of neuropathic pain as well as patient-specific factors.

Neuropathic pain is overall a more severe form of pain when compared to other nonneuropathic pain conditions, and it can be accompanied by anxiety and depression. Patients with neuropathic pain also reports quality-of-life metrics similar to patients with other serious conditions such as cardiac disease, poorly controlled diabetes mellitus, and clinical depression.^{8,9,18} The armamentarium for neuropathic pain treatment (Table 1) is vast and includes medication classes such as sodium channel blockers, opioids, local anesthetics, antiepileptic

Table 1. Types of neuropathic pain and clinical management.

Types of neuro-pathic pain	Examples	Management
Sympathetic neuropathic pain	CRPS types I and II	<p>Physiologic therapies group therapy, individual therapy.</p> <p>Medications <i>Anticonvulsants:</i> Gabapentin, carbamazepine, valproate, clonazepam.</p>
Peripheral neuropathic pain	<p>Postherpetic neuralgia</p> <p>Trigeminal neuralgia</p> <p>Chemotherapy-induced peripheral neuropathy</p> <p>Diabetic peripheral neuropathy</p>	<p><i>Antidepressants:</i> Tricyclic antidepressants (nortriptyline and amitriptyline), serotonin selective reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors.</p> <p><i>Opioids:</i> Oxycodone, hydrocodone/acetaminophen, oxycodone/acetaminophen, tramadol, morphine sulfate controlled release, oxycodone hydrochloride controlled release tablets, hydromorphone, methadone.</p> <p><i>Topical analgesics:</i> Lidocaine patch, capsaicin</p>
Central neuropathic pain	<p>Phantom limb pain</p> <p>Poststroke pain</p> <p>Pain from spinal cord injuries</p>	<p><i>Interventions</i> Sympathetic blocks, epidural and transformational steroid injections, spinal cord stimulators, peripheral nerve stimulators, intrathecal pumps.</p> <p>Physical and alternative therapies Massage therapy, acupuncture, nutritional counseling.</p> <p>Mirror therapy Phantom limb pain and complex regional pain syndrome only.</p>

CRPS: complex regional pain syndrome.

medications, tricyclic antidepressants, and serotonin reuptake inhibitors. The efficacy and specific uses of these various medications have been discussed elsewhere and will not be discussed here.¹⁹ In addition, a robust group of invasive procedures joins the list of treatment options. This list of invasive procedures includes facet joint injections, facet joint denervation, epidural steroid injections, transforaminal epidural injections, spinal cord stimulators, and peripheral nerve catheters. Despite the multitude of treatment options available, neuropathic pain is extremely difficult to treat with only 50% of patients reporting relief from the various available treatments. This relief is also often only partial and accompanied by a host of side effects. The numerous conditions resulting in neuropathic pain certainly contribute to its challenging management; despite this, the primary obstacle in neuropathic pain treatment is its complex pathophysiology.

Neuropathic pain pathophysiology

In the past, an etiology-based approach was used to understand the pathophysiology of neuropathic pain. One of the primary limitations of this approach was that the diverse causes of neuropathic pain made selecting the appropriate model difficult. Furthermore, many authors suggested that data acquired from using a specific neuropathic pain syndrome as a model to study the pathophysiology of neuropathic pain had limited generalizability to other neuropathic pain syndromes. More recently, there has been a shift in philosophy away from an etiology-based approach and more toward a mechanism-based approach. This approach is favored both for understanding the pathophysiology of neuropathic pain and treating it. One of the many benefits of the mechanism-based approach is that it somewhat circumvents the conundrum of selecting the most appropriate model or syndrome in which to study neuropathic pain, and it allows for maximum generalizability of research findings. The two widely accepted mechanism-based causes leading to neuropathic pain are central and peripheral sensitization, and each warrants a more detailed discussion. Prior to exploring each further, it must be mentioned that much of our current knowledge on both mechanisms have been derived from animal models. While these models certainly have important implications, they often do not precisely predict human pain processes because neuropathic pain conditions in humans have very complicated causes and are influenced by many factors including genetics and epigenetics.

Central sensitization as a mechanism of neuropathic pain

The dorsal horn of the spinal cord and brainstem is a region of the CNS where sensory information about mechanical, thermal, and painful stimuli carried by peripheral afferent nerves is integrated and then conveyed to the brain.²⁰ Dorsal horn neurons receive millions of inputs per minute; however, the majority of these inputs are subthreshold and the synaptic strength is too weak to produce an action potential.²¹ However, if the synaptic efficacy in the sensory neurons in the dorsal horn is increased, and then these once subthreshold stimuli are able to elicit action potentials.²¹ Sustained peripheral noxious stimuli, tissue injury, or nerve damage can cause increased synaptic efficacy in the sensory neurons of the dorsal horn in the spinal cord and brainstem, which can lead to central sensitization in the spinal cord and brainstem nociceptive pathways.^{20,21} As a result of this increased synaptic efficacy, there is a reduction in pain thresholds, amplification of pain responses, and spread of pain sensitivity to uninjured tissues. Clinically, central sensitization contributes to pain hypersensitivity in the skin, joints, muscles, and viscera. There are several subtypes of central sensitization, some of which include wind-up, activity-dependent classical central sensitization that outlast the initiating stimulus, long-term potentiation, late onset transcription-dependent, and late onset activity-independent sensitization.^{20,21} Each of these subtypes has distinct mechanisms utilizing various transcription factors, voltage-gated channels, and neurotransmitters. The precise mechanisms governing these subtypes are beyond the scope of this article. Ji et al. provide an excellent summary of the mechanisms underlying each of these subtypes in their previous paper²¹ and the details will not be restated here. In addition to the enhanced dorsal horn neuron efficacy, other mechanisms that may contribute to central sensitization include the loss of function of dorsal horn inhibitory neurons (disinhibition), changes in the intrinsic electrophysiological properties of dorsal horn neurons, and alterations of A β -afferent nerve chemical phenotypes and terminal distributions in the dorsal horn.²⁰ Suffice to say these various mechanisms contribute to the global process of central sensitization. A process which ultimately results in subthreshold stimuli gaining access to the ability to trigger action potentials in nociceptive pathways from the dorsal horns to the brain regions involving the perception of pain.

Peripheral sensitization as a mechanism of neuropathic pain

The key event for peripheral sensitization is nerve damage which ultimately leads to neuroma formation. This is usually followed by abnormal excitability and

increased sensitivity to different forms of stimulation including chemical, thermal, and mechanical stimuli. The increased excitability can be developed at multiple sites including the neuroma itself, dorsal root ganglion, peripheral nerve endings, and neighboring intact afferents. Numerous mechanisms contribute to the pathophysiology of peripheral sensitization. The known mechanisms can be grouped into changes in ion channel expression and functions, changes in cytokines, and changes in intracellular signaling pathways.²²

A number of studies reported changes in voltage-gated sodium channel expression after nerve injury. Sodium channel Nav1.3, Nav1.7, Nav1.8, and Nav1.9 have been implicated in the primary afferent hyperexcitability resulting in peripheral sensitization. Studies have shown the new formation of clusters of sodium channels at the injured nerve sites and the intact dorsal root ganglion following nerve injury.²² Clinically, sodium channel blockers have been used in treating neuropathic pain with varying degree of success. There are several studies highlighting the importance of cytokines such as tumor necrosis factor- α (TNF- α) and interleukin (IL)-1 β in the pathophysiology of peripheral sensitization. It has been reported that peripheral nerve injuries increase TNF- α and IL-1 β immunoreactivity in dorsal root ganglia of both injured and uninjured ipsilateral adjacent afferents.²³ Peripheral sensitization can also result from the upregulation of several proteins that have limited expression under physiological conditions.²⁴ Upregulation of transient receptor potential channel expression has been shown to contribute to neuropathic pain resulting from sciatic nerve transection and spinal nerve ligation.^{25–28} Specifically, upregulation of TRPV1 channels, the thermal receptors that are activated by noxious heat, contributes to neuropathic pain.^{27,29} Upregulation of TRPM8 channels, the cold-sensing receptors, contributes to cold allodynia and hyperalgesia in animals following sciatic nerve injury.³⁰ A number of signaling pathways such as extracellular-regulated kinases, protein kinase C, and mitogen-activated protein kinase play an important roles in peripheral sensitization.²⁴

Downregulation of Kv7 channel functions and expression as a potential mechanism of peripheral hypersensitization and neuropathic pain

Voltage-gated K⁺ channels are involved in action potential repolarization and damping membrane depolarization and are fundamentally important in controlling neuronal excitability. Neuronal membrane hyperexcitability due to the loss of function of voltage-gated K⁺ channels is an important mechanism underlying

neuropathic pain. Studies have suggested that changes in potassium channel expression may be important in the pathophysiology of peripheral sensitization and neuropathic pain. Ishikawa et al. showed changes in the expression of voltage-gated potassium channels in the dorsal root ganglion following axotomy.³¹ Kim et al. showed a downregulation of gene expression of voltage-gated potassium channel alpha subunits in the dorsal root ganglion following chronic constriction injury in rat sciatic nerves.³² Yang et al. showed altered potassium channel mRNA expression following peripheral nerve lesion.³³ Considerably less research has been done on medications-targeting potassium channels, especially compared to sodium channel blocking agents. Medications affecting potassium channels may be a powerful addition to the currently available treatments for neuropathic pain, and they warrant a more in depth discussion.

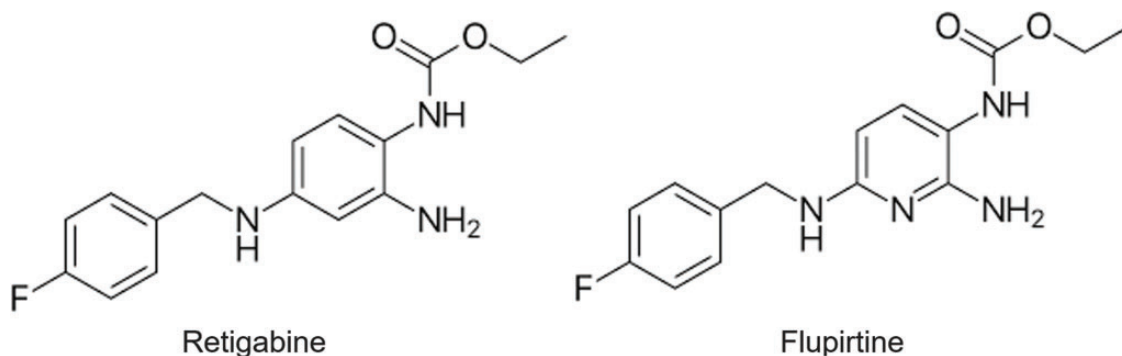
In the large family of voltage-gated K⁺ channels, the KCNQ gene family encodes a subfamily of voltage-gated potassium channels termed Kv7 channels (Kv7.1–Kv7.5). These channels stabilize membrane excitability via non-inactivating K⁺ currents termed M currents.^{34,35} Kv7.2–Kv7.5 channels are found in many neuronal tissues, while Kv7.1 are located in cardiac as well as various smooth muscle and epithelial tissues.³⁴ Kv7.2 and Kv7.3 are predominantly expressed in nociceptive dorsal root and trigeminal ganglion neurons,³⁴ suggesting their potential role in regulating nociception. Kv7 channel activity can be modulated by biological factors including intracellular signaling from G-protein-coupled receptor pathways associated with muscarinic acetylcholine receptors, or by covalent modification of cysteine residues by hydrogen peroxide or N-ethylmaleimide.^{36–42} Phospholipase C-mediated inhibition of Kv7 channels is reported to contribute to peripheral inflammatory pain.⁴³ These signaling pathways lead to functional downregulation of Kv7 channels that contribute to peripheral hypersensitivity of nociceptors. Expression of Kv7.2 channels in somatosensory neurons have been shown to be downregulated in animals following peripheral neuropathy induced by chemotherapy drug oxaliplatin.⁴⁴ The downregulation of Kv7.2 channel expression in the primary afferent nerves is also thought to be an underlying mechanism of neuropathic pain.⁴⁴

Kv7 activators and their therapeutic uses for neuropathic pain

Kv7 channels have been explored as therapeutic targets for treating diseases due to neuronal membrane hyperexcitability. Compounds that either potentiate or directly open neuronal Kv7 channels can produce an inhibitory effect on action potential initiation. This inhibitory effect can be beneficial in treating diseases

Table 2. Kv7 channel activators.

Compound name	Kv7 channel subtypes targeted
Acrylamide (S)-1	Kv7.2, 7.3, 7.4, 7.5 and Kv7.2–Kv7.3
Acrylamide (S)-2	Kv7.2
4,4-diisothiocyanatostilbene-2,20-disulfonic acid	Kv7.1–KCNE1
Maxipost (BMS-204352)	Kv7.2, 7.3, 7.4 and 7.5
Diclofenac	Kv7.2, 7.3 and Kv7.2–Kv7.3
Flufenamic acid	Kv7.1–KCNE1
Meclofenamic acid	Kv7.2, 7.3 and Kv7.2–Kv7.3
Mefenamic acid	Kv7.1–KCNE1
NH6	Kv7.2–Kv7.3
Niflumic acid	Kv7.1–KCNE1
Retigabine	Kv7.2, 7.3, 7.4, 7.5 and Kv7.2–Kv7.3
(Retigabine analog) flupirtine	Kv7.2
L-364 373 [(3-R)-1, 3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-methyl-2H-1,4-benzodiazepin-2-one (R-L3)]	Kv7.1, Kv7.1–KCNE1
Zinc pyrithione	Kv7.1, 7.2, 7.4, 7.5 and Kv7.2–Kv7.3

**Figure 1.** Chemical structures of retigabine (left) and flupirtine (right).

involving neuronal hyperexcitability such as epilepsy and neuropathic pain.^{45,46} A list of synthetic compounds that can directly bind to Kv7 channels to cause a conformational change leading to channel opening is shown in Table 2.

Among them, retigabine (Figure 1) has been most extensively studied for its actions on Kv7 channels in the neurons of the CNS and peripheral nervous system. Retigabine directly opens most Kv7 channels, including heteromeric Kv7.2–Kv7.3 channels, causing enhancements of M currents. The drug exerts a hyperpolarizing effect on neurons, and an action attributed to its ability to activate Kv7 channels expressed in many neurons.^{47,48} Other studies have shown that retigabine is also involved in the potentiation of other channels, including gamma-aminobutyric acid (GABA) receptors.⁴⁹ A study conducted in rats found that Kv7.2 channels were expressed on cold-sensing trigeminal ganglion neurons, and that through treatment with retigabine, the excitability of nociceptive cold-sensing neurons was suppressed.⁵⁰ The study further showed that orofacial cold

allodynia and hyperalgesia induced by trigeminal nerve injury in rats could be effectively alleviated by retigabine.⁵⁰ This study concluded that Kv7.2 channels can be targeted for treatment of trigeminal neuropathic pain. Another study performed in 2003 found similar results, and the study found that injection of retigabine significantly reduced hypersensitivity to injured paws of rats.⁵¹

In humans, retigabine was introduced under the trade name Potiga in the United States and approved in 2011 by Food and Drug Administration for adjuvant treatment of partial-onset seizures in epileptic patients. Its potential uses in treating other disorders such as anxiety and neuropathic pain were also discussed.^{51–53} However, clinical use of retigabine has been discontinued since June 2017 due to its side effects. Clinical trials with retigabine have identified mostly CNS-related adverse. These include dizziness, somnolence, headache, and fatigue.^{54,55} Additional unique adverse effects include urinary retention and pigment changes in the skin and retina after prolonged use.⁵⁶ Clinical use of retigabine is

also limited by its short half-life of 8 h, requiring frequent dosing. Flupirtine, a structural analog of retigabine (Figure 1), has been used in Europe for the treatment of acute and chronic pain since the 1980s; it is not clinically available in the United States. Flupirtine has a similar mechanism of action as retigabine at Kv7 channels, and it has also been shown to potentiate GABA-mediated analgesia and muscle relaxation.^{57,58} The potential role of flupirtine in the treatment of neuropathic pain and fibromyalgia has been previously discussed.⁵⁹ In addition, bis(1-hydroxy-2(1H)-pyridineselonato-O,S) zinc, commonly known as zinc pyrithione (ZnPy), has recently been shown to be a strong Kv7 activator, potentiating all Kv7 channels except Kv7.3.⁶⁰ There are no clinical trials of zinc pyrithione for a potential treatment of neuropathic pain.

Concluding remarks

Neuropathic pain is very challenging to manage and despite the numerous treatment options, many patients are still not able to get sustained relief from their neuropathic pain. As a result, researchers and clinicians are constantly exploring additional treatment options. One such option is potassium channel activators which have shown very promising results as a potential therapy for certain types of neuropathic pain in animal models. Neuronal Kv7 channels are of particular interest, as they can be targeted by their activators to suppress neuronal hyperexcitability. Retigabine is one such Kv7 channel activator, and there is a growing body of literature describing its potential use in the treatment of various neuropathic pain conditions. Studies using a rat model of neuropathic pain found that hypersensitivity to injured paws was reduced and orofacial cold hyperalgesia was alleviated through treatment with retigabine.^{50,51} However, the clinical use of retigabine (for treating seizures) has been discontinued due to its side effects. Future research is necessary to identify the additional activators of Kv7.2 channels as well as other K⁺ channels with high efficacy and low side effects for the treatment of neurological disorders including neuropathic pain.

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Authors' Contributions

All authors participated in the writing of the manuscript. AA-E and JG finished the final version of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Abd-Elsayed is a consultant for Medtronic, StimWave, Sollis, and Avanos.

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