N-Methyl-D-Aspartate Antagonists and Neuropathic Pain: The Search for Relief

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Received June 15, 2006

Neuropathic pain, generally defined as a chronic pain state resulting from peripheral or central nerve injury, can devastate the lives of patients and their families and friends. The pain, which can result from both acute events (amputation, back injury) and systemic disease states (e.g., viral infection, diabetes, and multiple sclerosis), often persists long after tissue injury has subsided. Symptoms vary depending on the condition but are usually the manifestations of allodynia (painful response to nonpainful stimuli) and/or hyperalgesia (increased sensitivity to painful stimuli). Pathological changes to the peripheral nerve(s) and spinal cord have been implicated in the induction of chronic pain.[1] Changes in the brain have also been reported, but less is known about these alterations.[2−4] Currently available treatments for neuropathic pain, including tricyclic antidepressants and the current "gold standard" gabapentin, typically show limited efficacy in the majority of patients.[5]

Considerable evidence suggests that activation of glutamate receptors plays a major role in the induction of pain associated with peripheral tissue and nerve injury.[5,7] Under conditions of normal (nociceptive) pain, the excitatory signal received from afferent neurons in the spinal cord dorsal horn is mediated primarily by the fast-inactivating kainate and AMPA[a] subtypes of the glutamate receptor. However, painful stimuli of greater duration and intensity result in accumulating, prolonged, slowly depolarizing synaptic potentials that relieve the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor from its tonic block by Mg^{2+} ions. Activation of NMDA receptors accentuates the sustained depolarization and contributes to an increase in the discharge of dorsal horn nociceptive neurons in a process called "windup". The NMDA receptor is also well-known for its roles in synaptic plasticity and long-term potentiation. Prolonged activation of NMDA receptors can lead to modifications in cellular signaling pathways that enhance the responsiveness of the nociceptive neuron to activation in a collection of processes referred to as "central sensitization". Central sensitization includes both short-term reversible components (such as post-translational modification of proteins) and long-term elements. One such long-term element thought to be associated with neuropathic pain is an enhanced response of the NMDA receptor itself to excitatory input through up-regulation of the modulatory tyrosine kinase Src.[8]

The pursuit of an NMDA receptor antagonist for the relief of neuropathic pain dates from the late 1980s, when it was shown that NMDA antagonists inhibit the "windup" response.[9,10] NMDA receptors are located on nerves in peripheral tissues and in the spinal cord and are widely distributed in the brain. Studies involving local injections of glutamate or NMDA and subsequent blockade of the resulting nociceptive behavior by local injections of NMDA antagonists suggest a potential utility for peripherally acting NMDA antagonists.[4] It has been shown that peripherally administered NMDA antagonists can attenuate the hyperalgesia induced by inflammation.[11] However, the hypersensitivity that results in neuropathic pain can only be partially explained by changes in the periphery. The central sensitization that occurs in the spinal dorsal horn is widely held to be an important event in the pathway leading to neuropathic pain. Consequently, centrally acting NMDA antagonists may be required for broad-spectrum efficacy. However, the search for an NMDA-based drug has been hindered by the propensity for many antagonists to display psychotomimetic "PCP-like" behavioral side effects at doses that provide significant blockade of the centrally located receptor.[12]

The NMDA receptor complex (Figure 1) is one of a family of ligand-gated ion channels (kainate, AMPA, and NMDA) that, when activated, permit the passage of Na^+ and K^+ ions.[6,12] Unlike the other two subtypes, the NMDA ion channel also allows passage of Ca^{2+} ions, which can affect numerous intracellular signaling and processing systems. At resting membrane potential the NMDA ion channel is blocked by extracellular Mg^{2+} ions. This tonic block can be relieved by membrane depolarization, but actual channel opening also requires the binding of the two coagonists glutamate and glycine. An X-ray crystal structure of the ligand binding domains of the NR1/NR2A heterodimer has recently been published.[13] The rates at which NMDA receptors activate and deactivate are significantly slower than that seen with the non-NMDA receptors, a phenomenon that allows the NMDA receptor to control the postsynaptic membrane potential. The combination of slow kinetics, permeability to Ca^{2+}, and ligand gating confers upon the NMDA receptor an integral role in synaptic plasticity.[14]

Functional NMDA receptors consist of heterotetrameric assemblies of subunits.[15] They comprise a pore-forming NR1 subunit that binds glycine in combination with at least one glutamate-binding NR2 subunit and, in some cases, a glycine-binding NR3 subunit. Multiple NR2 (A−D) and NR3 (A and B) subunits and at least eight splice variants of the NR1 subunit have been identified. Limited reports suggest that the NR3 subunit may be more important during development than in the adult.[16] The pharmacology and deactivation kinetics of the ion channel complex depend on the actual subunit composition. There are numerous allosteric sites on the various subunits that influence function. These include a Zn^{2+} ion binding site, a proton sensor, and a polyamine binding site that, when occupied by endogenous polyamines such as spermine and spermidine, shield the proton sensor. Within the ion channel lies the binding site for Mg^{2+} and the so-called noncompetitive antagonist site that binds numerous basic amine-containing compounds, including the recreational drug phencyclidine (PCP). The kinetics of the receptor complex can be further controlled through phosphorylation. Subunit composition varies with anatomical location of the receptor. Data are far from comprehensive, but some

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[a] Abbreviations: PCP, phencyclidine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

10.1021/jm060728b CCC: $37.00
Published on Web 05/10/2007

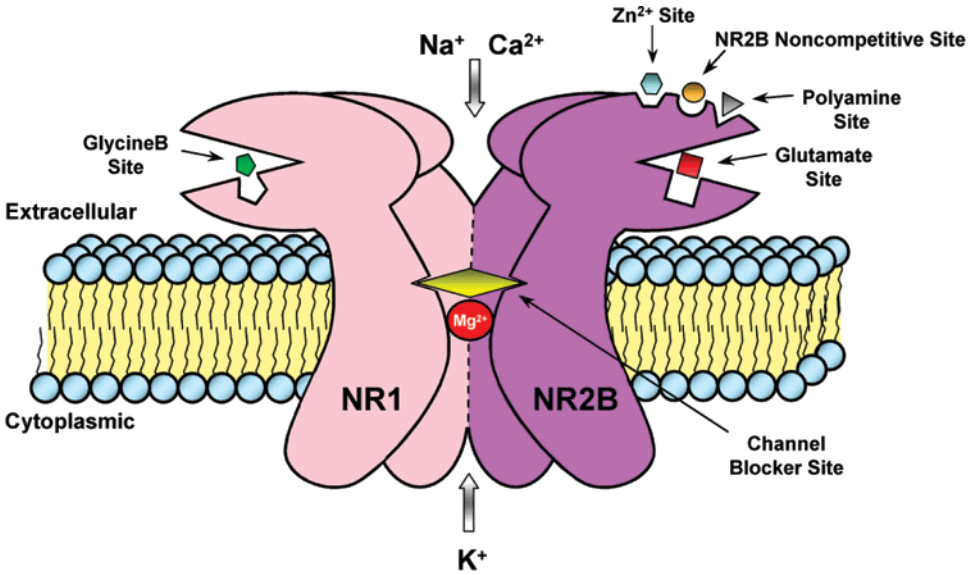

Figure 1. Drawing of an NR1/NR2B heterotetramer of the NMDA receptor with modulatory sites.

evidence suggests that NR2B-containing receptors may be concentrated in areas thought to be important for pain signaling.[17]

Thus, a number of pharmacological targets exist within the context of modulating NMDA receptor activity. Potent, selective ligands for the glutamate binding site and many of the modulatory sites have been described in the past 25 years, and several of these compounds have been examined for efficacy against chronic pain in animal models and in the clinical setting. Each of the targets for which significant data exist will be discussed below.[18]

Competitive Receptor Antagonists

Several selective, potent competitive NMDA receptor antagonists (compounds that bind to the glutamate recognition site on the NR2 subunit) have been identified and characterized.[12] Prototypical compounds contain phosphonic acid and α-amino acid moieties within their structures. As a result, compounds such as 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP, **1**, Figure 2) display poor oral bioavailability and poor central nervous system (CNS) penetration. A few compounds, such as selfotel (**2**, Figure 2) entered clinical trials for stroke but were abandoned because they caused unacceptable psychotomimetic side effects at doses at or below the dose that provided neuroprotective efficacy in animal models.[19] Preclinical data suggest that competitive NMDA antagonists can relieve some of the symptoms of neuropathic pain, especially those associated with the "windup" phenomenon.[6] However, only one clinical trial has been reported. Intrathecal administration of **1** (Figure 2) did not relieve the basal pain or allodynia in a patient suffering from surgery-induced nerve injury but did prevent "windup"-associated afterdischarge and radiation of the pain outside the territory of the injured nerve.[20] The presence of psychotomimetic side effects resulted in the termination of the study.

More recently, perzinfotel (EAA-090, **3**, Figure 2) has been described as a potent, selective competitive NMDA antagonist that exhibits a superior therapeutic index for efficacy versus psychotomimetic side effects.[21] The compound possesses a bioisosteric squaric acid amide in place of the typical α-amino acid and is reported to be 10-fold selective for rodent NMDA receptors possessing the NR2A subunit over NR2B-containing receptors.[22] Compound **3** demonstrated efficacy in animal models of inflammatory pain when administered both intraperitoneally and orally.[23] The compound was also reported to be active in neuropathic pain models, although data were not presented. The authors suggested that both peripheral and central NMDA receptors may be involved in the antinociceptive activity seen with perzinfotel. In a pair of poster presentations, the same group described WAY-129 (**4**, Figure 2), a derivative of perzinfotel. Compound **4** demonstrated oral efficacy (5−10 mg/kg po for EAA-129 vs 30 mg/kg po for **3**) in inflammatory and neuropathic pain models, with pharmacokinetics that supported once daily dosing.[24,25]

Noncompetitive Ion Channel Blockers

In contrast to the polar, often zwitterionic structure of competitive antagonists, the structure of the typical noncompetitive ion channel blocker is characterized by lipophilic groups and basic amine moieties.[12] As a result, ion channel blockers tend to be CNS-penetrant. Channel blockers such as ketamine (**6**, Figure 2) and dizocilpine (MK-801, **7**, Figure 2) have shown positive activity in a number of preclinical inflammatory and neuropathic pain models.[6] Some compounds have also demonstrated varying degrees of efficacy in neuropathic pain clinical trials, depending on the drug, the dose, and the cause of the pain syndrome. In this context, compound **6** is arguably the most studied NMDA antagonist in the clinical setting, where it relieved pain intensity, "windup", and allodynia in a number of pathological pain syndromes, including postherpetic neuralgia, spinal cord injury-induced central neuropathic pain, and peripheral neuropathy.[6,26−28] Unfortunately, the therapeutic potential of potent NMDA ion channel blockers has been limited by the prevalence of unacceptable psychotomimetic behavioral side effects resembling those induced by PCP. A few studies using carefully controlled intravenous administration of **6** suggest that the peripheral action of a noncompetitive ion channel blocker might provide some efficacy against neuropathic pain without eliciting behavioral side effects.[29]

However, the search for a greater therapeutic index in this class of compound has trended toward the identification of low-affinity channel blockers (Figure 2). Preclinical evidence suggests that the faster unblocking kinetics and the greater voltage dependency seen with low-affinity ligands might allow for such drugs to inhibit the low levels of ongoing spinal neurotransmission presumed to occur in neuropathic pain

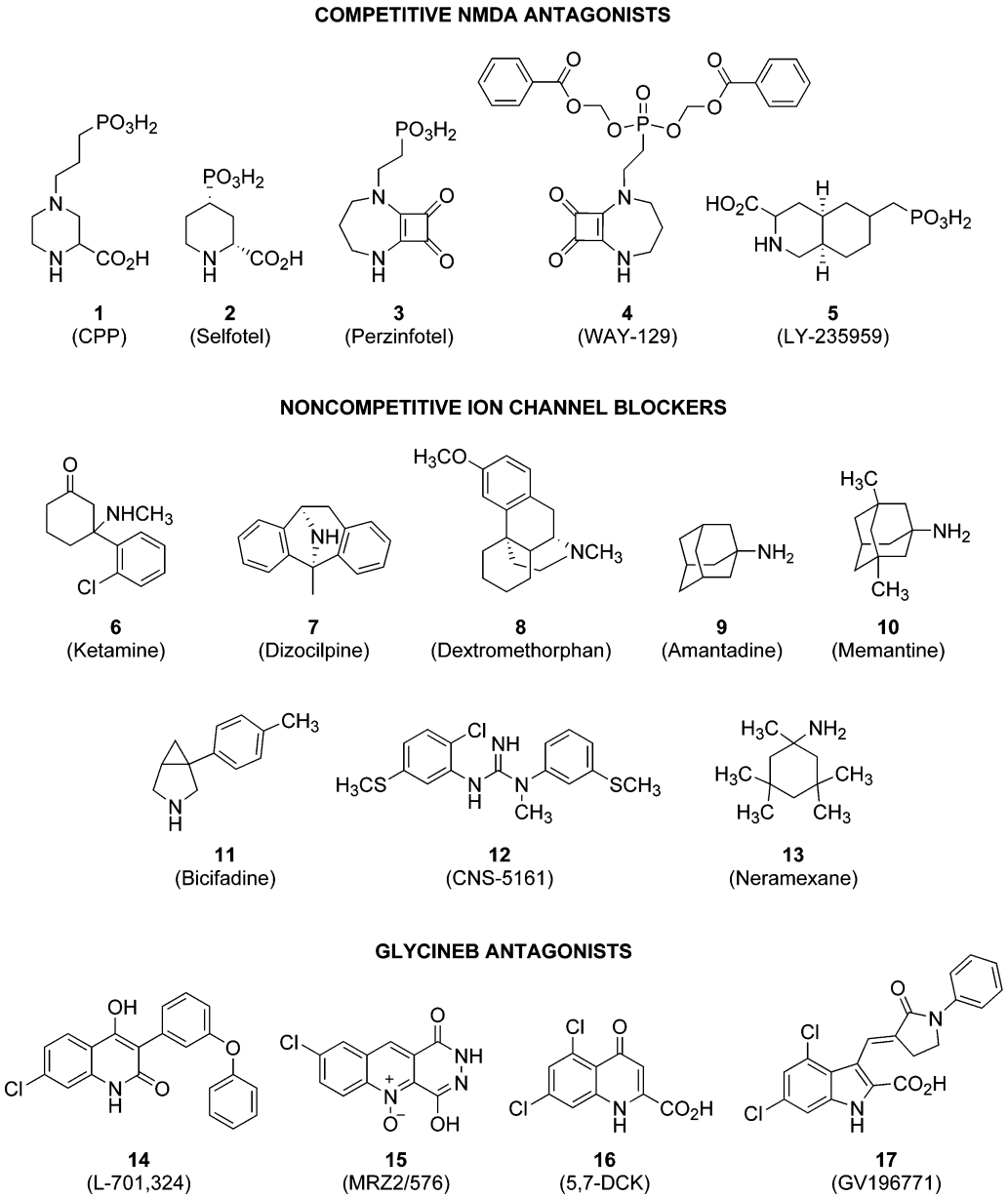

Figure 2. Structures of competitive NMDA antagonists, noncompetitive ion channel blockers, and glycineB antagonists.

without inducing the side effects that are characteristic of potent, long-term ion channel blockade.[6] The clinical results, however, have been largely disappointing. High doses of dextromethorphan (**8**) showed modest effects (24% reduction in pain intensity) in diabetic neuropathy patients but had no effect in postherpetic neuralgia.[30,31] One clinical trial reported that high doses of amantadine (**9**) helped relieve the intensity of ongoing postsurgical neuropathic pain in cancer patients by 31% compared to placebo.[32] However, the structurally related analogue memantine (**10**) demonstrated equivocal results in clinical trials examining diabetic neuropathy and postherpetic neuralgia syndromes despite its positive activity in animal models.[6,33−35] Another low-affinity channel blocker, bicifadine (**11**), did not show a statistically significant effect in a recently completed phase III clinical trial examining chronic back pain, although an earlier clinical report described positive effects against postoperative pain.[36] Cambridge Neuroscience recently reported the results of phase II clinical trials with **12** (CNS-5161), a guanidine-based ion channel blocker.[37] Intravenous administration of the compound was associated with a trend toward improvement in pain levels associated with a variety of pathological etiologies. An absence of psychotomimetic side effects was noted in a press release, although an increase in blood pressure was reported with higher doses. Neramexane (MRZ2/579, **13**) is also reported to be in phase II clinical trials for chronic pain, but no results have been published.[38]

GlycineB Binding Site Antagonists

Glycine acts as a coagonist on the NMDA receptor by binding at a recognition site on the NR1 subunit that is commonly referred to as the glycineB binding site.[6] This glycine binding site is different from the inhibitory strychnine-sensitive glycine binding site, which is itself an antinociceptive target. The binding of glycine to the glycineB site potentiates NMDA receptor responses by reducing the rate of desensitization of the receptor. GlycineB antagonists enhance desensitization and reduce NMDA responses. Thus, glycineB antagonists might be able to target ongoing, continuous effects of NMDA receptor activation and situations where NMDA receptor function has

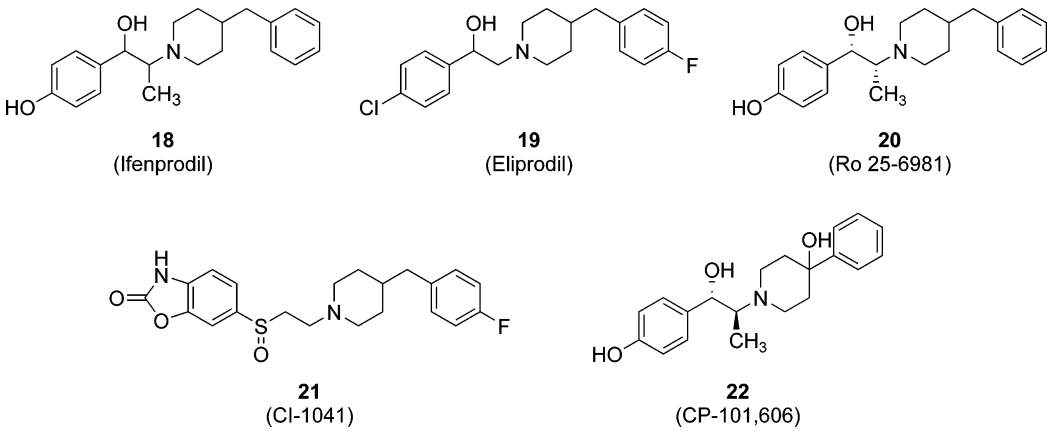

Figure 3. Structures of NR2B-specific noncompetitive NMDA antagonists.

been up-regulated (such as central sensitization), without dramatically effecting normal physiological processes.

However, the development of glycineB antagonists has been problematic. Different glycineB antagonists appear to have differing effects on the kinetics of NMDA desensitization, the reasons for which are not well understood. Furthermore, while selective glycineB antagonists do not appear to cause the disturbing psychotomimetic effects seen with competitive NMDA antagonists and potent noncompetitive ion channel blockers, they are plagued with ataxic/sedative side effects as well as poor brain penetration and the potential for inducing renal toxicity.[12] Nevertheless, glycine antagonists (Figure 2) such as **14** (L-701,324), **15** (MRZ2/576), and the prototypical 5,7-dichlorokinurenic acid (5,7-DCK, **16**) have shown efficacy in animal neuropathic pain models.[6] In fact, the antinociceptive efficacy seen with the peripherally restricted **16** and its lack of ataxic side effects lend some support to the argument in favor of peripherally acting NMDA antagonists for the treatment of neuropathic pain.[39] The results of one clinical trial examining a glycineB antagonist have been reported.[40] Oral administration of **17** (GV196771, Figure 2) did reduce the areas of static and dynamic mechanical allodynia, although no improvement in evoked pain intensity or pain relief was realized. Some of the possible reasons cited for the weak performance of **17** included species differences, the poor predictive value of animal models, and insufficient CNS penetration. One recent report describes an unsuccessful attempt to increase the CNS penetration of **17** using a prodrug approach.[41]

NR2B-Specific Noncompetitive Receptor Antagonists ("Polyamine Antagonists")

Although the NR1 subunit is widely distributed in the CNS, the distribution of the NR2B subunit is restricted in rat and human brain primarily to the cortex, hippocampus, striatum, thalamus, and olfactory bulb.[42] It is also found in dorsal root ganglion cells and the superficial layers of the dorsal spinal horn. These areas are pivotal in the transmission of pain signals and are thought to be key sites in the development of central sensitization. As part of an effort to identify neuroprotective NMDA antagonists with reduced psychotomimetic potential, compounds that antagonized the positive modulatory effect of polyamines (such as spermine and spermidine) were discovered. Ifenprodil (**18**, Figure 3) and eliprodil (**19**, Figure 3) were the first such compounds described in the literature. They were originally thought to be competitive antagonists of polyamine binding to the NMDA ion channel complex and were subsequently dubbed "polyamine antagonists". More recent data show them to be use-dependent, selective blockers of NMDA receptors possessing the NR2B subunit.[6,12] Their inhibitory effect appears to involve a noncompetitive allosteric interaction on the NR2B subunit that results in a reduction in receptor affinity for the polyamines.

Noteworthy among the pharmacological properties described for these compounds is an apparent lack of psychotomimetic side effects. However, early compounds possessed affinity for other targets such as serotonin receptors, α1-adrenergic receptors, and the cardiac ion channel hERG (human ether-a-go-go), which restricted their use in humans.[6,42] More selective NR2B antagonists have emerged since the disclosure of ifenprodil (Figure 3). These "second-generation" compounds (e.g., **20** (Ro 25-6981), **21** (CI-1041)) have demonstrated efficacy in a number of animal pain models and appear to possess superior side effect profiles compared to earlier analogs.[6,42] One compound, traxoprodil (CP-101,606, **22**, Figure 3) has progressed to phase II clinical trials. A preliminary report indicates that intravenous administration of the compound provided relief from pathological pain, although the effect was greater in patients suffering from central pain (spinal cord injury) than in those experiencing peripheral neuropathic pain (monoradiculopathy).[43] Typical psychotomimetic effects were not observed in these patients, although centrally mediated side effects such as dizziness, depression, and hypoesthesia were present. Interestingly, evidence from NR2B overexpressing transgenic mice as well as localized dosing experiments using **22** suggests that NR2B antagonists may exert their antinociceptive effect at a supraspinal location.[44,45] However, more studies are needed to unequivocally identify the site(s) of action for these agents. Other NR2B-selective antagonists reported to be in clinical trials include Gideon Richter's RGH-896[46] and Evotec's EVT 101[47] (structures not disclosed).

NMDA Antagonists and Opiates

While opiates are still the primary treatment for severe pain management, their prolonged use is accompanied by side effects. In addition to the typical side effects associated with acute opiate administration (constipation, nausea, dizziness, and loss of mental alertness), prolonged opiate exposure can induce analgesic tolerance (the requirement for higher and more frequent doses of opiates) and paradoxical hyperalgesic pain that is not confined to the initial pain complaint.[48] Some evidence points to opiate-induced increases in NR1 and NR2B protein levels as a contributor to these tolerance responses.[49] Preclinical data from one group suggest that combinations of morphine and NMDA antagonists may exert synergistic effects in neuropathic pain models, and a few clinical trials have been reported.[50,51] Compound **6** appears to act synergistically with morphine in

cancer and postherpetic neuralgia patients, but the use of **6** is limited by its psychotomimetic side effects.[6] Of the clinically tolerated NMDA antagonists, **8** and **9** (Figure 2) have received the greatest attention.[52] Neither of these agents significantly reduced the level of pain in postoperative patients. However, administration of **8** lengthened the time between operation and first analgesic request, and administration of either agent reduced overall opiate consumption.[52,53] A competitive NMDA antagonist, **5** (LY 235959, Figure 2), appears to potentiate the antinociceptive effect of a number of opiate analgesics in animal models, but no clinical data with competitive antagonists have been reported.[54]

Conclusion

It has been nearly two decades since the search began for a glutamate antagonist to treat neuropathic pain. Despite sound mechanistic hypotheses and encouraging preclinical data, that search has yet to produce a truly effective drug for the relief of this devastating collection of pain conditions. The most optimistic results in terms of overall pain relief have been obtained with compounds that provide potent blockade of the NMDA receptor and readily penetrate the CNS, such as **6**. However, these compounds will probably never see widespread clinical use because of their psychotomimetic side effects. Compounds that do not possess these behavioral liabilities, because of weak receptor affinity, limited CNS bioavailability, or subtype selectivity, also display limited or equivocal clinical efficacy.

That is not to say that many of these compounds are without effect. NMDA antagonism via most of the modulatory sites provides reduction in some of the aspects of neuropathic pain, such as "windup", allodynia, hyperalgesia, and radiation of pain outside the injured area. Peripheral NMDA receptors may play a role in this antinociceptive activity, but the most impressive results to date come from agents that penetrate the spinal cord (and brain) or are administered to those locations. Some preclinical data suggest that NMDA antagonists may act synergisticly with opiates, either by enhancing their antinociceptive effect or by blocking analgesic tolerance. To that end, NMDA antagonists have shown a hint of promise when combined with opiates. However, only weak noncompetitive blockers have been studied in humans. Clinical trials examining combinations of newer NMDA antagonists such as glycineB antagonists and NR2B-selective modulators would be of great interest.

Of the possible routes to block NMDA neurotransmission, NR2B-selective receptor modulation currently appears to hold the most interest for researchers. Several of these types of agents are still reported to be in clinical trials, and many recent NMDA antagonist patents and applications disclose compounds with ifenprodil-like structures. One appeal for these compounds is their apparent lack of psychotomimetic side effects. This benefit may arise at least partly from the selectivity for NR2B-containing receptor complexes, although the efficacy and reported lack of psychotomimetic side effects seen with the NR2A-selective competitive antagonist perzinfotel raise questions regarding this explanation for the theraputic index seen with "polyamine antagonists". Other indirect methods for modulating NMDA-mediated neurotransmission are currently being pursued, but their application in the clinic has yet to be tested. After almost 20 years of pursuit, the path to an effective NMDA antagonist that can treat neuropathic pain is still not clear. What is clear is that as more is learned about NMDA receptor distribution, function, and modulation, efforts to identify an NMDA antagonist-based agent with an improved therapeutic index (relative to current compounds) for this and other indications will continue.

Acknowledgment. The authors thank Jonathan Gross for his assistance in the preparation of this manuscript.

Biographies

Wayne E. Childers, Jr. received his B.A. degree from Vanderbilt University in Chemistry (1979) and his Ph.D. in Organic Chemistry from the University of Georgia (1984) under the direction of Dr. Harold Pinnick. After postdoctoral research in bioorganic chemistry in the Department of Pharmacology at The Johns Hopkins University School of Medicine under the supervision of Dr. Cecil H. Robinson, he joined Wyeth in 1987. His research interests lie in the areas of synthetic and bioorganic chemistry and drug design. He has made contributions in the discovery of NMDA antagonists, serotonin receptor ligands, and proteolytic enzyme inhibitors. He is currently focusing his efforts on the identification of agents for the treatment of neuropathic pain.

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JM060728B