**Proceedings Supplement**

**NMDA-Receptor Antagonists: Evolving Role in Analgesia**

Update on the Neurophysiology of Pain Transmission and Modulation: Focus on the NMDA-Receptor

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**Abstract**

Pain is detected by two different types of peripheral nociceptor neurons, C-fiber nociceptors with slowly conducting unmyelinated axons, and A-delta nociceptors with thinly myelinated axons. During inflammation, nociceptors become sensitized, discharge spontaneously, and produce ongoing pain. Prolonged firing of C-fiber nociceptors causes release of glutamate which acts on N-methyl-D-aspartate (NMDA) receptors in the spinal cord. Activation of NMDA receptors causes the spinal cord neuron to become more responsive to all of its inputs, resulting in central sensitization. NMDA-receptor antagonists, such as dextromethorphan, can suppress central sensitization in experimental animals. NMDA-receptor activation not only increases the cell's response to pain stimuli, it also decreases neuronal sensitivity to opioid receptor agonists. In addition to preventing central sensitization, co-administration of NMDA-receptor antagonists with an opioid may prevent tolerance to opioid analgesia. J Pain Symptom Manage 2000;19:S2–S6. © U.S. Cancer Pain Relief Committee, 2000.

**Key Words**

NMDA-receptor antagonists, pain transmission, opioid tolerance, central sensitization, allodynia, hyperalgesia, neuropathy

**Introduction**

For many years, the neurophysiological analysis of pain transmission focused on responses evoked by an acute noxious stimulus, e.g., a pinprick or a few seconds exposure to painful heat. It was realized that clinically significant pain might be very different, but the hope was that it would be different in degree, not in kind. We now know that this is not true—chronic pain caused by inflammation or nerve injury (neuropathic pain) is due, at least in part, to unique mechanisms in the peripheral and central nervous system.¹

**Peripheral Nervous System**

The skin, muscle and tendon, periosteum and synovium, heart and blood vessels, and the viscera (or the connective tissues capsules that encase them) are all innervated by somatosensory primary afferent neurons that are specialized to respond to stimuli that cause, or threaten to cause, tissue injury. These pain-sensing afferent neurons, called “nociceptors,” come in two general types, one with slowly conducting unmyelinated axons (C-fiber nociceptors) and the other with thinly myeli-

¹ Please note that the citation is incomplete and may require further verification or correction.
nated axons (A-delta nociceptors). In normal tissue they are silent in the absence of tissue injury; when injury occurs, their rate of discharge increases as a function of the amount of tissue damage, i.e., nociceptors signal the occurrence of pain and encode its intensity.

In the presence of inflammation, nociceptors acquire new characteristics and are said to be sensitized: (1) They begin to discharge spontaneously. This spontaneous, or ongoing, discharge is at least partly responsible for the ongoing pain (soreness) that follows a tissue injury. (2) Their threshold for activation is decreased such that normally innocuous stimuli now cause pain (e.g., the pain felt when lightly touching a burn; a phenomenon called allodynia). (3) Their stimulus–response curves are shifted to the left, such that a noxious stimulus causes more pain than normal, a condition called hyperalgesia (e.g., the pain of being slapped on a sunburnt back). The decrease in threshold and the leftward shift of the stimulus–response function underlie the tenderness of an injured region and its immediate surround. Sensitized nociceptors also acquire an excitatory response to norepinephrine; thus, there is a link between pain and sympathetic nervous system discharge.²⁻⁴

In the case of neuropathic pain, nociceptors also change their characteristics. If their axon has been interrupted, the regenerating sprout may discharge spontaneously and become extremely sensitive to mechanical, thermal, and ionic stimulation. Similar, but less pronounced, changes are seen in nociceptors that escape injury themselves but travel in the vicinity of damaged axons.⁴⁻⁶

Central Nervous System

Spontaneously discharging nociceptors will give rise to ongoing pain. Unfortunately, that is not all. Unmyelinated (C-fiber) nociceptors release glutamate as their neurotransmitter. The spinal cord neurons that receive input from C-nociceptors express three subtypes of glutaminergic receptor: the N-methyl-D-aspartate (NMDA) subtype, the kainate/AMPA (l-amino-3-hydroxy-5-methylisoxazole-propionic acid) subtype, and the metabotropic subtype. Glutamate released from C-nociceptors and acting at NMDA receptors evokes a change in the sensitivity of the postsynaptic cell such that it responds more strongly to all of its inputs (Figure 1), an effect called central sensitization. Very recent data suggest that something simi-

Fig. 1. An experiment showing the effects of NMDA-receptor antagonists on central sensitization. Following decerebration and spinalization under general anesthesia, rats were prepared for the electrophysiological recording of the discharges of flexor motoneurons innervating the thigh. Flexor motoneuron discharges were evoked by a standardized painful pinch to the toes every 5 minutes. The motoneuron discharge causes the pain withdrawal reflex; in humans, the magnitude of the reflex corresponds to the magnitude of pain perceived. Prior to painting the skin with mustard oil (MO), each pinch evokes a fairly constant baseline pain withdrawal reflex. Mustard oil, a vesicant that selectively excites C-nociceptors, causes an intense burning pain sensation of about 1 minute duration. Following the pain input caused by MO, the reflex is greatly enlarged for over an hour. The increased reflex, and the increased perceived pain that would accompany it, indicate the presence of central sensitization. Pretreatment (left-hand graph) with NMDA antagonists (CPP or MK-801) prevents central sensitization, whereas post-treatment (right-hand graph) reverses it. Reproduced with permission from Woolf and Thompson.⁷
lar may also be happening via glutamate activation of kainate/AMPA channels, but most of the data in hand implicates the NMDA receptor.

Activation of the NMDA receptor causes the spinal cord neuron to become more responsive to all of its inputs, including input from damaged or sensitized nociceptors and input from low-threshold mechanoreceptors (“touch” fibers). It is important to note that central sensitization is evoked by any kind of C-nociceptor input. Normal input from uninjured tissue produces a small and fleeting amount of central sensitization, but the large and prolonged input from C-nociceptors that are sensitized as a consequence of tissue inflammation, or that discharge spontaneously because of nerve injury, can produce prominent and long-lasting central sensitization.

Central sensitization has been demonstrated in animals, even in the presence of a surgical level of general anesthetic. It can be demonstrated also in the normal human volunteer. For example, an intradermal injection of capsaicin (the active ingredient in chili peppers and a specific stimulant for C-nociceptors) produces a very strong burning pain sensation that lasts for about 20 minutes. After the injection pain has waned (and even before that), the skin surrounding the injection site becomes allodynic and hyperalgesic for hours (Figure 2). The allodynia and hyperalgesia can be reversed by NMDA-receptor blockade.

**NMDA-Receptor Antagonists**

There is universal agreement that NMDA-receptor antagonists of diverse chemistry suppress central sensitization in experimental animals (Table 1), and there are several demonstrations of efficacy in humans. NMDA-receptor blockers that have been shown to be effective include some familiar drugs that happen to have NMDA antagonist properties, e.g., dextromethorphan, dextrorphan, memantine, ketamine, and amantadine. The clinical usefulness of some of these drugs is limited by a very narrow therapeutic index due to unacceptable effects on mental functioning. Ketamine, for example, has demonstrable efficacy as an NMDA-receptor antagonist, but its psychotomimetic effects will probably preclude its use in the clinic. On the other hand, dextromethorphan is an antitussive that has been on the market for many years and has established an excellent safety record. Memantine also has been shown in European studies to be well-tolerated in elderly patients to retard the progression of Alzheimer’s disease.

Clinical experience indicates that neuropathic pain is relatively (in some cases almost completely) resistant to opiate analgesics. Data from experiments on diverse topics show that this is due to an interaction between the intracellular events that mediate central sensitization and those that regulate the sensitivity of the mu subtype of opiate receptor. Pain-evoked NMDA-receptor activation increases the cell’s responses to its stimuli, while it also decreases the efficacy of mu-receptor agonists. Thus, a patient with neuropathic hyperalgesia has a sort of pain-evoked opiate tolerance, even in

![Fig. 2. Central sensitization demonstrated in a normal human volunteer. An intradermal injection of 100 μg of capsaicin (in a volume of 10 μl) is made on the volar forearm. Ten to 20 minutes of intense burning pain follows the injection. Thereafter the skin surrounding the injection site becomes allodynic and hyperalgesic for hours (Figure 2). The allodynia and hyperalgesia can be reversed by NMDA-receptor blockade.](image-url)
the absence of opiate treatment. Conversely, opiate tolerance appears to engage intracellular events similar to those engaged by pain-evoked NMDA-receptor activation. Thus, the opiate-tolerant patient has a central sensitization–like hyperalgesia.

**Conclusion**

The resistance of certain kinds of pain to opiate analgesia, or tolerance, was generally thought to involve simple receptor downregulation. We now know that the mechanisms of tolerance interact directly with pain sensitivity. Understanding these mechanisms, which include glutamate-mediated activation of NMDA receptors, points to the possibility of improving opiate analgesic therapy with the co-administration of an NMDA-receptor antagonist.

**References**


### Table 1

**Effects of Diverse NMDA-Receptor Blockers on Neuropathic Pain Seen in Experimental Models of Painful Peripheral Neuropathy in the Rat**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Model</th>
<th>Route</th>
<th>Test</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-801</td>
<td>CCI</td>
<td>i.p.</td>
<td>heat</td>
<td>Davar et al.</td>
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<td></td>
<td>CCI</td>
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<td>Yamamoto and Yaksh</td>
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<td></td>
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<td>heat, spon</td>
<td>Mao et al.</td>
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<td>K &amp; C</td>
<td>i.t.</td>
<td>M-allo</td>
<td>Chaplan et al.</td>
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<td>AP-5</td>
<td>CCI</td>
<td>i.t.</td>
<td>Heat</td>
<td>Yamamoto and Yaksh</td>
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<td>i.t.</td>
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<td>Chaplan et al.</td>
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<td>CCI</td>
<td>i.t.</td>
<td>heat, spon</td>
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<td></td>
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<td>heat</td>
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<tr>
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<td>i.t.</td>
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<td>Xiao and Bennett</td>
</tr>
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</table>

CCI = the chronic constriction model of Bennett and Xie; K&C = the spinal nerve ligation model of Kim and Chung; i.p. = intraperitoneal dosing; i.t. = intrathecal dosing (onto the surface of the lumbar spinal cord); heat = heat-hyperalgesia; spon = spontaneous pain behaviors; M-allo = mechano-allodynia.


