Original Article

Mechanistic Stratification of Antineuralgic Agents

Ahmad Beydoun, MD and Misha-Miroslav Backonja, MD
Department of Neurology (A.B.), University of Michigan Medical School, Ann Arbor, Michigan, and Department of Neurology (M.-M.B.), University of Wisconsin Medical School, Madison, Wisconsin, USA

Abstract
Current treatment options in neuropathic pain include antidepressants, antiepileptics, antiarrhythmics, and analgesics. However, stratification of treatments based on their original therapeutic class is inadequate, as drugs belonging to a particular class may have distinct antineuralgic modes of action. It is therefore useful to review the mechanisms of action of these drugs and determine which of these mechanisms is most likely responsible for the drugs' efficacy in the symptomatic treatment of neuropathic pain. Switching from the traditional therapeutic class stratification to one based on putative antineuralgic mechanisms of action will allow more rational selection of therapies, and aid evaluation of the additive or synergistic effects of drugs when used in combination. J Pain Symptom Manage 2003;25:S18–S30.

Key Words
Neuropathic pain, antineuralgic agents, peripheral sensitization, central sensitization, inhibitory pathways

Approaches to the Treatment of Neuropathic Pain

Neuropathic pain is defined as pain secondary to an injury to, or dysfunction of, the nervous system. In a recent publication, the complex interplay between etiology, pathophysiology, and symptoms of neuropathic pain was well described.[1] Nerve damage can result from a variety of conditions, including metabolic, ischemic, immune-mediated, toxic and infectious causes. In some patients, the nerve damage can lead to maladaptive pathophysiologic changes that result in various symptoms of spontaneous or evoked pain or in the syndrome known as neuropathic pain. The complexity resides in the fact that various underlying etiologies can be associated with similar symptoms, different pathophysiologic mechanisms can be responsible for similar symptoms, and different pathophysiologic mechanisms might be at play in similar underlying etiologies.

Despite this complexity, one can approach the treatment of neuropathic pain according to this representation by evaluating the efficacy of drugs against the underlying cause, according to the pain characteristics or based on the underlying pathophysiologic mechanisms that initiate and maintain the pain. The problem associated with an etiologic approach is that the vast majority of clinical trials assessing the efficacy of various agents in the treatment of neuropathic pain have so far been conducted in just three conditions: painful diabetic neur-

Address reprint requests to: Ahmad Beydoun, MD, Department of Neurology, University of Michigan Medical School, 1500 East Medical Center Drive, IB300/0036, Ann Arbor, MI 48109, USA.

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opathy, post-herpetic neuralgia, and trigeminal neuralgia. Physicians subsequently extrapolate the efficacy results from these trials and apply them to patients with other types of neuropathic pain. Although this approach is generally successful, the efficacy results can vary across conditions. A case in point is a recent study that evaluated the efficacy of amitriptyline in HIV-related painful neuropathy.[2] In this randomized, double-blind, placebo-controlled clinical trial, there was no significant improvement in patients receiving amitriptyline compared with those on placebo[2]—this was despite the fact that tricyclic antidepressants have demonstrated efficacy in the treatment of painful diabetic neuropathy and post-herpetic neuralgia.

A second approach is to choose drugs according to the symptoms and characteristics of the pain, in addition to the types of sensory abnormalities detected on physical examination. Although such an approach is attractive, there are only limited data supporting this method.

A third approach to the selection of treatments for neuropathic pain is a mechanistic approach, based on the underlying mechanisms thought to be responsible for initiating and maintaining neuropathic pain.

Mechanistic Approach to the Treatment of Neuropathic Pain

Ideally, a true mechanistic approach to the treatment of neuropathic pain would be one in which the selection of drugs was individualized; this would be achieved by determining the underlying mechanisms operating in each individual patient (based on symptoms and signs) and then selecting agents that would modulate these specific mechanisms. However, this 'true' mechanistic approach is still far from being realized. In the future, it is hoped that the underlying mechanisms of specific symptoms and signs will be uncovered, allowing physicians to choose drugs based on the findings of physical and neurologic examinations.

An alternative, ongoing method focuses on a mechanistic approach to designing and developing new drugs for the treatment of neuropathic pain. This development can be largely attributed to the remarkable progress made over the last two decades in the characterization of various maladaptive pathophysiologic changes, in both the peripheral and central nervous systems, which could account for the development of neuropathic pain. These advances, coupled with a number of novel animal models of neuropathic pain, have resulted in the creation of several molecules designed to target underlying receptors and neurotransmitters believed to be responsible for neuropathic pain. However, these mechanistic advances have not yet resulted in 'designer' drugs with demonstrated safety and efficacy in human clinical trials.

A further mechanistic approach focuses on the drugs currently in clinical use for the treatment of neuropathic pain. These drugs, for the most part, were not initially developed as antineuralgic agents. Instead, they were originally intended to be antidepressant, antiepileptic or anti-arrhythmic medications, and were only subsequently found to have efficacy in the treatment of neuropathic pain. Currently, the drugs used to treat neuropathic pain are stratified according to their original therapeutic class (Table 1). However, this stratification is inadequate, since it indirectly implies that all drugs belonging to a particular class exert their antineuralgic effects through similar mechanisms. For instance, carbamazepine and gabapentin are both antiepileptic drugs, but they have distinct mechanisms of action that are blurred by such stratification. Therefore, there is a need for a better model that will stratify drugs according to their putative antineuralgic mechanisms of action. It is important to stress from the outset that this is not a precise undertaking, as it attempts to determine putative mechanisms of action through an inverse approach. The forward solution is a lot simpler. For example, it may be determined that a particular receptor, preferentially expressed following an injury to the nervous system, contributes to the development of neuropathic pain. If administration of a molecule designed to block this particular receptor were to result in pain relief, then one could be relatively confident that this particular mechanism was responsible for the molecule's antineuralgic effect. This conclusion would be further strengthened if the drug were to lose its efficacy in the presence of a competitive binder at that receptor site. The inverse approach, using the currently available drugs, is

Table 1
Stratification of the Drugs Currently Used to Treat Neuropathic Pain, According to Their Original Therapeutic Class

Therapeutic Class	Drugs
Antidepressants	Amitriptyline, imipramine, desipramine, nortriptyline (tricyclic antidepressants); selective serotonin re-uptake inhibitors; serotonin and norepinephrine re-uptake inhibitors
Antiepileptics	Carbamazepine, oxcarbazepine, gabapentin, lamotrigine, phenytoin, topiramate, levetiracetam
Anti-arrhythmics	Mexiletine
Topical formulations	Capsaicin, lidocaine, aspirin
Analgesics	Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, tramadol, opioids
Others	Levodopa, ketamine, dextromethorphan, memantine

much more difficult, as one has to determine which of the numerous mechanisms of action, some of which are still to be elucidated, is responsible for the drugs' antineuralgic effect.

For such a model to be clinically useful, it is essential that it be simple; some specificity must, therefore, be sacrificed in order to maintain clinical relevance. Ongoing evaluation of the paradigm should be possible, allowing it to be improved and modified in line with the acquisition of new knowledge. The model should, therefore, be viewed as a framework that is meaningful and useful to clinicians who are choosing drugs for monotherapy and, more importantly, for combination therapy for the treatment of neuropathic pain. The accuracy and predictive value of this model will need to be assessed by subsequent trials, which will determine if there is evidence of additive or synergistic effects when combining drugs with different putative antineuralgic mechanisms of action. The mechanistic stratification of drugs in current clinical use will be the focus of this review.

Nociceptive Pathways

The most distal fibers of the nociceptive pathways consist of specialized types of sensory fibers, referred to as nociceptors because they preferentially react to noxious stimuli, whether thermal, chemical or mechanical. These are comprised of lightly myelinated fibers, known as A-delta fibers, and unmyelinated fibers, known as C fibers. These fibers should be distinguished from the highly myelinated A-beta fibers, which carry sensory information about innocuous stimuli, such as the shape and texture of objects. The various fibers can be differentiated based on the conduction velocity of cutaneous sensory nerves, with the fastest being the A-beta (30–70 m/sec), followed by the A-delta (4-30 m/sec) and finally the C (0.5–2.0 m/sec). The A-delta and C fibers terminate at the level of the dorsal horn, where they preferentially synapse in Rexed Laminae I and II, while the larger A-beta fibers terminate in the deeper Rexed laminae.

Although a number of pathways are involved in the rostral transmission of noxious stimuli, the spinothalamic tract is the most important for signaling painful stimuli in humans. The axons of the spinothalamic tract decussate within the spinal cord, ascend in the anterolateral white matter, and terminate in different thalamic nuclei, the most important of which is the nucleus ventralis posterolateralis. A number of afferent projection fibers originate from the thalamus and transmit the signal more rostrally. Some project to the somatosensory cortex and are partly responsible for the sensory component of pain, whereas others project to the limbic system and play an important role in the emotional component of pain.

Etiology of Neuropathic Pain

The nociceptive pathways play a crucial, protective role in the body: they warn of impending or actual tissue damage and signal the need to protect the injured part during the healing process. The associated pain, known as nociceptive pain, is secondary to the ongoing stimulation of the peripheral nociceptors in acutely injured and inflamed tissue.

In contrast, neuropathic pain does not play any useful biological function. It can occur following an injury to the nervous system and develops as a consequence of maladaptive changes that result in chronically sustained

spontaneous and evoked pain. The mechanisms that follow a nerve injury, and that result in neuropathic pain, are multifactorial, complex and evolve over time. In addition, although a number of changes are known to occur as a result of peripheral nerve injuries or deafferentation, it is not yet clear which of these changes are directly responsible for the development of pain and which physiologic changes are of lesser or no importance in this regard.

Despite a number of other important contributing mechanisms, peripheral and central sensitization are central concepts for the development of neuropathic pain. It is well established that the release of inflammatory mediators following a nerve injury results in the altered expression and distribution of sodium channels at the level of the injured nociceptors and their associated dorsal root ganglia. In addition to sodium channels, novel ion channels can be expressed in the regenerating axons, including adrenergic receptors[3] and N-type or L-type calcium channels.[4] This results in a lowering of the nociceptor depolarization threshold and in ectopic discharges—a phenomenon known as 'peripheral sensitization.'[5,6] This initial reaction following a peripheral nerve injury may play a crucial role in the subsequent changes that result in chronic neuropathic pain, since blocking the activity of the peripheral nerve with local anesthetics prior to injuring a nerve prevents the development of hyperalgesic behavior in animals.[7]

Central sensitization following a peripheral nerve injury is believed to occur with the release of tachykinins, such as substance P and neurokinin A, from peripheral nociceptors. These neuropeptides bind with neurokinin receptors and trigger the release of intracellular calcium, facilitating the up-regulation of the N-methyl-D-aspartate (NMDA) receptor. Also, binding of excitatory neurotransmitters (such as glutamate) released from primary afferents results in a further influx of calcium into the cell. This intracellular calcium results in a cascade of enzymatic activity and genetic effects that have long-term consequences, such as a lowering of the threshold of spinal horn neurons, an increase in the magnitude and duration of the responses to stimuli, and an expansion in the size of the receptive field.

Other changes also may contribute to the development of neuropathic pain. For example, it is well established that mechanical allodynia is due to activation of low-threshold A beta mechanoreceptors that interact with a sensitized dorsal horn.[8] It has also been documented that reorganizational changes can occur at the level of the dorsal horn following a peripheral nerve injury. For example, low-threshold mechanoreceptors were shown to sprout from deep laminae and synapse in Laminae I and II of the dorsal horn following a peripheral nerve injury.

Modulators of Peripheral Sensitization

Sodium-Channel Modulators

Sodium channels are voltage-gated ion channels that are widely distributed in all neurons. They are partly responsible for the generation of action potentials and are critical for the propagation of the electric signal along the axon. The importance of sodium channel expression in the development of neuropathic pain is well established. Following a peripheral nerve injury, there is an abnormal accumulation of sodium channels at the level of the injury within the nociceptors, as well as in the associated dorsal root ganglia.[9,10] This accumulation alters the local electrical properties of the axon membrane by changes in sodium channel distribution and can lead to ectopic discharges and a lowering of the depolarization threshold of injured nociceptors.[11]

Voltage-gated sodium channels comprise a single, functional, large alpha-subunit in addition to beta subunits. The beta subunits play important regulatory roles in determining levels of channel expression and are able to alter the kinetics of channel inactivation. It is now known that there are at least eight voltage-gated sodium channels present in the nervous system of mammals, and that they differ in their pattern of expression within the nervous system, their kinetics, and their recovery from inactivation.[12,13] For example, certain sodium channels are preferentially or exclusively expressed in the dorsal root ganglia, secondary to down-regulation of certain sodium channel subtypes and the up-regulation of others.[13] The sodium channels are divided into tetrodotoxin-sensitive and tetrodotoxin-resistant channels, and both types are present and play a physiologic role in nociceptive impulses.[14]

However, there is evidence to suggest that there is preferential expression and accumulation of tetrodotoxin-resistant sodium channels following peripheral nerve injury.[15–17] Some of the best characterized tetrodotoxin-resistant sodium channels are the specific nervous system (SNS)/peripheral neuron-3 (PN-3) channel and the NaN/SNS-2 channel, which has a broader pattern of expression. The data seem to indicate that of these two channels, only the SNS/PN3 channel is relevant to the underlying mechanisms of neuropathic pain.[18] The importance of the tetrodotoxin-resistant voltage-gated sodium channels in the pathophysiology of neuropathic pain was shown in knockout SNS-null mutant mice. These animals, which only expressed tetrodotoxin-sensitive sodium channels, exhibited pronounced analgesia to noxious mechanical stimuli and delayed development of inflammatory hyperalgesia.[15]

A number of drugs modulate the sodium channels in the peripheral nervous system, and this mechanism is believed to be partly responsible for suppressing the ectopic discharges that originate within the injured nociceptors or at the level of the associated dorsal root ganglia (Fig.1). However, the available agents are not selective for the tetrodotoxin-resistant sodium channels and this non-specificity can result in multiple channel blockade, which can lead to significant toxicity at high drug concentrations. The therapeutic effects of these sodium channel-modulating drugs are due to the fact that they are able to prevent the generation of spontaneous ectopic discharges at concentrations lower than those required to block or inhibit normal impulse generation and propagation.

Since the various sodium channel subtypes have different kinetics, it is important to evaluate the effect of the sodium-channel modulators on the specific subtypes that are known to be preferentially expressed following a peripheral nerve injury—these data are sorely missing. So far, the effect of the available antineuralgics on tetrodotoxin-resistant sodium channels is not well characterized; the effects of these drugs on sodium channels have mostly been evaluated in normal mammalian myelinated nerve fibers[19] or isolated normal mammalian brain neurons.[20] The types, distribution and kinetics of these sodium channels differ from those expressed in nociceptors and associated dorsal root ganglia following a peripheral nerve injury.[13,21] For instance, it is well documented that tetrodotoxin-sensitive and -resistant sodium channels have different activation and inactivation kinetics and that, unlike the former, the latter can still be activated at depolarized potentials.[22] The cloning of a tetrodotoxin-resistant sodium channel from human dorsal root ganglia will hopefully make it easier to develop drugs that would selectively target this particular type of sodium channel.[23]

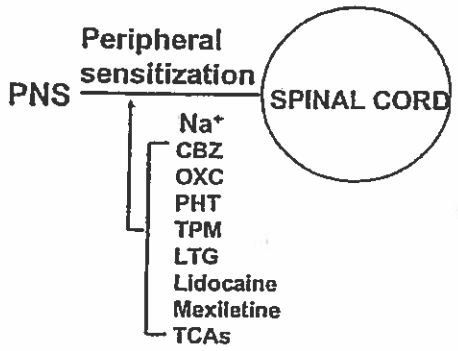

Fig. 1. Modulators of peripheral sensitization. PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPM = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressant.

Sodium-channel modulators, such as certain antiepileptic drugs, local anesthetics, and antidepressants, are used clinically for the treatment of neuropathic pain (Fig. 1). There are some data to suggest that sodium-channel modulators are most effective against neuropathic pain due to injury of the peripheral nervous system. In a retrospective study, it was found that patients with chronic nonmalignant pain were more likely to experience pain relief following intravenous lidocaine administration if the pain was the result of an injury to the peripheral rather than the central nervous system, or if the pain was idiopathic.[24,25] This concept was recently challenged by a small study that documented significant pain relief in patients suffering from central pain following intravenous administration of lidocaine.[26]

Carbamazepine

Carbamazepine is an iminostilbene derivative that is structurally related to the tricyclic

antidepressants. Carbamazepine enhances inactivation of voltage-gated sodium channels by reducing high-frequency repetitive firing of action potentials. This inactivation is voltage-dependent, with limitation of firing increased after depolarization and reduced after hyperpolarization.[27] This mechanism of action is believed to result from a shift in sodium channels to an inactive state, from which recovery is delayed, and is likely to be responsible for the reduction of spontaneous activity in experimental neuromas.[28] This frequency-dependent effect explains why carbamazepine is able to reduce the tonic discharges arising from nociceptors without affecting normal nerve conduction. The concentration-response curve of carbamazepine fits best with a first-order reaction, suggesting that carbamazepine binds to one receptor at, or near, the sodium channel, with a higher affinity for the inactivated form.[27] In experimental neuromas, carbamazepine inhibited ectopic discharges at clinically relevant serum concentrations.[28] Carbamazepine also diminishes the release of excitatory neurotransmitters, most likely a by-product of its effects on the sodium channels. In addition, carbamazepine was found to modulate the high-threshold L-type calcium channels, which are not believed to play a major role in central sensitization. Other mechanisms of carbamazepine include increased release of serotonin and enhanced dopaminergic transmission.

Oxcarbazepine

Oxcarbazepine is a keto analog of carbamazepine, which has an improved tolerability, safety and pharmacokinetic profile compared with carbamazepine. Unlike carbamazepine, which is metabolized via oxidative pathways, cytosolic enzymes reduce oxcarbazepine to the monohydroxy derivative (MHD), which is responsible for most of its pharmacologic effect. As a result, the active metabolite of carbamazepine that contributes to its adverse event profile and risk of cutaneous rash, the 10,11-epoxide, is not produced. Oxcarbazepine and MHD share the effects of carbamazepine on voltage-dependent sodium channels and inhibition of release of excitatory neurotransmitters.[29] In a recent study, administration of oxcarbazepine led to inhibition of high-frequency firing of cutaneous afferent fibers following repetitive stimulation, without affecting impulse conduction.[30] Oxcarbazepine also blocks penicillin-induced bursts in hippocampal slices, an effect that is reversed by administration of 4-aminopyridine, suggesting that this effect is modulated by increasing current through voltage-sensitive potassium channels. In addition, and unlike carbamazepine, oxcarbazepine has been shown to inhibit high-threshold N-type calcium channels.[31] By virtue of its effect on voltage-gated sodium and calcium channels, oxcarbazepine has the mechanistic potential to modulate peripheral and central sensitization.

Phenytoin

The antineuralgic properties of phenytoin are believed to be secondary to its effect on sodium channels and its ability to inhibit repetitive tonic-firing of injured peripheral afferents, suppress spontaneous ectopic discharges, and inhibit presynaptic glutamate release.[32]

Topiramate

Topiramate is a sulfonamide derivative with multiple mechanisms of action. Although initially believed to strongly modulate voltage-sensitive sodium channels, recent data have shown that at therapeutically relevant concentrations, topiramate limited sustained repetitive discharges to a variable extent in cultured mouse spinal neurons, causing no effect in about one-third of neurons and only intermittent limitation of sustained repetitive firing in another third.[33] In addition, it enhances the ability of gamma aminobutyric acid (GABA) to induce a flux of chloride ions through $GABA_A$ receptors and antagonizes the kainate subunit of the kainate/[3H]-L-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors.[34]

Lamotrigine

Lamotrigine is a phenyltriazine derivative, which is not structurally related to other antiepileptic drugs. It acts by stabilizing the slow inactivated conformation of sodium channels and inhibiting repetitive firing of action potentials under conditions of sustained neuronal depolarization.[35] This same mechanism could account for the inhibition of release of excitatory neurotransmitters.[36] More recent studies have indicated that lamotrigine also modulates the high-threshold N-type calcium channels,[37]

raising the possibility of a peripheral and central modulatory effect on neuropathic pain.

Lidocaine

Lidocaine is an amide-type local anesthetic that stabilizes neural membranes by modulating voltage-sensitive sodium channels. It was found to reversibly block tetradotoxin-resistant sodium channels derived from normal ganglion neurons[38] and was found to be effective in increasing the threshold of mechanical allodynia in animal models through peripheral mechanisms, by reducing the rate of discharges emanating from injured afferent fibers.[39] The peripheral antineuralgic mechanisms of lidocaine were also shown in other studies.[40,41]

Mexiletine

Mexiletine is an orally active local anesthetic, structurally similar to lidocaine, with antidysrhythmic properties. Like lidocaine, mexiletine is a sodium-channel modulator[38] that depresses the action potential upstroke and enhances repolarization. Mexiletine modulates the sodium channels in a frequency-dependent manner.

Tricyclic Antidepressants

In addition to their modulatory effects on the descending inhibitory pathways, the tricyclic antidepressants are also strong sodium-channel modulators. This mechanism will be expanded upon in the next section.

Modulators of Descending Inhibitory Pathways

A number of supraspinal pathways modulate the transmission of nociceptive impulses. One of the most important endogenous inhibitory systems originates in the periaqueductal gray, at the level of the midbrain, and modulates the nociceptive pathways at the level of the dorsal horn through descending fibers containing serotonin.[42] In addition, the locus ceruleus modulates the nociceptive pathways via norepinephrine containing neurons. These descending fibers terminate in Rexed Laminae I, II and IV of the dorsal horn, where they inhibit nociceptive neurons. Endogenous opioids have been shown to disinhibit (activate) the periaqueductal neurons. The inhibitory effect of those pathways at the level of the dorsal horn is at least partially modulated via the activation of GABAergic interneurons.[42]

Antidepressants

The antidepressants include the tricyclic antidepressants, the selective serotonin re-uptake inhibitors (SSRIs) and the serotonin and norpinephrine re-uptake inhibitors (SNRIs). One of the important antineuralgic mechanisms of this class of drugs is the inhibition of the re-uptake of biogenic amines, such as norepinephrine and serotonin (Fig. 2).[43] The tricyclic antidepressants are divided into two major categories: tertiary and secondary amines. The tertiary amines, such as amitriptyline and clomipramine, inhibit the re-uptake of both serotonin and norepinephrine, whereas the secondary amines, such as nortriptyline and desipramine, are relatively selective norepinephrine re-uptake inhibitors.[43] As the name implies, the SSRIs are relatively selective serotonin re-uptake inhibitors.[43] The SNRIs, such as venlafaxine and nefazodone, are balanced re-uptake inhibitors of serotonin and norepinephrine.[43]

In addition to their effects on biogenic amines, the tricyclic antidepressants have other mechanisms that probably contribute to their antineuralgic effects. For instance, amitriptyline was found to reversibly block tetrodo-

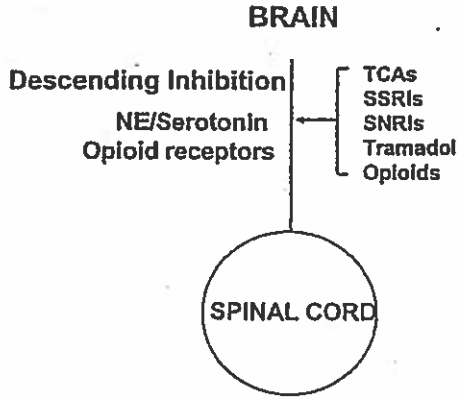

Fig. 2. Modulators of descending inhibitory pathways. NE = norepinephrine; TCA = tricyclic antidepressant; SSRI = selective serotonin re-uptake inhibitor; SNRI = serotonin and norepinephrine re-uptake inhibitor.

toxin-resistant sodium channels derived from normal ganglion neurons.[38] Similarly, amitriptyline, doxepin and desipramine were found to be strong sodium- channel modulators.[44] In contrast, trazodone had minimal effect on the sodium channels and the onset of fluoxetine effects was substantially slower compared with the tricyclic antidepressants.[44] In addition, the antidepressants could also exert their antineuralgic effects through alpha-2 adrenoreceptor agonist effects.[45] The presumed peripheral and central mechanisms of action of the tricyclic antidepressants are consistent with the results of an animal study, in which amitriptyline was effective in increasing the threshold of mechanical allodynia through both peripheral and central mechanisms.[39]

Opioids

The mechanisms of action of opioids are well described.[46] All of the three major classes of opioid receptors (mu, delta and kappa) are coupled to G proteins. Therefore, they can affect ion gating, intracellular calcium disposition and protein phosphorylation. Pre-synaptically, activation of opioid receptors results in closure of voltage-gated calcium channels,[47,48] thereby reducing neurotransmitter release, including norepinephrine, glutamate, serotonin, substance-P and acetylcholine. Post-synaptically, opioids hyperpolarize the cell by activation of an inward-rectifying potassium channel.[49] Although opioids exert their analgesic effect through predominantly central mechanisms (Fig. 2), there are also opioid receptors that mediate analgesic effects when activated by locally applied exogenous opioid agonists.[50]

Tramadol

Tramadol is a centrally-acting synthetic analgesic. In animal studies, it showed low-affinity binding to mu opioid receptors and weak inhibition of norepinephrine and serotonin re-uptake.

Modulators of Central Sensitization

In addition to the peripheral changes that occur following a peripheral nerve injury, there is evidence of excitability of central neurons at the level of the spinal cord, a phenomenon known as central sensitization. It is well documented that low frequency electrical stimulation of unmyelinated nociceptive afferents leads to an increased excitability of spinal cord neurons, the so called 'wind-up' phenomenon. Central sensitization is believed to occur with the release of tachykinins, such as substance-P and neurokinin-A from peripheral nociceptors following a peripheral nerve injury. These neuropeptides bind with neurokinin receptors (NK1 and NK2), triggering the release of intracellular calcium. This increases neuronal excitability and facilitates the up-regulation of the NMDA receptor. At normal resting membrane potential, the NMDA receptor's ion channel is blocked by the physical presence of a magnesium ion. This blockade is voltage-dependent, and the partial depolarization of the membrane induced by the intracellular calcium displaces the magnesium ion and allows the receptor ion channel to be patent. Binding of excitatory neurotransmitters, such as glutamate, released from primary afferents, results in a further influx of calcium and sodium ions into the cell.

Intracellular calcium leads to a number of changes, including the activation of protein kinase C, phospholipase C, nitric oxide synthetase, and the induction of early gene expression; these mechanisms have all been implicated in the maintenance of central sensitization. For example, protein kinase C can phosphorylate the NMDA receptor, causing a reversal of the magnesium ion blockade and leaving the receptor in a permanently patent state. There are at least six different calcium channels expressed within the nervous system,[51,52] which are referred to as the L, N, P, Q, R and T types. All are high-threshold channels except for the T-type channel, which has low depolarization and repolarization thresholds. Of the various types of calcium channels expressed in the nervous system, there is incremental evidence that the high-threshold N-type channels are expressed in synapses at the superficial Rexed laminae of the dorsal horn and are important in the central modulation of nociceptive input.[53–55] Specific antagonists of the N-type calcium channels, like ziconotide, which is derived from a marine snail venom, result in significant pain relief in patients with neuropathic pain.[56]

The importance of the altered role of the N-type calcium channels at the level of the dorsal horn following a peripheral nerve injury was also demonstrated in the Kim and Chung ro-

dent model of neuropathy.[57] In addition, it was also shown that mice lacking N-type voltage-dependent calcium channels showed markedly reduced symptoms of neuropathic pain induced by nerve injury, demonstrating the importance of the N-type calcium channel in the development of neuropathic pain (Fig. 3).[58]

Gabapentin

The mechanism of action responsible for the antineuralgic properties of gabapentin are still being evaluated. Data from animal models of pain have shown that the efficacy of gabapentin is not mediated by binding to GABA, opioid, dopamine, serotonin or NK1 receptors.[59] Gabapentin was found to increase the central nervous system concentration of GABA[60] and may enhance the release of non-vesicular GABA. It was also found to increase the whole blood concentration of serotonin,[59] although it is unknown if this relates to its antineuralgic effect. Gabapentin had no effect on the voltage-dependent sodium channels[38] and did not reduce peripheral nerve discharges in a rat model of neuropathic pain.[39] There are convincing data derived from animal models that indicate that the antineuralgic effect of gabapentin is at least partially modulated through central mechanisms, most likely at the level of the spinal cord.[61,62] The binding site of gabapentin was identified as the alpha2-delta subunit of a voltage-dependent calcium channel.[63] Within the spinal cord, gabapentin binds to those subunits in Laminae I and II, the termination site of the afferent nociceptors.

In a study of cultured rat dorsal root ganglion neurons, gabapentin was shown to potently inhibit the calcium channel current in a voltage-dependent manner.[64] The use of specific calcium channel antagonists revealed that the predominant effect of gabapentin was on the N-type calcium current.[64]

Levetiracetam

Levetiracetam is pyrrolidine acetamide, and is chemically unrelated to other antiepileptic drugs. Although it is not yet known how levetiracetam exerts its antineuralgic effects, a recent study found that this drug selectively inhibits the N-type calcium channels in CA1 pyramidal hippocampal neurons and reduces calcium influx by 37% at this channel.[65]

Oxcarbazepine and Lamotrigine

In addition to their modulatory effects on the voltage-gated sodium channels, oxcarbazepine[31] and lamotrigine[37] inhibit the high-threshold N-type calcium channels as was previously discussed in the 'Sodium-channel modulators' section.

Ketamine and Dextromethorphan

Ketamine and dextromethorphan are NMDA-glutamate antagonists that have shown efficacy in animal models of neuropathic pain.[66] The main problem with these agents is their low therapeutic index and poor tolerability at doses that can lead to effective pain relief. The development of selective NR_{2B} subunit NMDA-receptor antagonists may potentially provide potent antagonists that will be better tolerated in humans.

Memantine

Although not yet available in the US, memantine has been used in Europe for the treatment of conditions such as dementia and Parkinson's

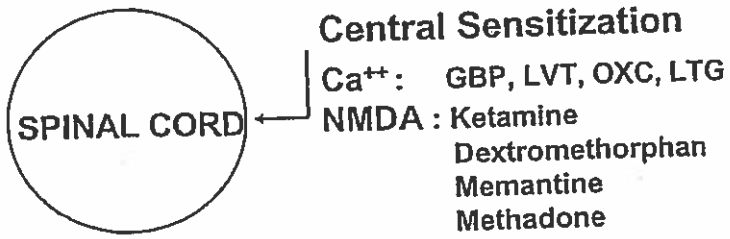

Fig. 3. Modulators of central sensitization. GBP = gabapentin; LVT = levetiracetam; OXC = oxcarbazepine; LTG = lamotrigine; NMDA = N-methyl-D-aspartate.

disease. Memantine could prove useful for the symptomatic treatment of neuropathic pain, since it is an NMDA antagonist and a sodium-channel modulator.[38] It was found to decrease mechanical hyperalgesia and mechanical allodynia in animal models of neuropathic pain.[67]

Modulators of Other Mechanisms

Capsaicin

Capsaicin, a product extracted from hot chili peppers, is a vanilloid agonist that interacts with C-fiber polymodal nociceptors. It acts at vanilloid receptors, causing initial short-term receptor activation followed by long-term calcium-dependent desensitization.[68]

Levodopa/Carbidopa

The antineuralgic mechanism of action of levodopa/carbidopa is unknown, although it could be related to an increase in dopamine in the central nervous system.

Nonsteroidal Anti-Inflammatory Drugs and Cyclooxygenase-2 Inhibitors

Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors exert their analgesic effects by inhibiting cyclooxygenase.

Mechanistic Stratification of Antineuralgics

Figure 4 depicts the peripheral nervous system, the spinal cord and the brain. Drugs that could enhance the descending inhibitory pathways include the opioids, SNRIs, SSRIs, tramadol and tricyclic antidepressants. Agents that could modulate central sensitization by interacting with high-threshold N-type, or possibly P-type, calcium channels include gabapentin, lamotrigine, levetiracetam and oxcarbazepine.

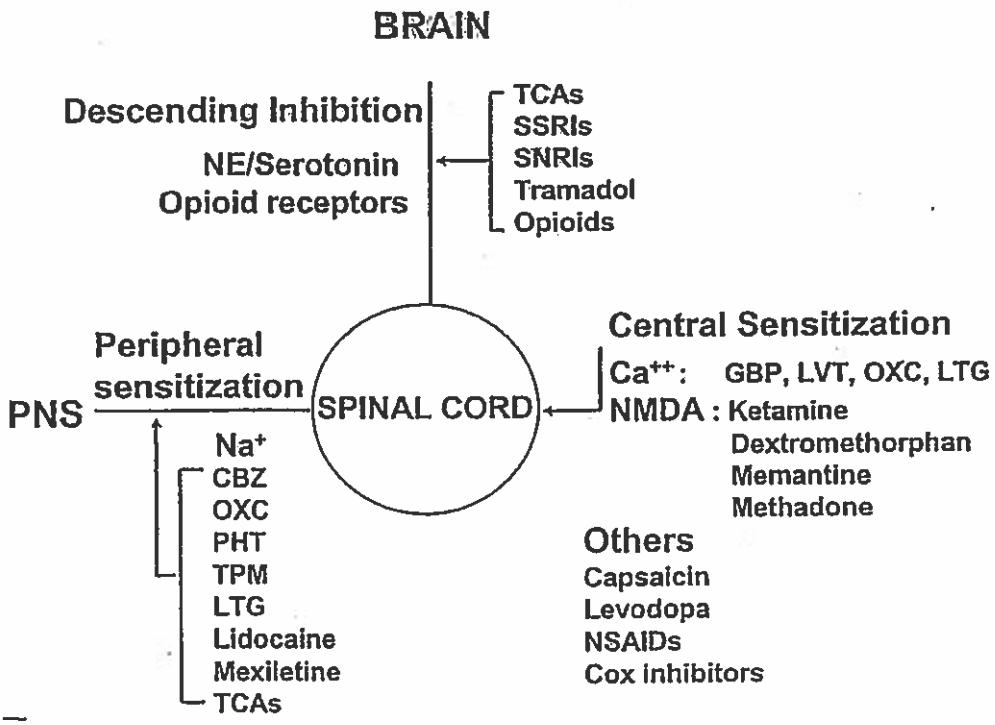

Fig. 4. Mechanistic stratification of antineuralgic agents. PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPA = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressant; NE = norepinephrine; SSRI = selective serotonin re-uptake inhibitor; SNRI = serotonin and norepinephrine re-uptake inhibitor; GBP = gabapentin; LVT = levetiracetam; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug.

Agents that could modulate central sensitization by their effects on the NMDA receptors include dextromethorphan, ketamine, memantine, and methadone. Substances that could modulate peripheral sensitization by inactivating voltage-dependent sodium channels include carbamazepine, lamotrigine, lidocaine, mexiletine, oxcarbazepine, phenytoin, topiramate, and tricyclic antidepressants. It is hoped that switching from the traditional therapeutic class stratification (Table 1) to one based on putative antineuralgic mechanisms of action (Fig. 4) will allow more rational selection of drugs for monotherapy and, more importantly, for combination therapy. In addition, the mechanistic stratification will make it easier to evaluate the additive, infra-additive, or synergistic effects of drugs when used in combination, first in animal models of neuropathic pain and subsequently in randomized clinical trials.

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