Future Pharmacologic Management of Neuropathic Pain

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Neuropathic pain therapy remains enormously challenging despite the increases in knowledge of pain etiology and mechanisms drawn from animal studies. Mechanism-based discovery underlies key approaches toward reduction of peripheral and central hyperexcitability. These include a number of poorly validated molecular targets, such as ion channels, G-protein coupled receptors, purinergic receptors, and chemokine receptors, as well as downstream regulators of protein phosphorylation. Improvement in translating these approaches into the development of drugs for use in the pain clinic remains a significant but surmountable challenge.
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The management of neuropathic pain states is a large unmet therapeutic need. Indeed, of all neurologic diseases, neuropathic pain is the most challenging with respect to understanding the relationships between symptoms and mechanisms, as well as rationalizing approaches to treatment. Most neuropathic pain states have been considered to arise from peripheral rather than central nervous system (CNS) injuries. This account will focus on targets restricted to peripheral and spinal pain pathways.

Chronic neuropathic pain conditions are relatively resistant to opioid and nonsteroidal anti-inflammatory drug (NSAID) therapy but respond to some extent to ion channel-blocking drugs such as the anticonvulsant gabapentin, the antiarrhythmic mexiletine, and the antidepressant amitriptyline. A variety of untoward side effects set efficacy limitations on all current therapies. Thus, new therapeutic approaches can address improvements in either efficacy or safety relative to the current clinical choices.

Pain Mechanisms and Targets

Drug discovery approaches have been based on symptom management directed at the most commonly described clinical symptoms,

namely spontaneous pain, mechanical and cold allodynia, hyperalgesia, and hyperpathia. However, multiple symptoms may be present at the same time and may change over time. Indeed, it seems quite likely that there may be an etiological and progressive relationship between the initiation and maintenance of chronic neuropathic pain. Unfortunately, there is a paucity of clinical information relating the relative incidence of such symptoms to the major neuropathic pain states, such as those produced by infections (postherpetic neuralgia, human immunodeficiency virus), metabolic disorders (diabetic neuropathy), cytotoxic or radiation therapy, or traumatic nerve injury, or to complex regional pain syndromes (CRPS), including disorders of the sympathetic nervous system.

An understanding of the major mechanisms underlying neuropathic pain provides powerful alternative strategies to direct drug therapy. The major mechanisms include ectopic or spontaneous nerve activity as well as peripheral and central hyperexcitability, phenotypic changes in pain-conducting pathways, secondary neurodegeneration, and morphologic reorganization.[1,2] In addition, chronic inflammatory conditions appear to precipitate nerve damage; thus, some researchers encourage a more holistic view about chronic pain etiology and treatment.[3,4]

Mechanism-based approaches to chronic neuropathic pain have relied heavily on animal studies and used relatively few disease-related models. The mechanism-based approaches most often have involved peripheral nerve lesions, such as sciatic nerve ligation, partial sciatic nerve transection, transection of sciatic nerve branches (spared nerve model), or ligation of L4 or L5 spinal nerves.[5] There are relatively few studies from other disease-related models (eg, diabetic neuropathy or cytotoxic injury) to provide a balanced view about the relative importance of key mechanisms.

Studies using microarray gene analysis of pain pathways have revealed a number of gene changes—both increases and decreases of genes and gene products.[6] Many of these changes highlight the expression of channels, receptors, and enzymes. These potential molecular targets represent an abundance of opportunities, which will be briefly reviewed. The potential roles of a few of these in future pain management will then be highlighted.

Peripheral Changes and Targets

Mechanistic work has highlighted the importance of hyperexcitability in small and large peripheral sensory nerves as a driving neuropathic pain, which can account for the initiation and maintenance of central hyperexcitability.[1,2] Clinical data have shown convincingly that blockage of excitability by a local anesthetic at concentrations that do not affect normal nerve conduction reverses primary and secondary allodynia.[7] This is due to the well-known activity-dependent increase in channel affinity for local anesthetics. Although peripheral excitability may be regulated by many molecular mechanisms, selective depression of small and large fiber excitability appears to be a valuable way to pursue new therapies.

Changes in the expression and activity of several voltage-gated sodium, potassium, and calcium channels have been highlighted following nerve injury. For example, the tetrodotoxin (TTX)-resistant sodium channel (TTX-r: Na_v 1.8) is uniquely expressed in small sensory neurons. It may be down-regulated in small injured axons but up-regulated in adjacent uninjured C fibers and in human neuropathic dorsal root ganglion (DRG).[8] Na_v 1.8 appears important for the generation of spontaneous activity in damaged sensory axons,[9] and knockdown of Na_v 1.8 in models of neuropathic pain produce a marked reduction in abnormal pain responsiveness.[10] Na_v 1.3 is also overexpressed in large Aβ-fibers from chronic pain patients and in the spinal cords of pain models.[8,11] This channel may also be an important substrate for oscillation in peripheral and central neuron excitability, which is considered important for neuropathic pain.[12] A new sodium channel blocker, NW-1029, with activity at both TTX-sensitive and TTX-resistant channels, has been found to produce activity-dependent block of peripheral nerves and has been shown to be antihyperalgesic in models of inflammatory and neuropathic pain.[13] However as yet, sodium channel blockers are of insufficient selectivity to minimize side effects on the heart or in the CNS.

With respect to calcium channels, N-type channels are unique to neurons and critical for pain-related neurotransmission. Thus, deletion of the N-channel gene can reduce inflammatory and neuropathic pain, while blockers such as Ziconotide (Elan) and the orally administered NeuroMed (NMED)-12 and NMED-160 have shown efficacy across a range of chronic pain conditions. However, side effect limitations have not yet been completely resolved. Another and possibly more validated approach targets the α2 δ-1 calcium channel subunit, the substrate for the anticonvulsant gabapentin. This subunit is important for channel assembly and is expressed in small DRG

neurons and in spinal neurons. Its overexpression has been associated with allodynia in a number of specific pain models.[14]

Finally, potassium channel modulation has been proposed as an important mechanism for the regulation of abnormal neuronal "pacemaker currents," Ih, which drive the rhythmic and spontaneous generation of action potentials following nerve injury. Important in the regulation of Ih are cyclic nucleotide-modulated channels, particularly hyperpolarization-activated HCN-1. Blockade of Ih (and HCN-1) with the drug ZD7288 can prevent repetitive firing in damaged DRG neurons, and this drug can reverse touch-induced hypersensitivity in neuropathic pain models.[15]

A variety of G protein–coupled receptors (GPCRs) is also preferentially expressed on sensory neurons to regulate their excitability. These may be targeted specifically by drugs designed to act outside the brain, and this strategy may avoid potential central side effects. With respect to this approach, cannabinoid (CB) receptors are widely distributed in the nervous system. Pain is modulated via CB1 receptors located in the CNS and in the periphery and also via CB2 receptors, which are found mainly in peripheral tissues. Several clinical studies have increased confidence in the therapeutic efficacy of CBs, but improvements in efficacy and reduction of CNS side effects are still needed. Although the exact peripheral mechanism of action is unclear, a number of CB2 selective ligands (HU-308, AM 1241) show antinociceptive effects in a variety of pain models[16] without deleterious side effects (catalepsy, motor impairments). On the other hand, peripherally restricted CB1 agonists[17] have also been shown to reduce peripheral nerve excitability and neuropathic pain behaviors without deleterious side effects.

A more recently identified target is a family of DRG-specific receptors, the sensory neuron–specific receptors (SNSRs). These are related to a larger and phylogenetically diverse family of Mas-related genes. They are selectively expressed in a subset of sensory neurons of the DRG and trigeminal ganglion.[18] Many SNSRs are colocalized with the noxious heat-responsive vanilloid receptor-1 to peripheral nociceptors. Several ligands have been reported for SNSRs, such as bovine adrenal medullary peptide 22 (BAM22), which is processed from the opioid peptide precursor proenkephalin A. Another endogenous processing fragment, BAM8-22, as well as 2 unrelated peptides, melanocyte-stimulating hormones (MSHs), γ2-MSH and CT-γ2-MSH, have high activity at SNSRs, but none of these have activity at opioid receptors. Functional evaluation of these SNSR ligands has recently revealed increased spinal excitability and potentiation of nociceptive responses evoked by thermal and mechanical stimuli.[19] So far, no endogenous ligand for this receptor has been identified, although current data indicate the need for a receptor antagonist to provide analgesia.

Spinal Changes and Targets

As mentioned earlier, a variety of spinal changes have been associated with the initiation and maintenance of hyperexcitability associated with chronic neuropathic pain. Three opportunities to reduce this excitability are examined in this section:

- Block of sensitizing GPCRs (neuromedin-U [NMU])
- Modulation of downstream events through the inhibition of mitogen-activated protein kinase (MAPK)
- Use of P2X receptor and chemokine receptor antagonists to alter neuroglia function related to modulation of spinal excitability as well as possible neuroglial-mediated spinal neurodegeneration

NMU, a C-terminally amidated peptide with 23 amino acids, activates NMU receptors NMUR1 and NMUR2. NMUR1 is more abundant in peripheral tissues, particularly in subpopulations of small- and medium-size sensory neurons, while NMUR2 is more abundant in spinal laminae I and II. Spinal administration of NMU-23 evokes pronociceptive responses to mechanical and thermal stimuli and enhances the excitability of dorsal horn neurons and their responsiveness to noxious mechanical stimuli.[20] However, it is currently unclear how NMU receptor subtypes contribute to spinal excitability in chronic pain, as subtype-selective agonists and antagonists are not available.

A number of protein kinases, including protein kinase-A, protein kinase-C, and MAPKs, are considered important downstream regulators of spinal excitability. These protein kinases alter gene transcription and modify target proteins posttranslation. In particular, MAPKs, such as extracellular signal-regulated kinases (ERKs), cJUN N-terminal kinase, and p38 kinase, are important in producing long-term central hypersensitivity related to chronic pain. For example, p38 kinase is activated in DRG neurons and spinal neurons by nerve injury and inflammatory mediators[3] such as tumor necrosis factor α (TNFα) and nerve growth factor, while spinal ERK

expression is increased in a model of diabetic neuropathy. In addition, p38 inhibitors such as SB203580 and CNI-14930 reduce heat and mechanical allodynia in chronic pain models, while the MAPK/ERK inhibitor PD 198306 reduces pain behavior in diabetic neuropathy.[21] However, it is unclear how kinase inhibition will affect pain therapy, since p38 kinase expression and signaling may be transient. Neither the TNFα antagonist etanercept nor the p38 inhibitor SB203580 produces a sustained reduction in neuropathic pain.[22]

Neuroglial cells (microglia, astrocytes, DRG satellite cells, Schwann cells) have recently been highlighted in the etiology of neuropathic pain. Many of these cell-types have close junctional connections that provide a means of spreading excitability changes beyond the boundaries of spinal segmental input. In addition, these cells secrete a number of mediators (nitric oxide, neurotrophins, TNFα, free radicals) which have been associated with changes in spinal and afferent neuronal excitability and secondary neurodegeneration, particularly the loss of inhibitory interneurons.[4,23] The release of inflammatory mediators is likely to be regulated via glial receptors for adenosine triphosphate (ATP), kinins, prostanoids, and *N*-methyl-D-aspartate, all of which may also modulate spinal excitability. In this respect, a number of purinergic and fractalkine receptors have recently been implicated. For example, the $P2X_7$ subtype of purinergic receptors, which is expressed in microglia and satellite cells, is up-regulated in human chronic pain patients, while deletion of the $P2X_7$ receptor gene produces a complete absence of mechanical and thermal pain in mice.[24] Other studies have shown that increased spinal microglial $P2X_4$ expression occurs after peripheral nerve lesions were formed and was related to mechanical allodynia. This could be blocked by the selective antagonist trinitrophenyl-ATP (TNP-ATP), and remarkably, spinal administration of activated microglia was reported to reproduce the TNP-ATP–sensitive mechanical allodynia in naive animals.[6,25] With respect to fractalkine receptors, CXCR4, CCR2, and CX3CR1 have been shown to be expressed in glial and sensory neurons, and preliminary data have shown that block of CX3CR1 by a fractalkine receptor–neutralizing antibody induces powerful antiallodynic effects, while CCR2 knockout mice show absence of neuropathy-induced allodynia.[26]

In conclusion, neuropathic pain therapy remains enormously challenging despite increases in knowledge drawn from animal studies of pain etiology and mechanisms. Detailed clinical knowledge is still lacking, particularly with respect to the complexity of overlapping mechanisms and time-related changes underlying the progression of pain. Key approaches, based on mechanism-based discovery, to the reduction of peripheral and central hyperexcitability include the choice of a number of poorly validated molecular targets. Improvement in translating these approaches into the development of drugs for use in the pain clinic remains a significant but surmountable challenge.

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