

Effect of Pretreatment with Intrathecal Excitatory Amino Acid Receptor Antagonists on the Development of Pain Behavior Caused by Plantar Incision

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Background: Drugs that block spinal excitatory amino acid receptor activation may prevent pain after surgery. The authors previously studied the effect of excitatory amino acid receptor antagonists after incision. In the present study, we examined the role of N-methyl-D-aspartate (NMDA), non-NMDA, and metabotropic glutamate receptors (mGluRs) on the development of pain behavior after plantar incision.

Methods: Rats with lumbar intrathecal catheters were anesthetized with halothane. Fifteen minutes before an incision was made, drug [40 nmol MK-801; 20 nmol NBQX; or 200 nmol (+)-MCPG] or vehicle was injected intrathecally followed by an infusion of the same drug for 75 min. Withdrawal thresholds to calibrated von Frey filaments applied adjacent to the wound and response frequencies to a blunt mechanical stimulus applied directly to the wound were measured before incision and 1, 2, 4, and 6 h after incision and then once daily for 6 days.

Results: Preincision treatments with antagonists against the NMDA (MK-801) and group I and II metabotropic receptors [(+)-MCPG] did not inhibit the development of mechanical hyperalgesia caused by incision. Preincision treatment with the non-NMDA receptor antagonist NBQX increased withdrawal thresholds at 1 and 2 h and on postoperative day 1 compared with the vehicle group; response frequencies were reduced 1 and 2 h after incision and on postoperative day 2 ($P < 0.05$). In

an additional group, postincision treatment with NBQX was similar to preincision treatment.

Conclusion: Spinal NMDA and mGluR antagonists may not be useful for preventing postsurgical pain. Spinal non-NMDA receptor antagonists reduced pain behaviors, but a preventive effect using preincision treatment was not apparent. (Key words: Mechanical hyperalgesia; plasticity; postoperative pain; preemptive analgesia.)

LONG-term changes in synaptic strength may be induced by conditioning stimuli in dorsal horn neurons of the spinal cord,¹ suggesting that plasticity in pain control systems occurs. It has been suggested that the injury-induced discharge by trauma or surgery produces enhanced synaptic efficacy and prolonged excitability in the spinal cord similar to learning and memory in the brain.² Presumably, injury-induced nociceptor drive and intense dorsal horn neuron activation causes a cascade of events in the dorsal horn that increases second messenger systems, activates intracellular enzymes, and phosphorylates proteins, resulting in persistent pain.^{3,4}

A strong argument has been made that excitatory amino acids (EAAs) such as glutamate and aspartate are involved in synaptic plasticity in the dorsal horn. In particular, the N-methyl-D-aspartate (NMDA) receptor has been suggested to be critical for the development of central sensitization and plasticity.^{1,3} Presumably, release of EAA from the central terminals of nociceptors during injury causes sustained depolarization of dorsal horn neurons, removes the voltage-dependent magnesium block from the NMDA receptor complex, and allows calcium influx. Activation of calmodulin-dependent protein kinases, nitric oxide production, and protein phosphorylation can occur, and these processes can in turn increase synaptic strength.^{5,6} This series of events in the dorsal horn during injury has been the basis for pretreatment strategies using MK-801, a noncompetitive NMDA receptor antagonist, to inhibit the development of plasticity that causes persistent pain behaviors in animal models.⁷⁻⁹

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Less is known about the role of other EAA receptors, metabotropic glutamate receptors (mGluRs) and non-NMDA (α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid [AMPA]/kainate) receptors, in the development of plasticity, central sensitization, and persistent pain after tissue injury. Either group could be important. Activation of G protein-coupled mGluR affects phosphorylation of proteins, causing calcium release from internal stores, which could enhance the excitability of neurons.^{10,11} Some non-NMDA receptors are also calcium permeable,¹² have been implicated in long-term potentiation in higher centers,¹³ and may be important for increased responses of dorsal horn neurons induced by persistent noxious stimuli.⁴

Thus, it is possible that an early antinociceptive treatment preventing intense excitation of dorsal horn neurons by EAAs may be important for reducing persistent pathologic pain. We previously examined the effect of EAA receptor antagonists on pain behaviors after incision.¹⁴⁻¹⁶ We hypothesized that activation of EAA receptors during incision may be important for the development of long-lasting pain behaviors and may be different than results from treatments after incision. The effect of preincision intrathecal administration of EAA receptor antagonists was studied. One antagonist from the NMDA, mGlu, and non-NMDA receptor group was administered 15 min before incision and continued for 1 h after incision. Early effects of the treatment were measured; most importantly, later effects, through 7 days after incision, were examined to determine if a long-term reduction in pain behaviors occurred.

After analyzing the data for these four groups receiving a preincision treatment, an increased withdrawal threshold on postoperative day 1 and an increase in the response frequency on postoperative day 2 were observed in the group pretreated with NBQX. To determine if the reduction in pain behavior by intrathecal NBQX administration was an effect of pretreatment before incision *versus* an effect of the drug administered after incision, a vehicle and a group receiving NBQX after incision were studied.

Methods

General

These experiments were reviewed and approved by the Animal Care and Use Committee of The University of Iowa. The animals were treated in accordance with the Ethical Guidelines for Investigations of Experimental Pain in Conscious Animals as issued by the International

Association for the Study of Pain. Experiments were performed on 48 adult (weight, 250–350 g) male Sprague-Dawley rats (Harlan, Indianapolis, IN) housed in pairs before surgery; food and water were available *ad libitum*. Postoperatively, the animals were housed individually with organic cellulose bedding (Shepherd Specialty Papers, Inc., Kalamazoo, MI). The incisions were checked daily; at the end of the protocol, all rats were euthanized with an overdose of a mixture of pentobarbital and phenytoin.

Intrathecal Catheter Placement

For subarachnoid drug administration, a lumbar intrathecal catheter was placed using a modified technique¹⁷ to one described previously.¹⁸ After halothane anesthesia was administered (1–2%), the lumbar skin was cleansed and incised. The intervertebral space between L5 and L6 was punctured with a hypodermic needle, and a 32-gauge polyurethane catheter (10-cm length; Micor Allison Park, PA) was advanced through the needle cranially so that 3.5 cm remained beneath the skin. The distal end was secured, inserted into PE-10 tubing, and tunnelled to the cervical region. The catheter (8- μ l dead space) was flushed and sealed. The intrathecal catheter was tested 1 day after surgery using 20 μ l of 2% lidocaine¹⁵ and verified at the end of the experiment by injecting 30 μ l methylene blue, euthanizing the rat and dissecting the lumbar spinal cord.

Plantar Incision

Rats were anesthetized with 1.5–2% halothane delivered *via* a nose cone and administered an intramuscular injection of penicillin, 30,000 IU, in the triceps muscle. As described previously,¹⁹ the plantar aspect of the right hind paw was prepared, and a 1-cm longitudinal incision was made through skin, fascia, and muscle of the plantar aspect of the foot. The skin was apposed with two 5-nylon sutures, and the wound site was covered with antibiotic ointment. Sutures were removed at the end of postoperative day 2.

Responses to Mechanical Stimuli

On the day of the experiment, the rats were placed individually on the mesh floor. After adaptation to the testing conditions, baseline pain behaviors before foot incision were measured as previously described.¹⁵

A 5-mm clear plastic disk attached to a von Frey filament (bending force 400 mN) was applied directly on the intended incision site.¹⁵ A positive response to the blunt mechanical stimulus was defined as a withdrawal

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response (flinch) or lifting the foot off of the mesh floor without bending the filament. From three repeated tests, the response frequency was calculated (0–100%). Withdrawal responses to punctate mechanical stimulation were determined using calibrated nylon von Frey monofilaments (Stoelting, Wood Dale IL) applied until bending to an area adjacent to the intended wound.¹⁹ Each von Frey filament (15, 30, 42, 65, 73, 98, 149, and 265 mN) was applied once starting with 15 mN and continuing until a withdrawal response occurred or 265 mN was reached. The lowest force from the three tests producing a response was considered the withdrawal threshold. For this study, 522 mN was recorded as the withdrawal threshold if there was no withdrawal response to the next lowest filament (265 mN).

Motor Function

MK-801 and NBQX produce motor dysfunction after intrathecal injection.^{14,15} The placing reflex was tested immediately after pain behaviors because this test has been shown to detect hind limb paresis after intrathecal non-NMDA and NMDA receptor antagonist administration. Motor impairment of both hind limbs was calculated as a cumulative score (2 = normal; 1 = delay of 1–2 s; 0 = > 2 s) from three measurements each test period with approximately 2–3 min between tests.

Experimental Protocols

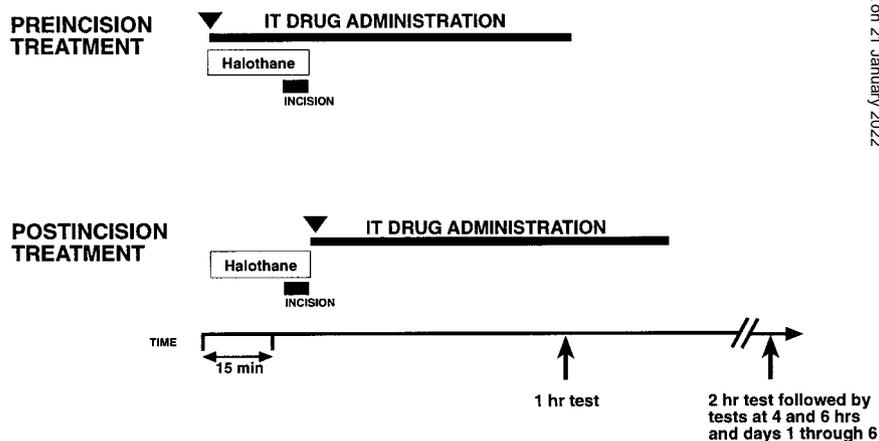
The investigator was blinded to the drug injected intrathecally. Each rat was anesthetized, and vehicle [20 nmol of NBQX, 40 nmol of MK-801, or 200 nmol of (+)-MCPG] was administered intrathecally 15 min before foot incision. The initial dose of drug was determined from studies of acute administration that prevented pain behaviors caused by intrathecal injection of

the corresponding agonist and from doses that eliminated pain behavior in this model.^{14–16,20} An intrathecal infusion of drug [20 nmol/h NBQX, 20 nmol/h MK-801, or 100 nmol/h (+)-MCPG] or vehicle was started immediately after the bolus injection and continued for 75 min (fig. 1). The dose used to maintain non-NMDA and NMDA receptor blockade was determined by examining side effects. In preliminary studies, hind limb paresis was sustained by the NBQX and MK-801 infusions. Greater doses of (+)-MCPG caused sedation. For (+)-MCPG, the total dose was three times the dose needed to block agonist-induced pain behaviors for 60 min.²⁰ Glutamate release in the extracellular fluid of the dorsal horn of the spinal cord has been measured after the same incision. An increase has been observed for approximately 45 min after incision.²¹ Based on these data, we continued the infusion for 1 h after incision. Responses to the blunt mechanical stimulus, von Frey filaments, and pin pricks were measured 1, 2, 4, and 6 h after incision and daily for the next 6 days (fig. 1B). The placing reflex was performed 1, 2, 4, and 6 h after incision and on postoperative day 1. Sixteen rats were administered either vehicle or NBQX intrathecally immediately after incision. Responses were measured at the same time after incision as in the pretreatment groups.

Drugs

NBQX (MW = 336) and MK-801 hydrogen maleate (MW = 337) were purchased from Research Biochemicals Inc. (RBI, Natick, MA). NBQX was dissolved in 0.01 N NaOH in saline, and the pH was adjusted with 1 N HCl. MK-801 was dissolved in preservative-free saline. (+)-MCPG (MW = 209) was purchased from Tocris (Ballwin, MO), dissolved in 0.1 N NaOH in saline, and the pH was adjusted with 1 N HCl. pH-adjusted 0.1 N

Fig. 1. Experimental protocols. For preincision treatment (*top*), rats were anesthetized with halothane; the drug or vehicle was administered as a bolus injection (solid triangle) followed by an infusion (solid line). The incision (solid rectangle) was performed 15 min after the bolus intrathecal injection. For postincision treatment (*bottom*), the bolus injection (solid triangle) and the infusion (solid line) were started after the incision (solid rectangle). Rats were tested 1 h after incision and subsequently as shown.



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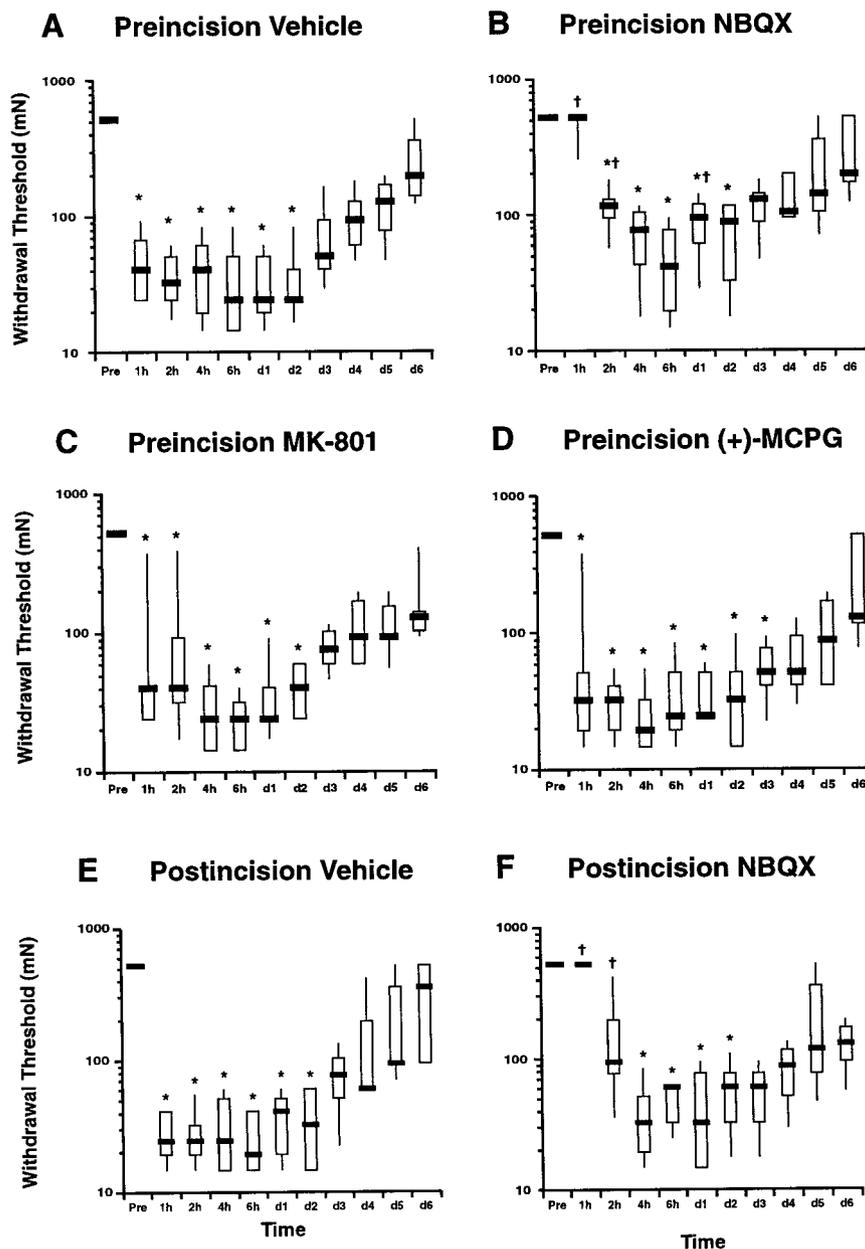


Fig. 2. Effect of excitatory amino acid receptor antagonists on the development of withdrawal to punctate mechanical stimulation. Rats were tested before incision, from 1 to 6 h after incision and on postoperative days 1–6. The results are expressed as median (horizontal line) with first and third quartiles (boxes) and 10th and 90th percentiles (vertical lines). (A) Withdrawal thresholds in eight rats receiving vehicle administration before incision. (B–D) Withdrawal thresholds in eight rats administered NBQX (B), MK-801 (C), or (+)-MCPG (D) before incision. (E and F) Withdrawal thresholds after incision in eight vehicle-treated rats (E) and in eight rats administered NBQX after incision (F). * $P < 0.05$ versus preincision by Friedman and Dunnett test. † $P < 0.05$ versus vehicle by Kruskal-Wallis and Dunn test.

the dorsal horn of the spinal cord.^{4,23–25} In models of inflammation^{7,23,26–28} and neuropathic pain,^{9,29–34} spinal NMDA receptors can be important for the development of later pain behaviors. There are several reasons why spinal NMDA receptor antagonism did not greatly affect later pain behaviors. Perhaps spinal NMDA receptors are most important after nerve injury, and the plantar incision does not involve nerve injury. In addition, inflammation may be important for the development of

some models of persistent pain, and this can be modified by spinal NMDA receptor blockade. Inflammation that is sensitive to spinal NMDA receptor blockade may not be as important for the development of pain behaviors in this model. Finally, the extent of injury in the plantar incision may not be sufficient to activate spinal NMDA receptors. It is possible that NMDA receptors could contribute to the development or maintenance of pain after more extensive surgery in patients.

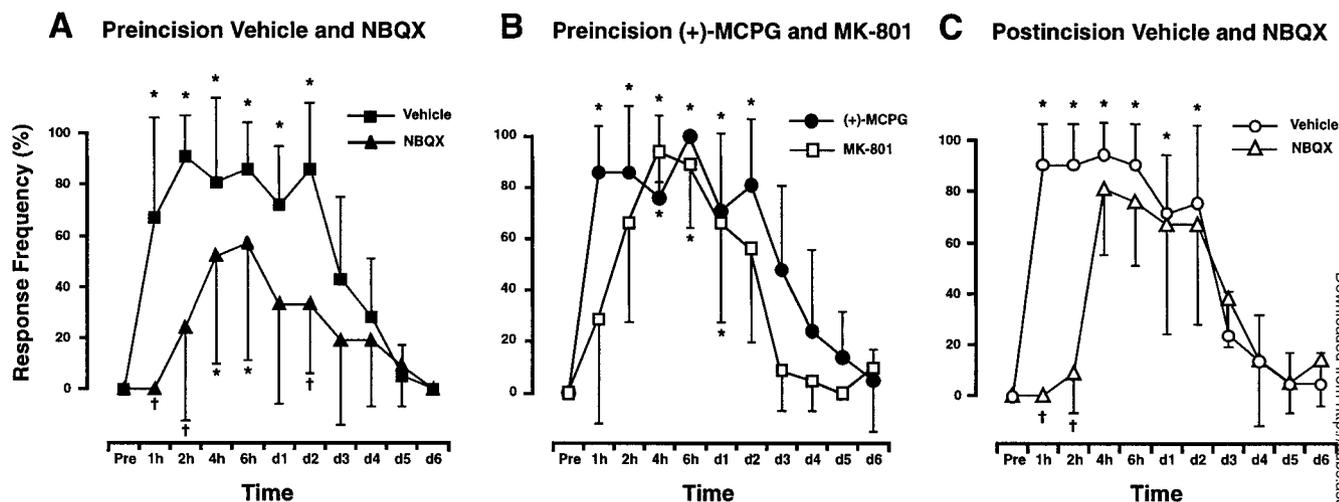


Fig. 3. Effect of excitatory amino acid antagonists on the development of response to the nonpunctate mechanical stimulus 1–6 after incision and on postoperative days 1–6. (A and B) Response frequency (%) to the blunt mechanical stimulus after preincision treatment with vehicle, NBQX, MK-801 and (+)-MCPG. (C) Response frequency to a blunt mechanical stimulus in eight vehicle-treated rats and in eight rats administered NBQX after incision. * $P < 0.05$ versus preincision by Friedman and Dunnett test. † $P < 0.05$ versus saline by Kruskal-Wallis and Dunn test. The results are expressed as the mean \pm SD.

Comparisons with Clinical Studies

Ketamine acts, in part, as a noncompetitive antagonist at the NMDA receptor complex. Clinical studies have used epidural ketamine to investigate the role of spinal NMDA receptors on the development of postoperative pain. Epidural injection of 30 mg ketamine before incision reduced analgesic requirements up to 24 h after hysterectomy.³⁵ In another study, no reduction in analgesic consumption or pain scores could be observed 1 and 2 days after upper abdominal surgery in patients administered 60 mg epidural ketamine before surgery.³⁶ Parenterally administered ketamine has also been administered before surgery for analgesia.³⁷ In studies like these, it is important to recognize that parenteral ketamine may not have a spinal action, and a supraspinal site for analgesia is likely. Ketamine is also highly lipid soluble, and epidural ketamine may have a systemic supraspinal effect as well as a spinal action. The results from the current study should not be compared with studies on parenteral ketamine pretreatment for postoperative pain relief.

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Spinal non-N-methyl-D-aspartate Receptor Antagonists

The importance of spinal non-NMDA receptors in the development of persistent pain has not been extensively investigated in animal models. The most notable positive result is from Sluka *et al.*²⁸ Spinal non-NMDA receptors

Table 1. Effect of It EAA Receptor Antagonists on Motor Function

Group	Placing Reflex Test	Pre	1 hr	2 hr	4 hr	6 hr	24 hr
Preincision vehicle	Left	6.0	6.0	6.0	6.0	6.0	6.0
	Right	6.0	6.0	6.0	6.0	6.0	6.0
Preincision NBQX	Left	6.0	2.0*	6.0	6.0	6.0	6.0
	Right	6.0	3.0*	6.0	6.0	6.0	6.0
Preincision MK-801	Left	6.0	0.5*	3.0*	6.0	6.0	6.0
	Right	6.0	1.0*	3.5*	6.0	6.0	6.0
Preincision + MCPG	Left	6.0	6.0	6.0	6.0	6.0	6.0
	Right	6.0	6.0	6.0	6.0	6.0	6.0
Postincision vehicle	Left	6.0	6.0	6.0	6.0	6.0	6.0
	Right	6.0	6.0	6.0	6.0	6.0	6.0
Postincision NBQX	Left	6.0	1.0*	6.0	6.0	6.0	6.0
	Right	6.0	0.5*	6.0	6.0	6.0	6.0

Motor function of both hindpaws was tested with the placing reflex. The median cumulative score is shown for three measurements ($n = 8$) within each test period.

* $P < 0.05$ versus preincision by Friedman and Dunnett tests. Results are expressed as median.

blockade before knee joint inflammation prevented joint swelling and reduced pain behaviors. Further studies suggested that spinal non-NMDA receptor antagonism inhibited dorsal root reflexes partly responsible for the generation of the inflammatory process producing joint swelling and pain behaviors. In the present study, small, intermittent, positive results were observed after pretreatment with NBQX, and there is a tendency for reduction in the responses to the blunt probe. It is possible that the variability is too great to observe a positive result from the treatment. No clinical studies have examined the role of non-NMDA receptors in postoperative pain.

Spinal Metabotropic Glutamate Receptor Antagonists

Like non-NMDA receptor antagonists, few studies have been undertaken to investigate the role of mGluR in the transmission of nociceptive input to the spinal cord and their contribution to spinal sensitization and persistent pain. One recent study demonstrated that group I mGluRs are involved in the development of neuropathic pain.³⁸ Selective depletion of lumbar mGluR1 using an antisense treatment demonstrated mGluR1 is important for the development of hyperalgesia caused by inflammation.³⁹

Conclusion

N-methyl-D-aspartate receptors are critical for the induction of persistent pain behaviors caused by peripheral inflammation and nerve injury. The results from the present study indicate that EAA receptor activation is not critical for the induction of incisional pain. These results suggest unique characteristics responsible for pain after particular types of injuries. The enhanced response to mechanical stimulation after an incision may be more dependent on peripheral sensitization than on central plasticity processes induced by EAA receptors during this distinct type of tissue injury.

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