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The Use of NMDA-Receptor Antagonists in the Treatment of Chronic Pain

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Abstract:

Chronic pain can be maintained by a state of sensitization within the central nervous system that is mediated in part by the excitatory amino acids glutamate and aspartate binding to the N-methyl-D-aspartate (NMDA) receptor. A number of antagonists to the NMDA receptor are antinociceptive in animal models but are associated with significant dose-limiting side effects. Commercially available NMDA-receptor antagonists include ketamine, dextromethorphan, memantine, and amantadine. The opioids methadone, dextropropoxyphene, and ketobemidone are also antagonists at the NMDA receptor. The NMDA-receptor antagonists have a significant impact on the development of tolerance to opioid analgesics. Consequently, NMDA-receptor antagonists may represent a new class of analgesics and may have potential as coanalgesics when used in combination with opioids.

Key Words: Central sensitization—Neuropathic—–NMDA—Pain therapy—Pain tolerance

The ideal approach to pain management would be to select the appropriate treatment based on the underlying pathophysiology that is maintaining the ongoing state of pain. Advances in pain research are beginning to make this ideal approach possible. Antagonists to the N-methyl-D-aspartate (NMDA) receptor are an example of this targeted approach to analgesic therapy.

TRANSMISSION AND MODULATION OF PAIN

Nociceptors are special somatosensory primary afferent neurons that are normally silent but become activated when exposed to stimuli that cause or threaten to cause tissue injury. Pain is detected by slowly conducting unmyelinated C-fibers and thinly myelinated A-delta nociceptive fibers. When exposed to inflammation, these receptors change their firing characteristics to become sensitized; they discharge spontaneously and produce ongoing pain.[1] The threshold for activation decreases, producing allodynia, the phenomenon in which normally innocuous stimuli cause pain.[2] Noxious stimuli can produce more pain than normal, a condition known as hyperalgesia.[3] These sensitized nociceptors acquire an excitatory response to norepinephrine, creating a link with sympathetic nervous system activity.[2,3] Structural changes can also occur. Interrupted axons regenerate sprouts that may discharge spontaneously and become sensitive to mechanical, thermal, and ionic stimuli. Nociceptors that travel in the vicinity of these damaged nociceptors may also be affected.[4–6]

The brief high-intensity excitation in the dorsal horn nociceptive neurons resulting from impulses in primary nociceptive afferents is followed by a lower intensity prolonged impulse discharge.[7] Continuous C-polymodal nociceptive afferents evoke temporal summation by activation of NMDA receptors[8,9] and provide part of the basis of hyperalgesia.

Temporal summation of C-afferent–evoked responses in the dorsal horn is likely to be mediated by the release of glutamate and aspartate and their activation of NMDA receptors, leading to prolonged depolarization.[8,10] In vitro preparations have shown that NMDA-receptor antagonists block prolonged depolarization evoked by dorsal horn neurons[8,10] and temporal summation evoked by stimulation of C-afferents in vivo without reducing the responses of these neurons to A-fiber stimulation.[7,8,10,11]

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Temporal summation of C-afferent–evoked responses in dorsal horn neurons mirror some of the mechanisms underlying centrally mediated hyperalgesia from nerve injury or inflammation.[7,8,10–13] Both involve the same NMDA-receptor mechanisms and some of the other intracellular consequences of NMDA activation.[7,8,10–13]

Central sensitization is the term used to describe the increased sensitivity of these postsynaptic cells to all input, including that from damaged or sensitized nociceptors as well as from low-threshold mechanoreceptors. Because central sensitization can result from any kind of C-nociceptor input, normal stimuli producing a small and fleeting amount of central sensitization and input from spontaneously active sensitized nociceptors can produce prominent and long-lasting central sensitization.[14]

NMDA-RECEPTOR ANTAGONISTS: EXPERIMENTAL MODELS OF PAIN

A number of experiments using antagonists to the NMDA receptors have helped to define the role of NMDA-receptor activation in the development of the mechanical hyperalgesia that follows peripheral nerve injury or tissue inflammation.

The antinociceptive effects of NMDA-receptor antagonists in animal models of nerve injury support the potential use of this class of drugs for the treatment of neuropathic pain. Dextrorphan and ketamine are the noncompetitive NMDA-receptor antagonists that are currently used in other clinical applications. In rats with peripheral mononeuropathy induced by loose ligation of the common sciatic nerve (chronic constrictive injury [CCI]), intrathecal dextrorphan and ketamine reliably attenuated hyperalgesia to radiant heat, spontaneous pain-related behaviors, and thermal hyperalgesia.[15] Dextrorphan given intraperitoneally relieved heat-evoked hyperalgesia in a dose-dependent manner in the CCI model, and intrathecal injection completely blocked heat-evoked hyperalgesia.[16] Intraperitoneal boluses of memantine, another clinically available NMDA-receptor antagonist, decreased withdrawal responses after mechanical stimulation for up to 6 hours after injection in neuropathic rats with hyperalgesia and allodynia.[17] Chronic treatment decreased nociceptive responses for 3 days after treatment. Intraperitoneal MK-801 prevented the development of hyperalgesia in the CCI model in the rat.[18] Spinal administration of MK-801, DL-2-amino-5-phosphonovalerate, and ketamine temporarily eliminated the hyperesthetic state induced by the CCI model.[19]

Spinal administration of the NMDA-receptor antagonists memantine, AP5, dextrorphan, dextromethorphan, MK-801, and ketamine produced a wide range of efficacies when evaluated in allodynia evoked by tight ligation of the fifth and sixth lumbar spinal nerves and in the formalin paw test.[20]

The induction and maintenance of mechanical and thermal allodynia after partial denervation of the tail was dependent on NMDA receptors.[21] Intraperitoneal injection of MK-801 before unilateral transection of the superior caudal trunk, which innervates the tail in rats, delayed the emergence of mechanical and thermal allodynia for at least 4 days after the injury.

Subcutaneous injection of formalin produces a biphasic pain response: an early transient phase followed by a late tonic phase. The late phase of formalin pain is due to NMDA-mediated activity during the early phase.[22] Blockade of the NMDA receptor by its noncompetitive antagonist, MK-801, before but not after formalin injection reduces pain during the late phase. Intrathecal administration of the NMDA-receptor antagonists dizocilpine maleate and (±)-2-amino-5-phosphonopentanoic acid significantly increased the mechanical threshold and reduced the response duration in inflamed hindpaw produced by an injection of complete Freund adjuvant.[23] Intraperitoneal memantidine blocked formalin-induced tonic and, to a lesser degree, phasic pain.[24]

In a joint inflammation model of acute arthritis pain, memantine reduced the responses to noxious and innocuous pressure[25] in anesthetized rats in which extracellular recordings from spinal neurones with knee joint input were obtained.

EXPERIMENTAL MODELS OF PAIN: HUMAN SUBJECTS

A number of studies on experimental neuropathic pain in human subjects have evaluated the analgesic potential of NMDA-receptor antagonists in the treatment of chronic pain and have helped to define the role of NMDA-receptor activation in the development of mechanical hyperalgesia.

Temporal summation of second pain via C-fiber–mediated responses of nociceptive neurons in the dorsal horn provides a psychophysical correlate of "windup," which is related to hyperalgesia[7,10,12] and central sensitization. Windup has been considered to be a predictive model for therapies designed to modulate central mechanisms of hyperalgesia.[7,8,11]

Supporting the role of second pain as a psychophysical correlate of windup is a study by Price et al.[26] In that study, doses of 30 and 45 mg but not 15 mg of dextromethorphan were effective in attenuating temporal summation of second pain produced in normal volunteer human subjects who underwent repeated painful electric shocks and repeated 52°C heat pulses.[26]

A placebo-controlled trial (12 volunteers) found that a

ketamine (0.5 mg/kg) bolus followed by a 20-minute infusion (9 μg/kg/min) inhibits central temporal summation in human subjects subjected to repeated nociceptive electric stimuli and has a marked hypoalgesic effect on high-intensity nociceptive stimuli.[27] The pressure-pain detection and tolerance thresholds were increased significantly by ketamine, whereas laser heat pain and tolerance thresholds remained stable compared with placebo results.[27]

Intradermal capsaicin produces a strong burning pain sensation that lasts for 20 minutes. The skin surrounding the injection site becomes allodynic and hyperalgesic for hours. This model produces an acute discharge of C-fiber nociceptors[28,29] and can be used as a potential screen for drugs to treat patients with central nervous system sensitization. This effect can be reversed by NMDA-receptor blockade.

Supporting the role of NMDA receptors in some of the central mechanisms underlying secondary hyperalgesia, ketamine inhibited the summation of activity in nonnociceptive and nociceptive afferents in a study of cutaneous hyperalgesia established by topical capsaicin in healthy volunteers.[30]

In a 3 × 3 crossover study by Park et al.,[31] single doses of intravenous ketamine, alfentanil, and placebo were assessed in an intradermal capsaicin experimental pain model. Ketamine and alfentanil produced significant analgesia in this model when compared with placebo. A trend was noted toward decreasing the spread of allodynia when ketamine was compared with placebo. The antiallodynic effect of alfentanil was significantly different from the effect of placebo. Both ketamine and alfentanil significantly diminished the spread of pinprick hyperalgesia. This study suggests that blockade of the NMDA receptor as well as use of the positive control alfentanil was able to provide analgesia.

In a burn model of pain, ketamine administered in a dose-dependent manner reduced the magnitude of both primary and secondary hyperalgesia as well as pain evoked by prolonged noxious heat stimulation[32] in 19 healthy volunteers.

In a double-blind, placebo-controlled, randomized, crossover study, the effects of morphine and ketamine on temporally summated pain and spatial aspects of secondary hyperalgesia were investigated in hyperalgesia produced by a local burn injury in 12 healthy volunteers. Primary hyperalgesia was significantly reduced within the injured area compared with the preinjury threshold. Ketamine significantly reduced the area of secondary hyperalgesia.[33]

Not all studies of NMDA-receptor antagonists have demonstrated an antihyperalgesic effect. In a double-blind placebo-controlled study, dextromethorphan (90 mg) given before intradermal injection of capsaicin in 10 volunteers did not affect ongoing or mechanically evoked pain.[34] Dextromethorphan (100 mg administered orally) did not significantly attenuate pain intensity or unpleasantness induced by experimental ischemia or topical capsaicin in healthy human subjects, nor did it increase the threshold for heat pain or mechanical pain.[35] The lack of efficacy may be due to the doses selected in these two studies.

NMDA-RECEPTOR ANTAGONISTS: TREATMENT OF CHRONIC PAIN

Because chronic pain states associated with hyperalgesia are often refractory to standard therapy, the potential of NMDA-receptor antagonists as a new type of analgesic has led to clinical investigations.

Single-dose intravenous ketamine was compared with alfentanil and saline in a 3 × 3 crossover study in patients with chronic posttraumatic pain with allodynia.[36] Ketamine provided statistically significant better pain relief than alfentanyl and placebo for both spontaneous pain and allodynia. Alfentanyl was similarly better than placebo. Dose-limiting side effects involving sedation, nausea, dissociative reactions, muteness, dizziness, and visual distortions occurred with ketamine. The psychomimetic effect occurred before the onset of analgesia and lasted longer than the analgesic effect.

The significant dissociative effects associated with some of the NMDA-receptor antagonists led Rogawski[37] to propose that lower affinity NMDA-receptor antagonists such as dextromethorphan might have fewer dose-limiting side effects than the higher affinity blockers such as ketamine and MK-801. The shorter duration receptor occupancy at the phencyclidine site might limit these side effects.

Nelson et al.[38] performed two randomized, double-blind, crossover trials comparing 6 weeks of oral dextromethorphan with placebo in two groups. Thirteen of 14 patients with painful distal symmetric diabetic neuropathy and 13 of 18 patients with postherpetic neuralgia completed the study. Doses were titrated to reach a level that did not disrupt normal activities. Diabetics reached a mean dose of 381 mg/day, and patients with postherpetic neuralgia reached a mean dose of 439 mg/day. Dextromethorphan decreased pain by a mean of 24% (95% CI: range, 6–42%; $p = 0.01$) relative to placebo in diabetic neuropathy but did not significantly reduce pain in postherpetic neuralgia (95% CI: range, 10% decrease in pain to 14% increase in pain; $p = 0.72$). Patients dropped out due to sedation or ataxia during dose escalation.

The side effects associated with dextromethorphan

may have potentially unmasked patients to the drug they were receiving. In a follow-up study, Sang et al.[39] compared dextromethorphan with memantidine and an active placebo (lorazepam) and confirmed a statistically significant difference in patients with painful diabetic neuropathy but not in patients with postherpetic neuralgia.

Lower doses of dextromethorphan (≤90 mg/day) did not relieve chronic neuropathic pain,[40,41] which supports the findings of Kinnman et al.[34]

Ketamine was found to relieve continuous, spontaneous, and evoked pain in patients with postherpetic neuralgia but was associated with intolerable side effects, including nausea, fatigue, and dizziness.[42]

Pain and sensory thresholds before and after intravenous administration of ketamine, morphine, or saline in eight patients with postherpetic neuralgia were evaluated in a randomized, double-blind, crossover study. Ketamine produced significant relief of pain and normalized abnormal heat-induced pain sensations in four patients. Allodynia was significantly inhibited by ketamine as well as by morphine. Windup-like pain was also significantly inhibited by ketamine.[43]

Patients with established stump and phantom limb pain[44] responded with a decrease in the rating of both types of pain after intravenous ketamine, which also increased pressure-pain thresholds significantly and significantly reduced windup-like pain.

In a double-blind placebo-controlled study, ketamine affected evoked pain and associated aftersensation in chronic neuropathic pain syndromes more than in the ongoing constant type of pain.[45] Ketamine (250 μg/kg intravenous slow push) was administered to six patients for control of chronic neuropathic pain.[45]

In another double-blind placebo-controlled study[46] in patients suffering from chronic neuropathic pain, ketamine produced a significant reduction in spontaneous pain and an area of allodynia. There was a significant correlation between the reduction in ongoing pain and the reduction in the area of touch-evoked allodynia.

One patient with postherpetic neuralgia obtained pain relief from subcutaneous and later oral ketamine after classic treatment had failed,[47] and another patient with postherpetic neuralgia was treated with ketamine for 4 years with good pain relief.[48]

In a double-blind experiment, intravenous ketamine provided pain relief in a patient with glossopharyngeal neuralgia. Ketamine provided statistically significant pain relief and reduction in pain intensity at a dose of 60 mg of oral ketamine administered six times a day when compared with placebo administered for 10 2-day periods.[49]

In a patient with neuropathic cancer pain unresponsive to opioid escalation and spinal administration of a combination of bupivacaine-morphine, a subcutaneous continuous ketamine infusion provided pain relief and a dramatic reduction in the oral morphine dose. A slow and progressive increase in subcutaneous ketamine and morphine dosage continued to provide adequate pain relief after 13 months of therapy despite signs of progressive disease.[50]

Infusion of the clinically available NMDA-receptor antagonist amantadine (200 mg) was statistically better than placebo in relieving surgical neuropathic pain in patients with cancer. Average pain was reduced 85% at the end of the amantadine infusion period versus 45% after placebo, and the mean pain intensity remained significantly lower during the 48 hours after amantadine treatment compared with the 48 hours before treatment. Amantadine also reduced windup-like pain in four patients.[51]

OTHER NMDA-RECEPTOR ANTAGONISTS

New evidence has demonstrated that some opioid analgesic medications are weak noncompetitive NMDA-receptor antagonists, which raises the possibility that they may have a dual mechanism of action.[52–54]

Ketobemidone has both mu-opioid agonist as well as NMDA blocking effects.[55] Ketobemidone applied to the spinal cord dose-dependently and selectively reduced C-fiber–evoked responses and blocked windup more effectively than morphine at equieffective doses but, unlike morphine, not in a naloxone-reversible manner. Further evidence comes from a binding study in which ketobemidone inhibited [^{3}H]MK-801 binding.[55]

Recent evidence supports a unique role for methadone in the treatment of chronic pain.[56,57] The racemic mixture of methadone demonstrates that the d- and l-isomers of methadone bind to the NMDA receptor.[58] The d-isomer is weak or inactive at the opioid receptor but is antinociceptive in neuropathic pain models as an antagonist at the NMDA receptor.[59]

A number of other opioids, including dextropropoxyphene,[54] bind to the NMDA receptor and have produced concentration-dependent reductions involving NMDA-receptor–mediated neurotoxicity. The nonopioid enantiomer of methadone and morphine exhibited a potency equal to or greater than that of the opioid enantiomer, and naloxone did not act as an antagonist.[52]

OPIOIDS AND NMDA-RECEPTOR ANTAGONISTS

The NMDA receptors seem to have a fundamental role in the development of opiate tolerance, and noncompeti-

tive NMDA-receptor antagonists may be effective adjuncts to opiates in the treatment of chronic pain. Advokat and Rhein[60] combined a subeffective dose of dextrorphan (15 mg/kg) with several doses of morphine and assessed the tail flick response of the acute spinal rat, an animal model of central injury. At doses that were individually ineffective, the combination of dextrorphan and morphine produced a significant antinociceptive response.

Trujillo and Akil[61] found that opiate tolerance is inhibited rapidly and at low doses by four different noncompetitive NMDA-receptor antagonists (MK-801, ketamine, dextrorphan, and phencyclidine). This inhibition results from blockade of NMDA receptors rather than from the side effects of a particular drug. Furthermore, the NMDA antagonists were able to prevent but not reverse tolerance.[61]

In the hot water tail immersion test of pain, competitive as well as noncompetitive NMDA-receptor antagonists enhance morphine's antinociceptive effect and prevent the development of morphine tolerance,[62] but neither competitive nor noncompetitive NMDA-receptor antagonists had an antinociceptive effect by themselves. When coadministered with intrathecal morphine infusions, MK-801 also inhibited the development of tolerance.[62]

The noncompetitive antagonists dizocilpine (MK-801) and ketamine and the competitive antagonist CGP 39551 reduced the intensity of tolerance to and physical dependence on morphine in morphine-treated mice. When given in a single dose 30 minutes before a subcutaneous naloxone-precipitated withdrawal syndrome, these drugs reduced the intensity of the abstinence behavior in mice chronically treated with morphine.[63]

Coadministration of low doses of an NMDA antagonist and an opiate might have clinical benefit for the relief of pain with reduced risk of the undesirable side effects that occur with NMDA-receptor antagonists and high-dose opioid analgesia. The NMDA-receptor antagonists may enhance the analgesic effects, extend their duration, and prevent tolerance to repeated administration of opioid analgesic therapy.

Because some NMDA-mediated events can be difficult to control with opioids alone (e.g., neuropathic pain states), NMDA-receptor antagonists may be helpful. Also, because opioids act presynaptically on C-fiber terminals to reduce transmitter release, the combination of an opioid and an NMDA-receptor antagonist produces synergistic inhibitions. Low-dose combinations may be possible with a low likelihood of side effects.[64]

Recent double-blind placebo-controlled studies of a combination product of morphine and dextromethorphan in a 1:1 ratio demonstrated significantly better pain relief than an equal analgesic dose of immediate-release morphine, with a faster onset of action and a longer duration of analgesia.[65]

CONCLUSIONS

The NMDA-receptor antagonists hold great promise for a targeted approach to analgesic therapy. Abundant data from animal and human models of hyperalgesia and placebo-controlled studies of chronic pain as well as anecdotal reports suggest that NMDA-receptor antagonists should be considered in the treatment of some refractory pain syndromes. Currently available NMDA-receptor antagonists are often accompanied by significant side effects when levels of adequate analgesia are obtained. A promising role for the NMDA-receptor antagonists is the potential for providing added analgesia by reversing opioid tolerance. It is likely that NMDA-receptor antagonists with better efficacy and fewer side effects will be an important part of the analgesic armamentarium in the near future.

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