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Miniperspectives: Recent Approaches in the Treatment of Neuropathic Pain

Current and Emerging Targets To Treat Neuropathic Pain

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Normal pain stimulus, or nociceptive pain, resulting from tissue damage or an imminent situation that could quickly result in tissue damage is considered to be a normal physiological response (feedback) to alert the body that tissue injury has occurred or is imminent if the appropriate action is not taken. Nociceptive pain typically responds well to treatment with analgesics and tends to subside readily when noxious stimuli are removed and/or tissue damage has healed. In contrast, neuropathic pain involves an abnormal processing of sensory input usually occurring after direct injury or damage to nerve tissue. Neuropathic pain is characterized by a spontaneous hypersensitive pain response and can typically persist long after the original nerve injury has healed. This unusually heightened pain response could be observed as hyperalgesia (an increased sensitivity to a noxious pain stimulus) or allodynia (an abnormal pain response to a non-noxious stimulus, e.g., cold, warmth, touch). While nociceptive pain is typically acute in nature and diminishes upon healing, patients suffering from neuropathic pain typically endure chronic, debilitating episodes that are refractory to the current pharmacotherapies and profoundly affect their quality of life.

It is estimated that neuropathic pain affects over 6 million patients in the U.S. and Europe and over 26 million patients worldwide, resulting in a worldwide healthcare cost of over $3 billion per year, with a significant portion of this money paid for drug therapies that were originally developed for other medical conditions. Neuropathic pain syndrome is actually a collection of disorders characterized by different etiologies including infection, inflammation, disease, trauma or compression to major peripheral nerves, and chemical or irradiation-induced nerve damage. The nerve tissue lesion may be found in the brain, spinal chord, or the peripheral nervous system. Clinically, chronic neuropathic pain has been associated with the following medical conditions: lumbar radiculopathy (lower back pain caused by disk compression or herniation), spinal chord injury, phantom pain, diabetic neuropathy, postherpetic neuralgia, and in some patients fibromyalgia and cancer-related pain.

As physicians are faced with an increasing number of patients with numerous neuropathic pain symptoms most likely stemming from multiple etiologies, they are forced to resort to the polypharmacia approach as the mainstay therapy. Current pharmacological treatment for neuropathic pain will typically include some combination of agents from several of the following drug classes: opioids, tricyclic antidepressants, anticonvulsant agents, or nonsteroidal anti-inflammatory drugs (NSAIDs)/analgesics. Ironically, even with such an impressive arsenal of powerful drugs, these approaches only provide an approximate 30−50% reduction in pain in about 50% of patients. Coupled with this limited efficacy, there are low levels of compliance due to intolerable side effect profiles associated with some of these drugs. These results profoundly illustrate that treatment of neuropathic pain is a hugely unmet medical need, and they underscore the importance of considering, validating, and pursuing alternative targets to treat refractory neuropathic pain.

This Miniperspective series of manuscripts will focus on newer developments in medicinal chemistry advances toward treating neuropathic pain. It will provide focused reviews of emerging targets by the experts in this field of research and, in doing so, will offer a snapshot of the current status of research within each of these drug classes. The following Miniperspective, authored by Jeffrey Kennedy of Wyeth Research, will provide a pharmacological overview of neuropathic pain. The

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main focus of this paper is to set the backdrop for the rest of the series by describing the etiology of this complex medical syndrome and dissecting the distinguishing properties of each type of pain sensation: nociceptive, inflammatory, and neuropathic pain. The paper will then focus on the underlying signaling mechanisms and molecular mediators or targets, which play key roles in pain propagation. In an attempt to tease apart the formidable complexity of debilitating neuropathic pain syndrome, the paper exposes a plethora of potential targets that have been pursued, some with modest success and others yet that hold continued or renewed promise as advances are made in our understanding of the physiology and pharmacology of pain.

While excitatory amino acids are crucial to normal physiological processes such as learning, memory, and cognition, they have been implicated to play an important role in the development and propagation of nociceptive and neuropathic pain signaling. The *N*-methyl-D-aspartate (NMDA) receptor, a ligand-gated ion channel comprising multiple protein subunits coupled with other proteins to provide a variety of regulatory sites including glutamate, glycine, polyamine, Mg^{2+}, and PCP binding sites, is an ionotropic receptor for L-glutamate. In animal models, blocking the NMDA receptor has also been shown to prevent the development of tolerance to opioid-mediated analgesia, thereby suggesting a potential benefit to coadministration of NMDA receptor antagonists with opioids. In the target-related Miniperspective, Wayne Childers and Reinhardt Baudy of Wyeth Research review the recent advances in the NMDA receptor antagonist pipeline for the treatment of neuropathic pain. Because of the complex nature of this receptor with a large number of regulatory subunits and a plethora of binding sites where an antagonist could interact, the NMDA receptor provides an unusually high number of attractive molecular targets for medicinal chemists to pursue. This review will focus on the varied strategies and rationale for pursuing compounds that act at specific sites on the NMDA receptor, both in the periphery and in those centrally located, as well as on the challenges scientists have met so far and the shortcomings of some of the most advanced NMDA receptor antagonists.

While glutamate-based efforts in neuropathic pain have focused mostly on ionotropic receptors like NMDA, AMPA, and kainate, recent focus has shifted to metabotropic glutamate receptors. On the basis of sequence homology, differential signal transduction mechanisms, and overall pharmacological profiles, the metabotropic glutamate receptors (mGlu1−8) have been classified into three groups: (i) group I receptors (mGlu1 and mGlu5), (ii) group II receptors (mGlu2 and mGlu3), and (iii) group III receptors (mGlu4 and mGlu6−8). The role of group I receptors (positively coupled to phospholipase C) in pathophysiological processes such as pain signaling, neuronal excitability, and nociception has been investigated. Expression of mGlu1 receptors to areas of the central nervous system (CNS) and periphery associated with pain propagation has made this an attractive target for chronic pain management. Antagonists of mGlu1 receptors have been shown to be effective in numerous models of epilepsy, neurodegeneration, and neuropathic pain. In their manuscript, Jeffrey Schkeryantz and colleagues describe and contrast two bodies of research on competitive and noncompetitive mGlu1 antagonists. While the earlier competitive mGlu1 antagonists based on constrained analogues of glutamic acid gave rise to several classes of amino acids with impressive subtype selectivity, their lack of oral activity has precluded their further development. Characterization of numerous classes of non-amino acid based noncompetitive mGlu1 antagonists has recently led to potent druglike leads with the potential for improved overall pharmaceutical profiles. Whether these molecules will provide better clinical candidates remains to be seen.

In addition to the reported progress in the field of ligand-gated ion channels, the voltage-gated ion channels continue to represent a significant body of research in the neuropathic pain arena. These families of diverse transmembrane spanning proteins acting as molecular conduits for the translocation of anions (Cl^-) and/or cations (Ca^{2+}, K^+, Na^+) in or out of cells play a key role in the regulation of cell membrane excitability, synaptic release of neurotransmitters, and overall generation and propagation of pain signaling. The next three manuscripts are illustrative of recent medicinal chemistry advances in the fields of three "families" of cationic channels and how newly designed ligands of these channels may offer new opportunities to effectively treat neuropathic pain.

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is considered by physicians to be the "gold standard" treatment for a variety of neuropathic pain. It is prescribed to over 50% of patients suffering from diabetic neuropathy or postherpetic neuralgia. The drug is well tolerated except for sedation seen at higher doses. Its rather cumbersome dosing regimen (three to four times daily) limits its broader use however. With the recent launch of the follow-on compound pregabalin ((*S*)-3-(aminomethyl)-5-methylhexanoic acid) in the U.S. and Europe, Pfizer has positioned itself at the forefront of the neuropathic pain arena. As a 3-substituted analogue of γ-aminobutyric acid (GABA), pregabalin offers a much-improved pharmacokinetic profile over gabapentin showing a bioavailability of 90%, thus allowing for a more acceptable dosing regimen. Although their mechanisms of action are not totally clear, compounds represented by gabapentin and pregabalin are thought to exert their effects of blocking neuropathic pain by binding to the $\alpha2$-δ subunit of voltage-gated Ca^{2+} channels. This interaction results in inhibition of calcium influx into neuronal cells, thereby inhibiting neurotransmitter release and suppressing the development of central sensitization. Jacob Schwarz and colleagues outline recent advances in the medicinal chemistry of potent $\alpha2$-δ ligands. In their Miniperspective, they track lead progression from the γ-amino acid class of $\alpha2$-δ ligands typified by gabapentin and pregabalin to structural variants in the β-amino acid and α-amino acid classes and then finally to newly discovered non-amino acid leads and prodrugs. In vivo activity associated with this class of molecules is usually only realized if the compound is a substrate for the system L amino acid transporter. The review nicely points out compounds that are potent in vitro ligands but yet fail to demonstrate efficacy in neuropathic pain models because of their low affinity for the system L transporter. The tendency for spiro-lactonization within the γ-amino acid class of ligands prompted the Pfizer scientists to evaluate and develop numerous carboxylic acid bioisosteres that are reviewed and shown to potently inhibit [^{3}H]gabapentin binding to the $\alpha2$-δ subunit. Binding affinity was found to correlate well with the acid pK_a value. Highlighted compounds were shown to be active in the footpad incision model of neuropathic pain. The inactivity of highlighted leads in R217A mutant mice lacking the $\alpha2$-δ subtype supports the mechanism of action of this compound class. Finally, the paper reviews recent evidence that suggests that $\alpha2$-δ-1 and $\alpha2$-δ-2 subunits are differentially expressed throughout the CNS, possibly providing encouragement for pursuing a subtype selective ligand that may provide an improved side effect profile.

Recent data have emerged that support the role and function of the KCNQ K^+ family of channels (K_v7) in the regulation of

neuronal excitability and nociception. All KCNQ channels can couple to muscarinic receptors and form M-currents that are gated (inhibited) by acetylcholine. Their localization in the CNS, spinal chord, and dorsal root ganglion makes them an attractive target for the treatment of neuropathic pain. In their Miniperspective, Gordon Munro and William Dalby-Brown from NeuroSearch A/S present an overview of K_v7 channel openers and their effectiveness in numerous neuropathic pain models. Originally developed as an antiepileptic agent, the prototypical K_v7 channel opener retigabine (ethyl [2-amino-4-[[(4-fluorophenyl)methyl]amino]phenyl]carbamate) and its analogues have been shown to attenuate neuropathic and nociceptive pain behaviors in several rodent models. Electrophysiological studies have shown that these compounds potently hyperpolarize neuronal cells. These hyperpolarization effects have been shown to be sensitive to linopirdine (1,3-dihydro-1-phenyl-3,3-bis(4-pyridinylmethyl)- 2*H*-indol-2-one) and XE-991 (10,10-bis(4-pyridinylmethyl)- 9(10*H*)-anthracenone), known blockers of the K_v7 family, thus suggesting involvement of these channels. The paper then introduces "second-generation" K_v7 ligands that differ in structure from the troublesome "trianiline" scaffold featured in retigabine. In addition to improved selectivity profiles favoring $K_v7.2$ and $K_v7.3$ channel subtypes and their more druglike features, these newer molecules may offer an improved safety profile over the first-generation K_v7 openers developed for epilepsy.

Multiple classes of drugs that have historically been associated with pain relief, including anticonvulsants, antidepressants, and class I antiarrhythmics, make up the third family of cation-channel modulators addressed in this series, the sodium channel blockers. Don Kyle and Victor Ilyin of Purdue Pharma L.P. provide a Miniperspective on how historical Na^+ channel blockers have shown utility in numerous preclinical and clinical pain studies. With the recent cloning of Na^+ channel subtypes and numerous subunits, the underlying role and function of these pore-forming proteins are becoming better understood, thereby leading to the identification of molecules that interact differently with the channel or to different states of the channel (open, inactivated, or resting states). This has opened exciting opportunities for the potential characterization of Na^+ channel blockers with optimized subtype selectivity profiles and overall pharmacological properties.

Since the discovery that capsaicin (*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-(6*E*)-6-nonenamide), a pungent natural product derived from hot chilli peppers, alleviated pain sensations after topical applications, its mechanism of action has been the focus of much research. It has since been shown to be a potent agonist for the transient receptor potential channel, vanilloid type 1 (TRPV1). In the final manuscript in this Miniperspective series, Susan Westaway of GlaxoSmithKline provides a concise survey of the recent primary and patent literature of newly developed modulators of TRPV1 for the treatment of neuropathic pain. TRPV1 is a member of a family of nonselective, ligand-gated ion channels predominantly located on primary afferent nociceptors in DRG. In addition to sensitivity to capsaicin and its more potent analogue resiniferatoxin, TRPV1 is also activated by an acidic environment and heat, thereby triggering cellular Ca^{2+} influx, causing subsequent depolarization, excitability, neurotransmitter release, and propagation of pain signals. Paradoxically, both TRPV1 agonists and antagonists have been shown to demonstrate efficacy in various animal models of neuropathic pain. Thus, topical application of capsaicin cream, while initially producing an uncomfortable burning sensation, eventually leads to analgesia due to the persistently high intracellular Ca^{2+} levels that subsequently desensitize the nociceptors fibers causing degeneration of pain signaling. A high-dose (8%) capsaicin transdermal patch (NGX-4010), currently being developed for the treatment of HIV related neuropathic pain and postherpetic neuropathy, might offer an advantage over the cream applied capsaicin. Of greater potential utility is the development of a plethora of newly identified TRPV1 antagonists for neuropathic pain. The prototypical TRPV1 antagonist capsazepine, a compound related to capsaicin that has been shown to block capsaicin-mediated behaviors in rodents, has become an invaluable tool for studying the effects of TRPV1 antagonists in neuropathic pain models. Attempts to improve on the poor physical properties associated with the capsazepine scaffold have led to a large number of urea, thiourea, and amide structures as potent and useful TRPV1 antagonists. Evidence is mounting that TRPV1 is also expressed in other areas of the CNS such as the brain, as well as outside the CNS such as in the GI system, lung, and bladder. With the availability of both agonists and antagonist tool ligands, the future utility of TRPV1 modulators may quickly spill outside the neuropathic pain arena.

While an exhaustive treatise of emerging approaches to treat neuropathic pain is virtually impossible in a venue of this type, the six molecular targets reviewed in this Miniperspective series (NMDA, mGlu1, Ca^{2+} channels, K^+ channels, Na^+ channels, and TRPV-1) are illustrative of the most active fields of research and hopefully represent some of the more promising strategies for discovering more effective and safer pain medications to meet the challenges of the future. According to opinion leaders, *improved efficacy* remains as the most significant underserved need in the neuropathic pain markets. Current pharmacologic treatments for neuropathic pain syndromes struggle to achieve a maximum of 50% reduction in overall patient pain scores. Trying to push beyond this level of relief by using higher doses of currently available drugs is typically fruitless because of intolerable side effects. A newly approved pain drug could easily achieve "blockbuster" status by merely exceeding this apparent efficacy ceiling, even while maintaining the same side effect profiles and dosing regiments of current therapies. However, the impact of a more efficacious pain drug that introduces other, more serious side effects will most likely be diminished. A neuropathic pain drug with the right balance of potency, efficacy, pharmacokinetics properties, and safety profile would clearly make a significant impact on the quality of life of millions of patients.

David J. Triggle, the Perspective Editor for the *Journal of Medicinal Chemistry* up to March 31, 2006, proposed the idea of this Miniperspective series on neuropathic pain following a session sponsored by the Division of Medicinal Chemistry at the 230th National Meeting of the American Chemical Society held in Washington, D.C., in the Fall of 2005. I am grateful to have had the opportunity to work with Dave on this project as we set the tone by inviting these distinguished contributors. I am equally grateful to William Greenlee, the current Perspective Editor for the *Journal of Medicinal Chemistry*, who provided a seamless transition from Dave and key leadership that facilitated the process of completing this project in a timely manner. Most importantly, we extend our gratitude to the contributors to this Miniperspective series on neuropathic pain. We thank them for their time and dedication in providing excellent reviews and making this a successful project.

Biography

John A. Butera received his Ph.D. in Organic Chemistry at the State University of New York at Stony Brook in 1985 under the

mentorship of Professor Paul Helquist. He then joined Wyeth Research (then Ayerst Laboratories, a division of American Home Products) in Princeton NJ where he contributed to the discovery of numerous clinical candidates in cardiovascular and metabolic diseases and in women's health. At Wyeth, he has held positions of increasing levels of responsibility. Currently, he is a Director in the Exploratory Medicinal Chemistry group within the Chemical and Screening Sciences Department, providing leadership for the hit-to-lead efforts at the Princeton, NJ, and Collegeville, PA, research sites. He has published over 24 peer-reviewed papers, is co-inventor of 37 U.S. patents, and has presented at numerous scientific meetings.

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