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Evidence of a Role for *N*-Methyl-D-Aspartate (NMDA) Receptors in the Facilitation of Tail Withdrawal After Spinal Transection

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GHORPADE, A. AND C. ADVOKAT. *Evidence of a role for* N-*methyl*-D-*aspartate (NMDA) receptors in the facilitation of tail withdrawal after spinal transection.* PHARMACOL BIOCHEM BEHAV **48**(1) 175–181, 1994.—Peripheral injury produces a characteristic excitation of spinal cord dorsal horn cells (wind-up) which is associated with a facilitation of spinal nociceptive reflexes (hyperalgesia). These phenomena are believed to be mediated by a trauma-induced increase in the release of excitatory amino acids (EAAs). A similar increase in the activity of dorsal horn neurons and spinal reflexes occurs after spinal transection. Therefore, the present studies examined the possibility that EAAs, acting through the NMDA receptor, might also be involved in behavioral hyperalgesia produced by central injury. The first experiment assessed the effect of pretreatment with the NMDA antagonist, ketamine, on the facilitated tail flick (TF) response of spinally transected rats. Separate groups of animals were spinalized under isoflurane anesthesia alone, intramuscular ketamine anesthesia alone, or a combination of isoflurane and intrathecal ketamine. The TF was examined 24 h later, before and 30 min after an intrathecal injection of morphine. In the second experiment, the effect of intraperitoneal or intrathecal ketamine on the TF was assessed in separate groups of rats that underwent spinal transection or sham surgery under isoflurane anesthesia. Pretreatment with either systemic or intrathecal ketamine did not alter TF facilitation or morphine-induced antinociception in spinal rats. However, both systemic and intrathecal ketamine significantly increased TF latencies in spinal, relative to intact rats. These results indicate that ketamine did not prevent the development of spinal reflex facilitation, but it selectively reduced this reaction once it was established in spinal rats. The data support an involvement of EAAs in reflex facilitation produced by spinal transection.

Spinal transection Ketamine Tail flick Antinociception

THE consequences of spinal transection on spinal reflex function have been appreciated for over a hundred years. Following a period of reflex suppression (spinal shock), there is an increase in excitability of both flexor reflexes and dorsal horn neurons in response to noxious peripheral input (19). These increases in neural activity are behaviorally correlated with a facilitation of spinal reflexes, such as the tail withdrawal response, elicited by nociceptive thermal stimulation (2,23). It is generally accepted that these effects of spinalization result from the loss of tonic inhibitory control, normally exerted by supraspinal input. At present, however, neither the origin(s) nor the neurochemical bases of tonic descending inhibition are well established (19).

Within the last few years, experimental evidence has appeared to suggest that the same spinal substrates modulated by descending inhibition may also be influenced by damage to peripheral tissue or nerves. That is, peripheral tissue or nerve injury may produce a variety of pathologic pain states that persist long after the injured tissue has healed. This observation suggests that changes in CNS function are involved (6).

The recent development of several animal models of prolonged pain syndromes supports this conclusion. The development of these paradigms was prompted by electrophysiological studies that characterized a neural phenomenon, termed "wind-up," which is produced by chronic noxious stimulation. First described nearly 30 years ago (32), wind-up refers to the fact that the activity of certain dorsal horn cells increases dramatically in response to constant, repetitive noxious electrical stimulation of peripheral C-fibers at a set intensity (14,15). The activity of dorsal horn cells to this constant nociceptive input rapidly increases, eventually reaching a plateau at a level many times greater than the original response (16,

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17). A similar effect has been produced by a variety of noxious agents, such as hindpaw injection of formalin (18,20), mustard oil (52), and carrageenan (47) or hindlimb ischemia (44).

Investigations into the neurochemical mediation of wind-up have produced compelling evidence for the involvement of excitatory amino acids (EAAs), acting through the NMDA (*N*-methyl-D-aspartate) receptor complex. The EAAs are known to be localized in primary afferent terminals (13,33,51) and to be released by noxious stimulation (22,45,46). Application of NMDA to the spinal cord produces hyperexcitation of dorsal horn cells (43) and behavioral signs of nociception (1), while numerous reports have shown that various antagonists of the NMDA receptor will selectively reduce wind-up of dorsal horn cells (12,16,17,20,40,44,52).

The emerging consensus is that chronic noxious peripheral input induces a hyperexcitation of dorsal horn cells, mediated by NMDA receptor activation, which is behaviorally expressed as hyperalgesia (an increase in pain) and is involved in the etiology of a variety of clinical pathologic pain syndromes. Behavioral results from the experimental models are consistent with this proposal. In most of these studies, chemical (8,35,36,38,39,53,54), thermal (7), ischemic (42), or nerve injury (11,27,28,29,41,48,55) is applied to one hindpaw or the tail of a rat or mouse, and the effect of this treatment is assessed by observing spontaneous, or elicited nociceptive reactions. These treatments reliably induce a hyperalgesic condition in the affected, relative to the untreated, limb, which may be worsened by EAA agonists (8,34). In most cases, the intrathecal [or systemic, (42)] application of NMDA antagonists, after the injury, reduces the hyperalgesic reaction of the affected limb, without altering the response of the uninjured limb [(28,29,38,39,48,53,55), but see (54) for a negative result]. The selective effect of NMDA antagonists on postinjury hyperalgesia suggests that these agents might provide a new class of analgesics.

Moreover (by analogy with the action of NMDA antagonists on long-term potentiation in the hippocampus), it has been proposed that the development of (postoperative) pathologic pain may even be avoided by pretreatment with these (and other) analgesic or anesthetic agents (14). Behavioral results also support this suggestion, in that spinal or systemic administration of NMDA antagonists before (or before and after) the application of noxious stimuli effectively reduced postinjury hyperalgesia (8,11,27,29,41,42,54).

The clinical relevance of preoperative analgesic treatment for reduction of postoperative pain (termed preemptive analgesia) has been discussed in several recent reviews (5,10, 31,50). In clinical applications of this procedure, human subjects, who received opiate analgesics or local anesthetics before surgery, reported less pain, or required less analgesic medication, after the surgery. While these studies have been criticized on several grounds (10,31), the phenomenon of preemptive analgesia, produced by opiates, anesthetics, or EAA antagonists, is an area of significant clinical and theoretical interest.

At present, the only NMDA antagonist available for clinical use is ketamine. Although it is an intravenous anesthetic, when given in subanesthetic doses, ketamine can produce analgesia in postoperative and experimental, ischemic pain conditions (24,30). The fact that ketamine has analgesic properties in clinical pain syndromes is consistent with its effects in animal models. That is, although systemic or intrathecal administration of ketamine produces only weak analgesic effects against acute, phasic, pain [such as the tail flick, (3,4,9)], several studies have shown that intrathecal injection reduces the hyperalgesic effect of hindpaw carrageenan injection (39) and sciatic nerve constriction (28,55), while intraperitoneal injection reduces the hyperalgesic effect of ischemia on tail withdrawal (42). In each case, there was no effect in the non-hyperalgesic condition. Surprisingly, no studies have specifically examined the effect of pretreatment with ketamine either in animal models of hyperalgesia or in a preemptive clinical paradigm.

In summary, there is considerable data to suggest that peripheral injury leads to activation of dorsal horn neurons and behavioral hyperalgesia, i.e., facilitation of spinal reflexes. These phenomena are also produced by spinal transection. Because there is compelling evidence that the neural and behavioral consequences of peripheral injury are mediatd by excitatory amino acids, it was possible that the same transmitter system might be implicated in the behavioral facilitation produced by spinal transection. If so, EAA antagonists might be expected to either prevent the development of spinalization-induced hyperalgesia or abolish this facilitation once it was established. Ketamine was chosen to test this prediction because it is the only clinically available NMDA antagonist, and, because of its anesthetic property, it could easily be administered as a preemptive treatment. The present studies investigated the possibility that a) ketamine anesthesia would prevent the development of spinalization-induced facilitation of the tail flick reflex in rats and/or enhance the postoperative effect of intrathecal morphine and b) ketamine would have an antinociceptive effect in spinally transected, but not intact rats.

METHOD

Subjects

A total of 116 male, albino Sprague-Dawley rats (Holtzman Laboratories, Madison, WI), weighing 350–500 g, were used as subjects. The animals were housed in suspended steel cages in a colony room maintained on a 12 L : 12 D cycle, with dark onset at 1700 h. Food and water were available ad lib.

Surgical Procedures

Intrathecal catheterization. The anesthetized animal (see Procedures, below) was placed in a stereotaxic frame. An incision was made behind the ears and the neck muscles were scraped to expose the back of the skull. An incision of the atlanto-occipital membrane allowed the insertion of an 8 cm long catheter of PE-10 polyethylene tubing filled with sterile saline into the spinal subarachnoid space. Prior to insertion, a loose knot was tied in the catheter and coated with dental cement so that it could be held in place against the skull with adhesive. This catheter length allowed drugs to be administered at the level of the lumbar enlargement, i.e., lumbar vertebrae 3–6, as previously determined by autopsy. The incision was closed and the exposed tip of the catheter was heat sealed. Any rat showing overt neurological deficit of a crippled limb postoperatively was eliminated from the study.

Spinal transection. In addition to the catheter implantation, several groups of rats also sustained a spinal transection. The skin incision was extended further and, after retracting the paraspinal muscles, a laminectomy was performed between thoracic vertebrae 6 and 9. A 1 to 2 mm portion of the spinal cord was removed, leaving the catheter intact. The excised tissue was replaced with gel foam to reduce bleeding, after which the incision was closed in layers and the cages placed on heating pads to maintain body temperature. On the morning after surgery, the hindquarters of each rat were washed with warm water and their urine was expressed manu-

ally by the application of pressure to their bladders. All experiments with spinal and intact animals were completed within 24 h after surgery, at which time the animals were euthanized with ether.

Drug Administration

For intrathecal (IT) injections, the tip of the catheter was cut, a 30 gauge needle was inserted into the catheter and 10 μl of the drug solution was infused followed by a 10 μl wash of the saline vehicle. Injections were performed manually with a 50 μl Hamilton syringe (Hamilton Co., Reno, NV) over a 2–3 min period.

The ketamine solution used for anesthesia [intramuscular injection; Ketaset, ketamine HCl)] was obtained from Fort Dodge Laboratories, Inc. (Fort Dodge, IA). Ketamine powder, used for intraperitoneal (IP) or intrathecal (IT) injections was obtained from Research Biochemicals, Inc. (Natick, MA) and morphine was obtained from Penick Corp. (Lyndhurst, NJ). Solutions of these latter two drugs were prepared such that the amount injected contained the desired dose of the drug.

Behavioral Tests

Tail flick. The tail flick (TF) was used for nociceptive assessment (IITC Life Sciences, Woodland Hills, CA). Noxious stimulation was provided by a beam of high-intensity light focused on the tail. The response time was measured automatically and was defined as the interval between the onset of the thermal stimulus and the abrupt flick of the tail. Each determination consisted of three to five trials; the mean score was taken as the response latency. Animals not responding within the 14 s limit were removed from the apparatus to prevent tissue damage, and assigned a score of 14 s.

Motor function. Subjects were placed on the mat of an inclined plane with the body axis perpendicular to the slope of the plane. The maximum inclination of the plane at which the rat could maintain itself for 5 s was recorded. Assessments were made in 5° increments; normal rats maintain their balance at an angle of 59 ± 3° (mean ± SD). A value of 55° or less provided evidence of motor impairment. An assessment was made on the inclined plane in studies using intact rats, before and after intrathecal administration of ketamine.

Righting reflex. The righting reflex was examined in intact animals receiving systemic ketamine. The animal was placed on its back and the time required to regain upright posture was measured using a stop watch. A normal animal regains an upright posture immediately, in less than 2 s.

Experimental Procedures

The first experiment was performed to determine whether preoperatively administered ketamine would alter the TF latency or the dose response function of intrathecal morphine on the antinociceptive TF test in spinal rats. The control condition for this study consisted of animals who were operated (catheterized and spinally transected) under isoflurane anesthesia, tested 1 day later on the TF, then injected IT with either 0.05, 0.10, 0.20, or 0.40 μg of morphine and retested 30 min later. Anesthesia was induced with a mixture of isoflurane (AErrane, Anaquest, Madison, WI) and oxygen, at a flow rate of 4 l/min. After the anesthetized animal was placed in the ear bars of the stereotaxic frame, anesthesia was maintained by allowing the animal to breathe a mixture of isoflurane and oxygen through a mask (flow rate 2 l/min).

The first experimental group consisted of rats that were anesthetized by an intramuscular injection of ketamine (100 mg/kg body weight; 1.0 ml/kg) for the surgical procedures. These rats were also tested on the TF 1 day later, before and 30 min after an IT injection of either 0.10, 0.20, or 0.40 μg of morphine.

The second experimental group consisted of rats that were anesthetized with isoflurane, and, after insertion of the intrathecal catheter, were also injected with 80 μg of ketamine. Initially, an attempt was made to transect the cord approximately 5 min after the intrathecal injection. Because this procedure proved to be lethal, subsequent transections were performed immediately after the ketamine injection. These animals were also tested on the TF 1 day after surgery, then injected IT with either 0.05, 0.10, or 0.20 μg of morphine and retested 30 min later.

The second experiment compared the effect of systemically administered ketamine (part A) and intrathecally administered ketamine (part B) in intact and spinal animals. In this case, all animals were operated under isoflurane anesthesia as described above.

In part A, the control group consisted of rats that received sham surgery; the incision was made, the vertebrae were exposed, and the incision closed in layers. The experimental group consisted of rats with a spinal transection. On the following day, all rats were pretested on the TF, injected IP with either 15, 20, or 50 mg/kg of ketamine, and retested 30 min later.

The righting reflex was assessed in intact animals approximately 15 min after injection of ketamine, to determine whether or not these doses were, in fact, subanesthetic. Although this reflex could not be examined in spinal rats, these animals were observed for head weaving movements and hyperactivity.

In part B, the control group consisted of Intact animals implanted with intrathecal catheters. The experimental group consisted of rats that sustained both an intrathecal catheter and a spinal transection. On the next day, all rats were pretested on the TF, injected with either 80, 160, or 720 μg of ketamine, and retested 30 min later. The inclined plane test was performed on intact rats receiving intrathecal ketamine, to determine whether these doses produced evidence of motor impairment. Because intrathecal ketamine has not been reported to produce anesthesia, the righting reflex was not assessed.

The protocol and procedures used in these experiments were reviewed and approved by the Institutional Animal Care and Use Committee of Louisiana State University. Application of the thermal stimulus was limited as much as possible and terminated as soon as the escape response occurred. All animals were capable of performing the withdrawal response.

Statistical Analyses

The effects of the experimental treatments were assessed on the day after surgery by analysis of a) predrug TF latencies and b) the difference scores, obtained by subtracting the predrug TF latency from the postdrug latency for each rat. Statistical tests (*t*-tests and analyses of variance, ANOVAS) were performed with the aid of a computer program (CRUNCH Interactive Statistical Program). Results were considered significant at $p < 0.05$ or less.

RESULTS

A *t*-test comparing the postsurgical, baseline TF latencies of intact and nonpretreated spinal rats from the two experiments showed a significant difference between the two condi-

tions [intact rats TF latency = 4.1 ± 0.12 s; spinal rats TF latency = 2.6 ± 0.10 s: $n = 56$, $t(1, 54) = 10.51$, $p < 0.001$]. This finding replicates the well-established observation that spinal transection significantly reduces the TF latency (produces hyperalgesia).

Experiment 1

The results of the first study concerning the effect of ketamine pretreatment on spinal opiate analgesia are summarized in Fig. 1, which shows the data from systemic (part A) and intrathecal (part B) pretreatment.

In part A, a *t*-test, comparing the baseline, predrug, TF scores of spinal animals operated under isoflurane vs. (systemic) ketamine anesthesia, showed no significant difference between the two groups [isoflurane = 3.1 ± 0.12 s; ketamine = 2.8 ± 0.08 s: $n = 42$, $t(1, 40) = 2.02$, NS]. This indicates that anesthesia induced by systemic ketamine did not reduce the hyperalgesic effect of spinal transection. Figure 1A summarizes the dose-response functions of postoperative morphine in these groups. As indicated, the effect of morphine did not appear to differ between the two conditions. A two-way analysis of variance confirmed this observation [$n = 37$, $F(1, 36) = 0.96$, $p = 0.34$, for the drug condition and, $F(1, 36) = 3.3$, $p = 0.05$, for dose].

In part B, a *t*-test, comparing the baseline scores of animals pretreated with intrathecal ketamine and those without such pretreatment showed no difference between the two groups [isoflurane = 3.1 ± 0.12 s, isoflurane ± IT ketamine = 3.0 ± 0.24 s: $n = 38$, $t(1, 36) = 2.06$, NS]. This indicates that the addition of intrathecal ketamine to isoflurane anesthesia also did not reduce the hyperalgesic response of spinal transection. Figure 1B summarizes the dose-response functions of postoperative morphine in animals injected with intrathecal ketamine while under isoflurane anesthesia, and those without such pretreatment. As indicated, the two conditions were not different [$n = 33$, $F(1, 32) = 0.91$, $p = 0.35$, for drug condition and, $F(1, 32) = 6.8$, $p = 0.004$, for dose].

Experiment 2

Figure 2 summarizes the dose-response functions of IP (part A) and intrathecal (part B) ketamine in intact and spinal rats. For part A, a two-way ANOVA showed a significant main effect [$n = 30$, $F(1, 29) = 43.7$, $p < 0.001$]. There was also a significant interaction between the two conditions (intact and spinal) and the dose of the drug, $F(2, 29) = 4.5$, $p = 0.022$, indicating that ketamine had a dose-dependent effect only in spinal animals.

All intact rats regained their upright posture in less than 2 s when placed on their back, confirming that the doses of ketamine were subanesthetic. All spinal rats exhibited head weaving and hyperactivity, as reported by Pekoe and Smith (37).

As shown in Fig. 2B, the effect of intrathecal ketamine differed significantly between intact and spinal rats. A two-way ANOVA showed a significant main effect [$n = 26$, $F(1, 25) = 9.6$, $p = < 0.01$], although there was no significant interaction. This suggested that ketamine had a significant effect only at the highest dose. A *t*-test comparing the intact group with the spinal group at this dose (720 μg) was significant [$n = 8$, $t(1, 6) = 2.9$, $p < 0.03$]. The nonparametric Mann-Whitney *U*-test also showed a significant difference ($U = 1.5$, $p < 0.05$).

The inclined plane test of motor function indicated an impairment in intact rats during the first 10–15 min after the injection of 720 μg of ketamine. As reported by Crisp and colleagues (9), this large dose of ketamine produced a flaccid paralysis that was apparent within 10 min after injection, but was gone after 30 min.

DISCUSSION

The present studies were prompted by the observation that both spinal transection and peripheral trauma produce a similar facilitation of spinal nociceptive reflexes and dorsal horn neuronal activity. Because the excitatory amino acids are believed to be involved in the mediation of these phenomena

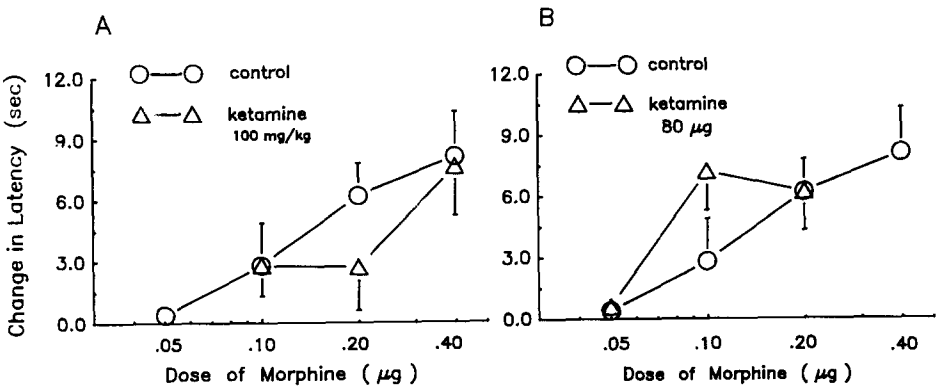

FIG. 1. Effect of ketamine pretreatment on morphine-induced antinociception in spinal rats. (A) Mean (± SEM) change in tail flick latency of separate groups of spinally transected rats, 30 min after intrathecal injection of morphine. Spinal transections were performed on the previous day, in animals anesthetized with either isoflurane (○) or an intramuscular injection of ketamine (△). (B) Mean (± SEM) change in tail flick latency of separate groups of spinally transected rats, 30 min after intrathecal injection of morphine. Spinal transections were performed on the previous day in animals anesthetized with either isoflurane alone (○; same as A) or in combination with 80 μg of intrathecal ketamine (△).

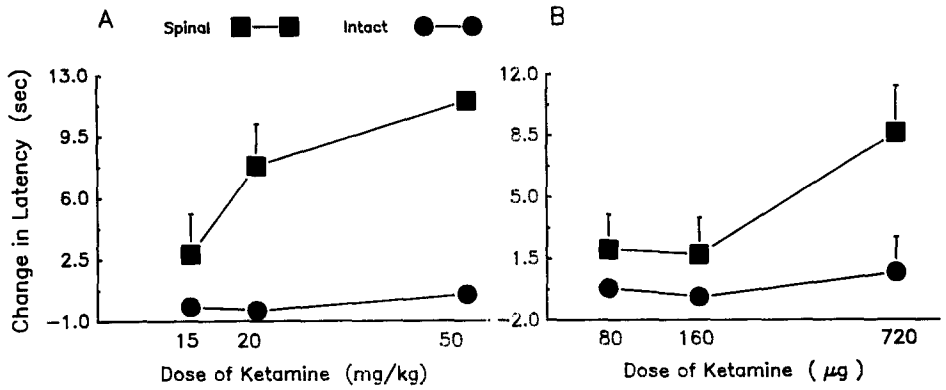

FIG. 2. Antinociceptive effect of ketamine in intact and spinal rats. (A) Mean (±SEM) change in tail flick latency of separate groups of rats, 30 min after an intraperitoneal injection of ketamine. On the previous day animals were either spinally transected (■) or underwent sham surgery (●), under isoflurane anesthesia. (B) Mean (±SEM) change in tail flick latency of separate groups of rats, 30 min after an intrathecal injection of ketamine. On the previous day animals were either spinally transected (■) or underwent sham surgery (●), under isoflurane anesthesia.

after peripheral injury, it was possible that this transmitter system was also responsible for spinalization-induced reflex facilitation. Moreover, because pre- as well as posttreatment with NMDA antagonists reduces the hyperalgesic effect of peripheral injury, it was hypothesized that a similar decrease of facilitation might also be produced by either procedure after spinal transection. Ketamine was chosen to test these predictions because it is presently the only clinically available NMDA antagonist as well as an anesthetic, which meant that it could easily be applied as a preemptive treatment. It was, therefore, predicted that ketamine anesthesia would prevent the development of TF facilitation after spinalization and/or enhance the antinociceptive effect of postoperative morphine and that ketamine would have an antinociceptive effect in spinal but not intact rats.

As expected, the baseline TF latencies of spinally transected rats were significantly lower than those of intact rats, indicating that spinalization produced reflex facilitation. However, the results of the first experiment did not reveal a preemptive effect of systemic or intrathecal ketamine on either baseline reflex latencies or morphine-induced antinociception.

With regard to the effect of systemic ketamine, it is possible that the drug concentration required to produce anesthesia was not sufficient to block the activation of those processes responsible for reflex facilitation. Yamamura and colleagues (56) have shown that the concentration of ketamine sufficient for the induction of anesthesia in lampreys (and other animal species) did not antagonize neural responses to nonNMDA agonists (kainate and quisqualate), even though the response to NMDA was significantly inhibited. If the activation of multiple EAA receptor types is required for the prevention of reflex facilitation, then an anesthetic concentration of ketamine may not be capable of exerting a preemptive effect.

The addition of intrathecal ketamine to animals anesthetized with isoflurane also failed to modify spinal reflex facilitation or opiate antinociception. This approach was adopted in an effort to restrict ketamine exposure to the spinal cord and limit its action to the presumed site of EAA-induced activation. When ketamine was injected 5 min before spinal transection, five out of the first seven animals died soon after, prior to spinalization. This suggested that the combination of the drugs was lethal. A similar potentiation of the lethal effect of pentobarbital anesthesia has been reported after IT administration of the NMDA antagonist MK-801 (34), perhaps indicating a general potentiation of CNS depressants by EAA antagonists (49).

To minimize anesthetic exposure, an attempt was made to perform the transection immediately after the ketamine injection. While this modification increased survival of the subjects, it also severely reduced the amount of preoperative exposure to ketamine. Therefore, due to the technical problems encountered with this procedure, the negative results of IT ketamine pretreatment may be inconclusive. It remains to be seen whether the outcome would be the same in behavioral or clinical paradigms of peripheral injury.

The fact that ketamine did not have a preemptive effect may be due to the nature of its antagonistic action. That is, ketamine is a noncompetitive antagonist, and blocks the ion channel coupled to the NMDA receptor. It is, therefore, "use dependent" and exerts its effects primarily after the channel has been opened, presumably by prior nociceptive stimulation. This could account for the lack of a preemptive effect of systemic ketamine, which was administered before surgery. Furthermore " . . . the onset of dissociative anesthetic block is also dramatically slow. . . . This slow onset also means that the receptor must be exposed to the dissociative anesthetic for relatively long periods before a steady state of blockade can be reached and equilibrium achieved" (26). This could account for the fact that the intrathecal pretreatment was ineffective.

The results of the second study showed that both systemic and intrathecal ketamine had an antinociceptive effect only in spinally transected animals. These data replicate an earlier report (37) showing a significant effect of systemic ketamine in spinal vs. intact rats. The present study confirms that this is due to a direct action of the drug on the spinal cord and is the first to show this effect after intrathecal ketamine in spinal rats.

The fact that ketamine had a negligible analgesic effect in intact rats is consistent with previous investigations which found that large doses of the drug (240- > 720 μg; 1- > 3 μM) are required to produce a detectable analgesic response in nonhyperalgesic animals (3,4,9). In contrast, substantial evidence (summarized in the Introduction) indicates that ketamine and other EAA antagonists are analgesic in the presence

of peripheral injury. The studies that included ketamine found it to be analgesic against carrageenan (39), ischemic (42), and sciatic nerve constriction-induced hyperalgesia [(28,55), see also (21)]. The results of behavioral investigations are in agreement with electrophysiological findings showing that ketamine selectively blocks neural facilitation (wind-up) in the dorsal horn, produced by electrical stimulation (12), hindlimb ischemia (44), hindpaw formalin injection (28), and injection of kaolin or carrageenan into the knee joint (40).

The present studies are, therefore, consistent with investigations of hyperalgesia induced by peripheral injury and support the involvement of EAAs in reflex facilitation produced by central injury. In this regard, it may be worth noting that excitation of dorsal horn neurons produced by NMDA in intact rats was significantly decreased by a procedure that activated diffuse noxious inhibitory controls [noxious stimulation applied to areas of the body remote from the receptive field, (43)]. This provides independent electrophysiological evidence of descending inhibitory control of spinal EAA activity in intact animals.

At present, the evidence suggests that ketamine produces its antinociceptive effects by antagonism of the NMDA receptor complex. However, because this drug, unlike other NMDA antagonists, is also an anesthetic, it is possible that its action in spinal animals does not involve this transmitter system. To confirm the hypothesis that reflex facilitation produced by spinal transection is mediated by EAAs, additional studies, using other EAA antagonists are in progress.

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