Comparison of the Antinociceptive Effects of Pre- and Posttreatment with Intrathecal Morphine and MK801, an NMDA Antagonist, on the Formalin Test in the Rat

Tatsuo Yamamoto, M.D.,* Tony L. Yaksh, Ph.D.†

Current thinking emphasizes that protracted small afferent input can evoke mechanisms that mediate a significant potentiation of spinal nociceptive processing and that this facilitatory component has a unique pharmacology. To investigate the behavioral parallels of this spinal facilitation, we evaluated the effects of pre- and posttreatment of intrathecal morphine (μ agonist) and MK801 (N-methyl-D-aspartate [NMDA] antagonist) on the formalin test. Intraplantar formalin resulted in a biphasic appearance of flinching behavior (phase 1 = 0–5 min; phase 2 = 10–60 min). Morphine and MK801 were administered intrathecally 15 min before formalin injection in the pretreatment study and 9 min after formalin injection in the posttreatment study. Pretreatment with intrathecal morphine produced comparable dose-dependent suppressions of the phase 1 and phase 2 behaviors (ED50 = 0.5 μg [95% CI = 0.3–0.9] and 0.3 μg [95% CI = 0.1–0.7], respectively). Posttreatment with morphine also resulted in comparable suppression of the phase 2 response (ED50 = 0.2 μg [95% CI = 0.1–0.3]). At the highest dose of intrathecal morphine (10 μg), an almost complete suppression of formalin-evoked behavior was observed. Pretreatment with MK801 inhibited the second-phase response more strongly than the first-phase response (ED50 = 1.6 μg [95% CI = 0.3–5.7] vs. 0.1 μg [95% CI = 0.3–0.4], respectively). In contrast, posttreatment with the highest dose of MK801 had no effect on the phase 2 response. These data yield the hypothesis that the focal stimulation provided by the presence of subcutaneous formalin exerts 1) a direct excitatory effect evoking clearly defined pain behavior that is independent of the spinal NMDA sites but subject to opioid modulation and 2) a second facilitatory component, in which the acute afferent barrage serves to up-regulate the organized response of the animal to an already noxious stimulus. This study suggests that the NMDA site is required to initiate this facilitatory component but not to sustain it. (Key words: Analgesics: morphine; opioid. Antagonists: MK801; NMDA. Receptors: NMDA; opiate. Windup.)

THE focal SUBCUTANEOUS injection of small amounts of an irritant such as formalin evokes an immediate and intense increase in the spontaneous activity of afferent C fibers.1 Recording from dorsal horn neurons thought to play a role in the spinal afferent link of pain processing (wide dynamic range neuron [WDR]) reveals that the subcutaneous injection of formalin evokes a progressive, biphasic increase in its activity.2 When given into the paw of the awake animal, the subcutaneous irritant injection also evokes a corresponding biphasic behavioral response characterized by flinching and licking of the injected limb.3,4 Because continued electrical stimulation of afferent C fibers is known to evoke a facilitated discharge of WDR neurons (windup),5 it is considered that the second phase of spinal neuronal activity and the correlated behavior observed after subcutaneous irritants may represent correlated events and that the behavior may possess pharmacologic properties associated with this spinal mediators. Two receptor classes of interest that may influence dorsal horn function are those of the opiate and the N-methyl-D-aspartate (NMDA) receptor.

Intrathecal opiates will block C fiber–evoked excitation WDR neurons, an action likely mediated by a presynaptic suppression of afferent transmitter release and a concurrent postsynaptic hyperpolarizing action on WDR neurons.6 WDR windup evoked by repetitive C fiber input can also be suppressed by opiates, but this inhibition is obtained only when the agonist is given at doses that block the early C fiber–evoked component.2,7 In single-unit studies, inhibition of the second-phase formalin response of the WDR neuron by a given dose of opiates was diminished if the opiate were administered after the formalin.2 In contrast, NMDA antagonists have no effect upon the acute C fiber–evoked activity in spinal neurons.8,9 This is consistent with the observation that the NMDA receptor is not located postsynaptic to primary afferent input; rather, it mediates excitation evoked by glutamate-releasing interneurons.10 In contrast, the windup, or facilitated component of the afferent-evoked response (but not the direct C fiber–evoked activity) is blocked by NMDA antagonists.8,9 These characteristics are consistent with the behavioral observation that NMDA antagonists (unlike opiates) have little or no selective antinociceptive effects as measured on acute thermal nociceptive endpoints such as the hot-plate test.11,12 In recent work, however, NMDA antagonists have been reported to be antinociceptive in the mouse formalin model.13 The difference in drug effect in acute versus protracted pain behavior models may reflect the role in spinal nociceptive processing of the central facilitatory states induced by an ongoing C fiber input, as is evoked by the focal subcutaneous injection of irritant.

* Visiting Fellow.
† Professor and Vice Chairman for Research.

Received from the Department of Anesthesiology, University of California, San Diego, La Jolla, CA. Accepted for publication June 3, 1992.

Address reprint requests to Dr. Yaksh: Department of Anesthesiology 0818, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92038.
The above observations data are thus consistent with the hypothesis that a centrally mediated facilitated state is initiated by the phase 1 portion of the formalin stimulus and that this facilitation augments the magnitude of the behavior observed in the second phase. Thus, the phase 2 behavior would have a component consisting of the direct excitation evoked by the afferent barrage as well as a second component that augments the response to the ongoing barrage. Based on the above considerations, it was predicted that opiate agonists, but not NMDA antagonists, would block the first phase, whereas the second phase response would be attenuated by the action of both. In the current investigations, we systematically studied the behavioral action of spinal morphine, a μ-opioid agonist, and spinal MK801, an NMDA antagonist, administered before and after the subcutaneous injection of formalin into the paw.

Materials and Methods

The following investigations were carried out under a protocol approved by the Institutional Animal Care Committee, University of California, San Diego. Male Sprague-Dawley rats (250–300 g) were prepared with chronic intrathecal catheters and examined for the effects of agents on the formalin test.

INTRATHECAL CATHETERS

Chronic intrathecal catheters were placed during halothane anesthesia by passing a PE-10 catheter through an incision in the atlantooccipital membrane to a position 9 cm caudal to the cisterna at the level of the lumbar enlargement.14 The catheter was externalized on the top of the skull and sealed with a piece of steel wire and the wound closed with 3-0 silk sutures. Rats showing neurologic deficits postoperatively were promptly killed by a barbiturate overdose (Beuthanasia; 50 mg/kg intraperitoneally).

FORMalin TEST

To carry out the formalin study, the animal was placed in a plastic box through which 3% halothane in oxygen was passed. After approximately 1 min, the rat typically showed disorientation and a loss of weight-bearing by the hind quarters. At this time, the animal was quickly removed from the box, and 50 μl 5% formalin was injected subcutaneously in the plantar surface of the right hind paw with a 30-G needle. In this anesthetic plane, during the brief period of handling and injection (approximately 10 s), the animal showed no agitation and emitted no vocalization. Immediately after injection, the animal was placed in an open Plexiglas box (10 cm × 20 cm), which permitted observation.

Recovery of full ambulatory function was typically observed within 1–2 min of removing the animal from the anesthesia. Within 1 min of the injection, the rat displayed the behavior typical of this model. After the injection, the animal typically held the injected paw just off the floor; during this period, spontaneous flinches of the injected paw could be observed. Flinches are readily discriminated and are characterized as rapid and brief withdrawals or flexions of the injected paw. To quantify the formalin response, the number of spontaneous flinches was counted at 1–2 min and 5–6 min and at 5-min intervals during the period 10–60 min after formalin injection. As previously described, two distinct phases were observed: phase 1, during the 0–6-min interval immediately after the intraplantar injection, and the phase 2, beginning about 10 min after formalin injection. For purposes of analysis, the first- and second-phase data were examined separately. Observations were carried out for a period of 1 h after formalin injection. The animals were killed at this time with an overdose of barbiturate (Beuthanasia; 50 mg/kg intraperitoneally).

Behavior

Motor function was evaluated by the presence or absence of two specific behaviors. 1) The placing/stepping reflex is evoked by drawing the dorsum of either hind paw across the edge of the table. This stimulus elicits an upward lifting of the paw from the surface of the table (stepping). 2) In the righting reflex, a rat placed supine shows an immediate, coordinated, twisting of the body around its longitudinal axis with crossed extension of its fore and hind paws to regain its normal crouching posture.

Drugs and Treatment Paradigms

The agents used in these studies were morphine sulfate (Merck); MK801 ((+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine; Merck Sharp and Dohme Research Laboratories). All drugs were dissolved in normal saline, such that the final dose was administered in a volume of 10 μl. Dose–response curves were carried out with the agent administered spinally 15 min (MK801/morphine) before the formalin (pretreatment study) or 9 min after the formalin injection (posttreatment study). In these experiments, parallel groups injected with formalin received only saline.

Naloxone HCl (Du Pont) was given to assess the ability to reverse the effects of morphine. In these studies, morphine 10 μg was injected intrathecally, 15 min before paw formalin, and naloxone (10 μg) was administered intrathecally 5 min before formalin. To consider the effects of naloxone alone, a similar experiment was carried out in which naloxone (10 μg) alone was given intrathecally 5 min before formalin.
STATISTICAL ANALYSIS

For the time–response analysis, the total number of responses was counted at 1–2 min and 5–6 min and at 5-min intervals and was expressed as responses per minute for each rat. For the dose–response analysis, data for phase 1 (1–6 min) and phase 2 (10–60 min) observations were considered separately. In each case, the mean of the responses per minute obtained for each counting period in the respective observation intervals (phase 1: 1–6 min; phase 2: 10–60 min) was calculated for each rat. These individual rat data were then used to construct phase 1 and phase 2 dose–response curves. To compare the dose–response curve between the first phase and second phase or the pretreatment and posttreatment, we calculated the percent of the phase 1 and phase 2 saline response, respectively. The dose–response lines for the phase 1 and phase 2 effects were then fitted using least squares linear regression analysis, and the doses that resulted in 50% of the saline response (ED₅₀) and their 95% confidence intervals were calculated. The slopes of each regression line with 95% confidence intervals were also calculated. One-way analysis of variance with a Duncan's multiple comparison test was used to define dose dependency. To compare the slopes and elevations of regression lines, we used the t test. For the antagonist study, Student's t test was used. Critical values that reached the P < 0.05 level of significance were considered to be statistically significant.

Results

BEHAVIOR

The subcutaneous injection of formalin resulted in a highly reliable biphasic display of flinching behavior of the injected paw. Similar injections of subcutaneous saline do not evoke such behavior (data not shown). The biphasic pattern or the magnitude of the phase 1 and phase 2 response was unaltered by the intrathecal injection of saline, as compared to noninjected control (noninjected control response not shown; P > 0.2).

Intrathecal morphine had no effect on placing, stepping, or righting reflexes. All animals, after even the highest dose of intrathecal morphine, displayed normal symmetrical ambulation and no detectable change in motor strength. Intrathecal injection of MK801 (1 µg) had no effect on motor function. At 10 µg, a mild but detectable motor dysfunction was observed in three of six rats. This dysfunction lasted no more than 10–15 min after injection. Thus, 10 µg was the highest dose used with MK801 in this study. It should be noted that these animals retained the righting reflex, the placing and stepping reflexes, the ability to ambulate, the ability to withdraw the paw in response to a strong pinch, and the ability to lift the hind paw to scratch the head and ears (normal grooming). Thus, although some weakness was observed, we do not believe that the animals had motor impairment sufficient to alter their ability to display the measured flinching response.

INTRATHECAL MORPHINE AND NOCICEPTION

When injected intrathecally 15 min before formalin injection (pretreatment study), morphine readily decreased the number of paw flinches in both phases 1 and 2. Figure 1 presents the time–effect curve of these effects. These effects on both the phase 1 and phase 2 responses displayed a significant dose dependency (fig. 2), with both dose–response lines being parallel and significantly greater than 0 (table 1).

When morphine was injected intrathecally 9 min after formalin injection (posttreatment study), morphine also

![Figure 1](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931325/)  
**FIG. 1.** Time–effect curve of morphine (top) and MK801 (bottom) given before injections of formalin into the right hind paw for the number of flinches per minute observed after formalin. Each line represents the group mean and SEM of four to six animals. Saline group is presented for comparison in both graphs. Dose–response analysis is given in figure 2 and table 1.
resulted in a dose-dependent suppression of the number of phase 2 flinches, with a maximum blockade of formalin-evoked behaviors at the highest dose examined (Figs. 2 and 3). As indicated in Table 1, the phase 2 ED50 value obtained for morphine in the pretreatment paradigm was not different from that determined in the phase 2 posttreatment paradigm.

**Intrathecal MK801 and Nociception**

With pretreatment, intrathecal MK801 decreased both the first and second phases of flinch behavior in a dose-dependent manner (Figs. 1 and 2). The slope of the dose-response curve for pretreatment phase 1 is equal to that of pretreatment phase 2, but the phase 1 ED50 for intrathecal MK801 is approximately ten times greater than the comparable phase 2 ED50 (Table 1). MK801, posttreatment, had no effect on the flinching response at the highest intrathecal doses used (P > 0.3) (Fig. 3 and Table 1). One-way analysis of variance comparison of the saline and the two doses of MK801 examined revealed no effect (P > 0.30).

**Antagonist Study**

The injection of naltrexone intrathecally 5 min before the injection of formalin had no effect on the phase 1 or phase 2 formalin response as compared to intrathecal saline (Fig. 4; P > 0.20, comparison of the respective mean number of flinches per minute). As previously shown, morphine (10 μg) resulted in a virtually complete abolition of the phase 1 and 2 flinch responses. In rats receiving naltrexone and morphine, however, flinching behavior did not differ either from the saline-injected control rats or from saline plus morphine.

**Table 1. Summary of Dose Response Analysis for Intrathecal Morphine and MK801 Given before Treatment (Pretreat) or after Treatment (Posttreat) with Formalin**

<table>
<thead>
<tr>
<th></th>
<th>Slope (95% CI)</th>
<th>ED50 (μg) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreat: phase 1</td>
<td>-37 (-49 - -25)</td>
<td>0.5 (0.3-0.9)</td>
</tr>
<tr>
<td>Pretreat: phase 2</td>
<td>-33 (-46 - -21)</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>Posttreat: phase 2</td>
<td>-79 (-111 - -47)</td>
<td>0.2 (0.1-0.5)</td>
</tr>
<tr>
<td>MK801</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreat: phase 1</td>
<td>-24 (-34 - -14)</td>
<td>1.6 (0.5-5.7)</td>
</tr>
<tr>
<td>Pretreat: phase 2</td>
<td>-20 (-29 - -10)</td>
<td>0.17 (0.03-0.4)</td>
</tr>
<tr>
<td>Posttreat: phase 2</td>
<td>Inactive</td>
<td>&gt;10 ‡</td>
</tr>
</tbody>
</table>

* P < 0.01 when compared to pretreat: phase 2.
† P < 0.01 when compared to pretreat: phase 1.
‡ Not different from saline, one-way ANOVA, P > 0.30.

**Fig. 2. Dose-response curves for intrathecal morphine (top) and MK801 (bottom), presenting the cumulative number of formalin-evoked flinches, expressed as a percent of saline control, during the first phase and second phase of the formalin test. ED50 values, slopes, and analysis presented in Table 1. Each point represents the mean and SEM of four to six animals.**

**Fig. 3. Time-effect curve for the number of flinches per minute observed after the subcutaneous injection of formalin in the right hind paw. As indicated, each line represents the group mean and SEM of 4-6 animals each with groups receiving saline, MK801 (10 μg), or morphine (1 μg) 9 min after the injection of formalin. Mean phase 2 flinch/min response: Saline > MK801 > morphine; one-way ANOVA, P < 0.05.**
the naloxone-injected rats ($P > 0.30$), indicating a complete reversal of the suppressant effects of spinal morphine. Intrathecal naloxone (30 µg) administered with MK801 (10 µg) had no effect on either the phase 1 or phase 2 effect ($n = 6; P > 0.50$, paired $t$ test; data not shown).

Discussion

The subcutaneous injection of formalin into the paw of the anesthetized rat results in a biphasic increase in the activity of dorsal horn WDR neurons. These biphasic changes in neuronal activation appear to correlate with the behavioral pattern commonly observed after comparable injection of formalin in the unanesthetized animal. Based on the characteristics of afferent nerve activity after subcutaneous formalin, it appears probable that the behavioral model represents, at the least, the animal’s response to the ongoing barrage associated with the continued presence of the formalin. In addition, repetitive C fiber stimulation is known to initiate a central facilitatory process that has been generically described as “windup.” Single recording studies have shown that relatively brief periods (20 s) of C fiber activation will yield periods of facilitation that last for periods of 10 min to 2 h. These effects appear to reflect a heterosynaptic facilitation of the response of the cell both to the input from the same root that conditions the facilitation as well as to input from adjacent roots. If such a poststimulus facilitation plays a role in the behavioral model, then it should be manifested in the pharmacologic characteristics of the first and second phases of the formalin-evoked behaviors.

OPIOID AGONIST: MORPHINE

Morphine, with an action limited to the spinal cord, resulted in a dose-dependent, naloxone-reversible decrease in the characteristic behaviors evoked in both phase 1 and phase 2 of the formalin response. The current thinking regarding the spinal mechanisms of opioids suggests a presynaptic inhibitory action on small unmyelinated primary afferent terminals and a hyperpolarization of higher-order spinal neurons. Studies by Dickenson and Sullivan have emphasized that spinal opioids may alter the facilitatory component generated by repetitive C fiber input (windup), primarily at doses that block C fiber-evoked excitation. The current observations showing the similar potency of intrathecal morphine in suppressing the phase 1 and phase 2 formalin-evoked behaviors are in accord with this observation.

Unexpectedly, spinal morphine was able to produce a complete suppression of the phase 2 behavior when administered after the phase 1. Moreover, the spinal morphine dose–response curves obtained with either pretreatment or posttreatment displayed indistinguishable ED₅₀ values for inhibiting the phase 2 response. This comparable potency of pre- and postformalin spinal morphine on phase 2 was unanticipated in light of the observations by Dickenson and Sullivan, who reported that posttreatment with a µ-selective agonist inhibited the second phase of the formalin-evoked excitation of dorsal horn neurons less effectively than did pretreatment. Several possibilities present themselves. First, it is possible that opioid-sensitive neuronal systems other than those classified as WDR neurons may play a role in the pain behavior evoked by the formalin test. The comparable pre- and posttreatment sensitivity observed in the current studies may demonstrate that difference. Second, the current studies were carried out in the unanesthetized animal, and the possibility of systematic changes in spinal cord response characteristics cannot be excluded.

NMDA ANTAGONIST: MK-801

NMDA antagonists have been reported to have little or no selective antinociceptive effects when examined on acute pain measures. In the present study, over the range of doses examined, pretreatment with MK801 reliably inhibited phase 2 more strongly than phase 1 (ED₅₀ values differed by a factor of 10). Given the similar potency of morphine in blocking the phase 1 and phase 2 activity, this difference for MK801 must reflect differences in the underlying mechanisms for the phase 1 and phase 2 response and not differences in stimulus intensity per
NMDA antagonists have been shown to have little effect on the direct C fiber-evoked excitation, but they appear to block the spinally mediated facilitatory component evoked by repetitive C fiber stimulation.\textsuperscript{8,9} Such actions are consistent with the observations that NMDA antagonism will reduce the polysynaptic but not the monosynaptic excitation in the spinal cord evoked by the stimulation of primary afferents.\textsuperscript{10} Based on the above comments, we suspect that the second-phase formalin response, which is sensitive to intrathecal MK801, reflects the role played by the spinal facilitatory processes that are mediated by the NMDA receptor.

While NMDA antagonists given poststimulus have been reported to antagonize the facilitation evoked by topical mustard oil,\textsuperscript{11} the current studies strongly indicate that intrathecal posttreatment of MK801 does not block the phase 2 response observed with formalin. These results are in close agreement with recent work by others in rats.\textsuperscript{5,6} Such observations suggest that once an afferent-evoked spinal facilitation is initiated, presumably by the phase 1 input, subsequent NMDA antagonism does not diminish the magnitude of the phase 2 response. This suggests that the central facilitation, following initiation in this model, reflects a sustained process. Consistent with this reasoning is the recent observation that the intrathecal injection of NMDA will evoke a significant dose-dependent hyperesthesia that is antagonized by pre- but not posttreatment with NMDA antagonists.\textsuperscript{5}

Significantly, this model outlined for the spinal cord appears remarkably similar to the phenomena of long-term potentiation (LTP). In LTP, brief high-frequency repetitive stimulation of afferent input into hippocampal neurons results in a progressive augmentation in the response of the several cells.\textsuperscript{19} The initiation of this prolonged facilitated state is blocked by pretreatment, but less effectively by posttreatment, with NMDA.\textsuperscript{20,21} The likelihood that such afferent input serves to trigger long-lasting functional changes that enhance cellular excitability is also supported by the observation that both calmodulin\textsuperscript{22} and kinase activity\textsuperscript{22,23} are required for LTP. These observations with LTP suggest striking parallels with the characteristics of the NMDA antagonist-sensitive spinal facilitation effects observed in the present experiments. The injection of formalin evokes an ongoing afferent barrage that, by an initial interaction with an NMDA receptor, results in sustained changes in WDR excitability. Whether the sustained changes observed in this spinal model display second messenger changes, as proposed for LTP, remains to be determined.

\textbf{Other Afferent Systems}

We recognize that the above proposed mechanisms concerning the NMDA receptor are not all-inclusive and that other systems also are involved. Although both spinal glutamate and substance P are released by subcutaneous formalin,\textsuperscript{24,25} nor intrathecal NMDA (present work) nor substance P antagonists acting the NK1 site\textsuperscript{26} can block the phase 1 response at low doses. This suggests the probable role of other neurotransmitters and/or receptors in mediating the behavioral components of the phase 1 response. In contrast, the second-phase behaviors observed after formalin injection are clearly depressed by pretreatment with either NK-1 or NMDA antagonists, suggesting that substance P, acting through a local NK-1 receptor, is required, along with glutamate acting on an NMDA site to evoke a facilitated state. It should be noted that, like LTP discussed above, activation of the NMDA receptor in fact requires a mild hypopolarization to allow removal of the Mg\textsuperscript{2+}-dependent block of the NMDA receptor.\textsuperscript{27} The slow depolarization mediated through an NK-1 receptor by concurrently released substance P might serve in such a capacity. Importantly, only in pain states where such concurrent, protracted activation of C fibers occurred, as in the formalin test, would these particular receptor antagonists (NMDA and NK1) be found to have an "antinociceptive" action.

In addition to the above mechanisms, a variety of spinal neurotransmitter systems have been identified that can also serve to facilitate spinal reflex activity. Thus, the spinal administration of a variety of neuropeptides, including galanin, vasoactive intestinal peptide, and cholecystokinin, has been shown to facilitate the flexion reflex.\textsuperscript{28-30} Similarly, a maintained afferent barrage can increase the extracellular levels of prostanooids in spinal cord,\textsuperscript{1} and there is evidence that spinal administration of cyclooxygenase inhibitors, in concentrations that diminish spinal prostaglandins release, can diminish the behavioral response to a peripheral inflammatory stimulus.\textsuperscript{31,32}

In conclusion, given the likely homology of spinal pharmacology and physiology thus far demonstrated in animals and humans, there appears little doubt that dynamic changes in cord function leading to altered nociceptive processing can play an important role in both intra- and postoperative pain management of the surgical patient. Two points should be emphasized. First, to the degree that a central facilitation can be generated by C fiber input, the animal studies suggest that it occurs with a surprisingly brief exposure. Second, many of the observations on dorsal horn windup and central facilitation have in fact been made in animals maintained at a plane of surgical anesthesia.

\textsuperscript{‡} Coderre T: Personal communication.
\textsuperscript{§} Malmberg AB, Yaksh TL: Unpublished observations.

\textsuperscript{†} Sorkin LS, Yaksh TL: Unpublished observations.
anesthesia (e.g., 1 MAC). Indeed, in recent studies, we have shown that volatile anesthetics, though able to suppress pressure, are surprisingly unable to prevent the biochemical changes that underlie the facilitary phenomena that appear after the volatile anesthetic has been removed.** These considerations suggest the potential significance of perioperative stimulation on the magnitude of the processed pain message. Aside from the suggestion that absolute blockade of C fiber–evoked activity may be of advantage in controlling the pain state, the observation that agents such as NMDA antagonists can attenuate this facilitated pain processing suggests the potential utility of systematic investigations into the preemptive use of such antagonists (e.g., systemic ketamine) in preventing the initiation of a state of central facilitation generated by the surgically driven afferent barrage.

** Abram S, Yaksh TL: Submitted for publication.

References


