Ketamine, an N-Methyl-D-Aspartate Receptor Antagonist, Inhibits the Spinal Neuronal Responses to Distension of the Rat Urinary Bladder

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Background: The effect of ketamine as a treatment of visceral pain is not known. The current study investigated the effect of ketamine on spinal dorsal horn neurons excited by urinary bladder distension (UBD). The effect of other clinically available N-methyl-D-aspartate receptor antagonists on these responses was also studied.

Methods: Extracellular recordings of neurons located in the L6–S2 spinal dorsal horn of cervical spinal cord–transected, decerebrate female rats were obtained. Cutaneous receptive fields of neuronal units excited by UBD were characterized for responses to segmental noxious and nonnoxious stimuli. Nonsegmental noxious stimuli were also applied, and neurons were classified as type I (inhibited) and type II (noninhibited) by the stimuli. The effect of intravenous ketamine (1, 3, and 10 mg/kg), dextromethorphan (5 mg/kg), and memantine (16 mg/kg) on neuronal responses of these units was measured.

Results: Spontaneous and evoked neuronal activity to UBD was reduced in a dose-dependent fashion by ketamine. Responses to nonnoxious cutaneous stimuli were also significantly reduced after treatment. Dextromethorphan inhibited neuronal activity evoked by UBD in type I neurons. A similar selective effect of treatment on type I versus type II neurons was observed after intravenous ketamine and memantine.

Conclusions: Intravenous ketamine produces dose-dependent inhibition of the spinal cord neuronal responses evoked by UBD. All three N-methyl-D-aspartate receptor antagonists showed selective effects on spinal cord neurons subject to counterirritation. This neurophysiologic evidence supports a spinal mediated analgesic effect of ketamine in this model of urinary bladder nociception, an effect likely caused by N-methyl-D-aspartate receptor antagonism.

We recently characterized the effect of ketamine on cardiovascular and visceromotor responses to urinary bladder distension (UBD) in the intact, halothane-anesthetized rat.7 A direct inhibitory effect on these responses was observed when ketamine was administered intravenously and intrathecally, with a similar effect as two other clinically available NMDA receptor antagonists, memantine and dextromethorphan. A spinally mediated NMDA receptor antagonist effect was thereby suggested.7 There are some limitations associated with anesthetized, intact animal preparations that prevent definitive conclusions related to the mechanism and site of action of ketamine. For example, in the intact animal, supraspinal effects of ketamine cannot be ruled out. This is important because an intact supraspinal descending system has been proposed to be essential to the ketamine spinal analgesic effect in somatic models of nociception.8 It is also known that general anesthesia modifies spinal and supraspinal neurons related to nociceptive transmission.9,10 The use of a spinalized-decerebrate preparation limits the effect of intravenous drugs to the spinal cord and peripheral afferents, ruling out supraspinal sites of action. Decerebration allows the use of unanesthetized animals.

To the best of our knowledge, no experimental studies have been performed related to the effect of ketamine on the spinal cord neuronal responses to noxious stimulation of the urinary bladder. The current study was undertaken to determine the neurophysiologic effects of ketamine on spinal neuronal responses to UBD by examining spinal cord dorsal horn neuronal responses to UBD in the acutely spinalized decerebrate rat. The effects of two other clinically available NMDA receptor antagonists, dextromethorphan and memantine, on these responses to UBD were also examined.

Materials and Methods

Electrophysiologic Preparation

These studies were approved by the Institutional Review Board for nonhuman studies at the University of Alabama (Birmingham, AL). Female Sprague-Dawley rats were anesthetized with halothane (2–5%) delivered by mask. Jugular venous, arterial carotid, and tracheal cannulae were placed, and the rats were artificially ventilated using a volume-cycled respirator. The cervical spinal cord was exposed at the level of the atlantooccipital joint, and 50 μL of 1% lidocaine hydrochloride was injected bilaterally. The spinal cord was then fully
transected at the level of C1, and the brain was mechanically pithed with a forceps. Halothane was then discontinued, and the rats were ventilated with a mixture of air and oxygen and allowed to recover 4 h or more, until demonstrating vigorous flexion-withdrawal reflex responses to tail pinch. Paralysis was then established with pancuronium bromide (0.2 mg/h administered intravenously). Blood pressure was continuously monitored. Normal saline was administered as needed to prevent hypovolemia. The lumbosacral spinal cord was exposed by laminectomy, and the rats were suspended from thoracic and lumbar vertebral clamps. The dura mater was carefully cut, and skin flaps were arranged to allow for the formation of a protective bath of warm paraffin oil over the exposed spinal cord. Tungsten microelectrodes (Micro Probe, Clarksburg, MD; 0.9 -1.3 Mega Ω) were used for conventional extracellular single-unit recordings 0–1 mm lateral to midline, 0–1 mm ventral to spinal cord dorsum. Brief, phasic 60-mmHg UBD (see next section for specifics) was used as a primary search stimulus. Isolated units that were reliably and reproducibly excited (± 20%) by UBD on three consecutive trials were characterized further. Only one unit per animal was studied for pharmacologic treatments. Convergent cutaneous receptive fields (CRFs) (excitatory-inhibitory) were determined by applying the following stimuli: brush with a cotton-tipped applicator (nonnoxious mechanical) and pinch with a rat-tooth forceps at sufficient intensity to produce pain in the investigator (noxious mechanical). Size of convergent CRFs and intensity of responses to noxious and nonnoxious stimuli were determined before treatments. The CRF was marked on the animal body using a marker, and intensity of responses to noxious and nonnoxious stimuli was determined by recording neuronal activity produced by a 5-s stimulus in the center of the CRF for pinch and brush. A nonsegmental distant noxious stimulus (pinch of the neck skin of the animal) was applied to determine a “counterirritation” effect on spontaneous activity. To quantify neuronal responses, units were displayed on an oscilloscope for continuous monitoring, discriminated conventionally from background, converted into uniform pulses, and counted and saved by computer as peristimulus-time histograms. Spontaneous activity (in hertz) was determined in the 10-s period before the onset of UBD. Total activity during UBD was determined as the total number of action potentials during the 20 s of UBD. Evoked activity was calculated as the difference between the total activity and the calculated spontaneous activity (mean rate in hertz × 20 s). Stimulus-response functions of activity evoked by graded UBD were plotted for each individual neuron. Because responses of different neurons to the same stimulus naturally vary in maximum response and total number of discharges, the response of each unit was normalized to that produced by the 60-mmHg response for purposes of between-group comparisons.

**Urinary Bladder Distension**

In all animals, a 22-gauge Teflon angiocatheter was placed into the urinary bladder via the urethra and held in place by a tight suture around the distal urethral orifice. UBD was administered as phasic stimuli (rapid onset, rapid offset) using compressed air and a previously described distension control device.11

**Drug Protocol**

All pharmacologic manipulations were performed as single bolus doses with the exception of six neurons, in which the effects of intravesical ketamine were investigated. In all experiments, a fresh solution of ketamine (1, 3, and 10 mg/kg), dextromethorphan (5 mg/kg), or meperidine (16 mg/kg) (Sigma Chemical Company, St. Louis, MO) was dissolved in saline. Doses were chosen based on a previous study of the effect of the drug on reflex responses to UBD. When drugs were administered intravenously, 1 ml/kg of volume solution was used, and the same volume of saline was intravenously used as a control. Pharmacologic manipulations were performed after three baseline responses to UBD (60 mmHg, 20 s) and one trial of graded responses to UBD (20–80 mmHg, 60 s) was obtained, and once size and intensity of pinch and brush CRFs were determined. Neuronal spontaneous activity and neuronal activity evoked by UBD (60 mmHg, 20 s, every 4 min) were monitored for 40–60 min after injections. To study drug effects on stimulus-response functions and CRF activity without interfering with the treatment time frame descriptions, second single bolus doses of drugs or saline were administered after 80% of the baseline responses to UBD were recovered. Neuronal activity evoked by graded UBD (20–80 mmHg) given in sequence was determined and convergent CRF activity characterized before and 12 min after second injections.

To investigate the site of action of ketamine, in six neurons, stable responses to UBD were obtained and then 1 ml/kg of a 3-mg/ml solution of ketamine was injected through the urinary bladder catheter into the bladder and allowed to dwell for 15 min. The solution was then allowed to drain spontaneously, and three responses to UBD (60 mmHg, 20 s) were obtained at 4-min intervals. After the response to UBD returned to a consistent, stable level (± 20% on three trials), an intravenous bolus dose of ketamine (3 mg/kg) was administered, and three responses to UBD (60 mmHg, 20 s) were obtained at 4-min intervals.

**Statistics**

Statistics are presented as the mean ± SEM unless otherwise stated. Data are presented as a percentage of baseline neuronal responses unless otherwise stated.

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Comparisons with control responses were performed using a two-way analysis of variance (ANOVA) for repeated measures and post hoc analysis with the Tukey-Kramer procedure, where significant main effects were seen. Unpaired t tests were applied at specified time points. The statistical program used for analysis was GB-STAT (Dynamic Microsystems, Inc., Silver Springs, MD). Statistical significance was defined as $P \leq 0.05$.

**Results**

**Neuronal Sample**

Fifty-five neurons in the dorsal horn of the L6–S2 spinal segment were identified and characterized; a summary of their characteristics is given in table 1. Similar to previous studies of neurons excited by visceral stimuli, these neurons encoded for the relevant visceral stimulus, UBD, in a monotonic, accelerating fashion. All neurons excited by UBD also had convergent excitatory CRFs in the perirenal area, hind paws, or tail. Neurons excited by both noxious and nonnoxious stimuli were categorized as class 2 neurons (wide dynamic range), and those only excited by noxious stimuli were categorized as class 3 neurons (nociceptive specific). As shown in table 1, most of the units were class 2 neurons. Approximately half of the neuronal sample was inhibited 20% or more by the application of a noxious mechanical stimulus to a distant site of the body (pinch on the neck). These neurons were classified as type I neurons, as opposed to those that were not inhibited, which were classified as type II neurons. There were no statistically significant differences between experimental neuronal groups in relation to baseline spontaneous neuronal activity or activity evoked by UBD, the only exception being a difference between the 10- and 3-mg/kg ketamine study groups ($P \leq 0.05$, unpaired t test, table 1). This difference was not considered to be physiologically relevant. A typical example of one dorsal horn neuron excited by UBD, with a suprasegmental inhibitory CRF (type I neuron), is shown in figure 1.

**Effect of Intravenous Ketamine**

A typical example of the inhibition produced by intravenous ketamine (10 mg/kg) on the spontaneous and evoked neuronal activity as well as on the convergent CRF is shown in figure 1.

**Time-dependent Effects.** Single bolus doses of 1 mg/kg (n = 10), 3 mg/kg (n = 10), 10 mg/kg (n = 8), or the same volume of saline (1 ml/kg, n = 10) were administered intravenously over 1 min. No changes in arterial blood pressure were observed after injection of ketamine. Ketamine produced a dose-dependent inhibition of spontaneous neuronal activity and neuronal activity evoked by UBD (60 mmHg, 20 s). Four minutes after the injection of 1, 3, and 10 mg/kg ketamine, neuronal spontaneous activity decreased in a dose-dependent fashion (fig. 2A). Statistically significant differ-

![Fig. 1. Typical example of ketamine effect on neuronal activity in a spinal cord unit excited by urinary bladder distension. (Left) Neuronal oscillographic tracings before and after treatment. (Right) Effect of ketamine (10 mg/kg) on neuronal activity evoked by urinary bladder distension. (Inset) Effect of distant nonsegmental noxious stimulus on spontaneous activity of the unit (type I neuron). Cartoons show convergent cutaneous excitatory receptive fields for noxious and nonnoxious stimuli of the same unit, before and after treatment with ketamine. Dark area indicates excitation by noxious pinch. Hatched area indicates inhibition by noxious pinch.]
Ketamine inhibits neuronal responses to bladder distension

Enrices were observed in comparison with the effect produced by saline at the same time point for 3 and 10 mg/kg (\(P \leq 0.01\) and \(P \leq 0.001\), respectively, unpaired \(t\) test). The neuronal activity evoked by UBD (60 mmHg, 20 s) was also dose-dependently inhibited by ketamine (fig. 2B). Four minutes after the injection of 1, 3, and 10 mg/kg ketamine, neuronal activity evoked by UBD was significantly decreased (\(P \leq 0.01\) for 1 and 3 mg/kg, \(P \leq 0.0025\) for 10 mg/kg, unpaired \(t\) test). Inhibition of spontaneous neuronal activity and neuronal activity evoked by UBD became more prolonged with higher doses. A time course of the effect of ketamine on both neuronal activities and statistically significant differences using two-way repeated-measures ANOVA followed by post hoc analysis with the Tukey-Kramer procedure are presented in figures 2A and B.

**Site-dependent Effects.** The site of action of the intravenous ketamine was briefly investigated by administering a 3-mg/kg dose of ketamine to an additional six neurons (three type I neurons, three type II neurons; all class 2 neurons) by first the intravesical route followed by the intravenous route after a return of stable response to UBD. In these experiments, 3 mg/kg ketamine was allowed to dwell in the bladder for 15 min and then allowed to drain. Responses to UBD were then determined at 4-min intervals. At the first measure, intravesical ketamine produced a 9.8 ± 20.1% decrease in the evoked response to UBD. In contrast, at the first measure after the intravenous administration of the same dose of ketamine, a 59.4 ± 6.1% decrease in the evoked response was produced. The intravesical administration of ketamine produced a brief 33.1 ± 22.6% reduction of the ongoing spontaneous activity of these neurons, suggesting that the drug was able to penetrate the urothelium. The intravenous administration of ketamine in these same neurons produced a greater, 44.7 ± 8.1% reduction of spontaneous activity. In all cases, the effects of the intravenous administration of the drug was greater than the intravesical administration of the same amount of drug.

**Effect on Stimulus-response Functions.** Figure 2C shows the effect of ketamine on the stimulus-response functions relating graded neuronal activity evoked by graded UBD (20–80 mmHg). Although no difference in the stimulus-response functions is observed between the two lower doses of ketamine, a greater inhibition was produced by 10 mg/kg. Two-way repeated measures ANOVA with post hoc analysis with the Tukey-Kramer procedure showed statistically significant differences in comparison with saline effects on the neuronal activity evoked by 60 and 80 mmHg of UBD pressure (\(P \leq 0.01\) at all doses).

**Effect of Ketamine on Neuronal Subgroups.** An analysis of a selective effect of ketamine on the two different groups of neurons defined by the inhibitory effect of a suprasegmental noxious stimulus (type I vs. type II) is shown in figure 3. Ketamine appears to be more effective in producing inhibition of type I neurons, an effect that is also dose-dependent. Figure 3 shows statistically significant differences between the two types of neurons with the two higher doses of ketamine using two-way repeated-measures ANOVA followed by post hoc analysis with the Tukey-Kramer procedure.

**Effect on Convergent Cutaneous Receptive Fields.** Intravenous ketamine produced changes in the size of convergent CRFs. After 1, 3, and 10 mg/kg intravenous ketamine, 81% (9 of 11), 80% (8 of 10), and 100% (8 of
8) of the neuronal sample, respectively, had a reduction of the size of the convergent CRF for noxious (pinch) and nonnoxious (brush) stimuli. Considering all the ketamine doses, the only neurons in which the size of convergent CRFs was not reduced by the drug were class 2 neurons. Although the number of class 3 neurons was significantly less than the number of class 2 neurons in all of the study groups, all of the former neurons (4 of 4) showed size changes in the convergent CRF. No differences in neuronal depth or neuronal type (I vs. II) were observed between units in which size changes in convergent CRF were observed and units in which such changes were not present. A typical example of the convergent CRF changes produced by 10 mg/kg ketamine is shown in figure 1.

Changes in the intensity of responses to noxious and nonnoxious stimuli were also observed and expressed as a percentage of inhibition of baseline responses. As shown in figure 4, intravenous bolus doses of 3 and 10 mg/kg ketamine produced an inhibition of the neuronal response to the application of a nonnoxious stimulus (brush) in the center of the convergent CRF, which was statistically significant ($P < 0.05$ and $#P < 0.01$, unpaired $t$ test). A slight but statistically insignificant inhibition of the neuronal application of a noxious stimulus (pinch) was observed with the highest dose of ketamine.

**Effect of Other N-methyl-d-aspartate Receptor Antagonists**

The effect of two other NMDA receptor antagonists on the neuronal activity of units excited by UBD was also investigated. Intravenous dextromethorphan (10 mg/kg, $n = 11$) and memantine (16 mg/kg, $n = 6$) were administered, and the effect on neuronal activities was studied following a protocol similar to that described for ketamine. After injection, memantine produced hemodynamic changes characterized by an initial increase followed by a decrease in arterial blood pressure. Because of such hemodynamic changes, we limited the number of neurons studied in this group. Dextromethorphan, on
the other hand, did not produce hemodynamic changes. Dextromethorphan inhibited neuronal activity evoked by UBD (60 mmHg) in type I neurons (figs. 5A and B), but no effect on type II neurons was observed (figs. 5C and D). Interestingly, the time course of neuronal activity inhibition observed in the current study is similar to that of a previous study of reflex responses to UBD.7 As shown in figure 5A, a reduction of the neuronal activity evoked by UBD, in comparison with saline, was observed 28 min after injection of the drug (72 ± 10% of the baseline response) with a maximal effect 60 min after injection (42 ± 20%, P ≤ 0.05, unpaired t test). Figure 5A also shows statistically significant differences between the group treated with dextromethorphan and control neurons using two-way repeated-measures ANOVA followed by post hoc analysis with the Tukey-Kramer procedure. No recovery of the response to UBD was observed 60 min after injection.

Four minutes after the injection of memantine, neuronal activity evoked by UBD was reduced to 27 ± 12% of the baseline response. This effect was statistically significant when compared with the effect produced by saline at the same time point (P ≤ 0.05, unpaired t test). The time course of the effect of memantine on the neuronal activity evoked by UBD (60 mmHg, 20 s every 4 min) is shown in figure 6A. Although not statistically different because of the small sample size, 4 min after intravenous memantine, type I neurons were more inhibited than type II neurons (6 ± 4% vs. 46 ± 25% of the baseline response, respectively, n = 3 in both groups). A time course of the effect of memantine in the two groups of neurons is presented in figure 6B. Memantine produced more inhibition of type I neurons when responses were monitored up to 40 min, reaching statistically significant
differences between groups after 32 min of injection ($P \leq 0.05$, two-way repeated-measures ANOVA followed by post hoc analysis with the Tukey-Kramer procedure, fig. 6B). Neuronal activity evoked by graded UBD was also inhibited by memantine, with a reduction of the slope of the stimulus response function (fig. 6C). Two-way repeated-measures ANOVA followed by post hoc analysis with the Tukey-Kramer procedure showed statistically significant differences in comparison with saline effects on the neuronal activity evoked by 60 ($P \leq 0.05$) and 80 mmHg of UBD pressure ($P \leq 0.01$). No significant changes in neuronal spontaneous activity or in the size and intensity of convergent CRFs were observed after dextromethorphan and memantine.

**Discussion**

The neurophysiologic consequences of ketamine were determined on a neuronal population located in the dorsal horns of the L6–S2 spinal segments of spinally transected decerebrate female rats. These neurons demonstrated an incrementally increasing neuronal activity evoked by UBD over a wide range of pressures (20–80 mmHg), including those that are viewed as noxious. Distension pressures in the range of 20–40 mmHg produce discomfort in humans during experimental UBD and activate pressor and visceromotor responses to UBD in female rats. Whereas the responses of spinal cord neurons localized in the lumbo-sacral segments of the spinal cord to noxious distension of visceral organs such as the colon or uterus have been studied quantitatively by multiple investigators in the rat, spinal neurons responsive to UBD have not been similarly characterized. A characteristic of neurons excited by UBD in our study is the presence of somato-visceral convergence. All of the neurons that were excited by UBD were also excited by nonnoxious or noxious stimuli, mostly limited to the perineal area, hind paw, and tail. In cats, Honda found a high degree of somatovisceral convergence with convergent CRFs in the perineum and hind limbs in sacral spinal neurons excited by UBD. Milne et al. obtained similar findings from primate sacral and thoracolumbar spinothalamic neurons excited by UBD. It would appear that rat spinal dorsal horn neurons have similar characteristics.

Another interesting characteristic of our neuronal sample is the existence of a neuronal group inhibited by conditioning noxious stimuli presented in nonsegmental sites (i.e., neurons subject to counterirritation), which we classify as type I neurons, and a group not inhibited by such stimuli, classified as type II. The existence of at least two different populations of spinal cord neurons excited by visceral noxious stimuli has been described previously in rats using the colorectal distension model. Among other characteristics, these groups share a similar differential response to conditioning noxious stimuli presented in nonsegmental sites. In addition, these groups of spinal neurons have been shown to be differentially affected by inflammation and systemic analgesics (i.e., morphine, lidocaine, $\kappa$-opioid receptor agonists).

To the best of our knowledge, the current study is the first report of an inhibitory effect of systemic ketamine on spinal cord neuronal responses to UBD. We demonstrate that ketamine produces a dose-dependent inhibition of neuronal activity evoked by UBD. These data suggest a direct spinal site of action of ketamine in
producing visceral antinociception, because in the splanchnic preparation supraspinal sites are excluded. This mechanism has been suggested in intact animals by the intrathecal administration of ketamine in rats subjected to colorectal distension and in our previous study using the mechanical distension of the bladder as a noxious stimulus. On the other hand, there are several neurophysiologic studies performed in splanchnic animals using somatic noxious stimuli, with contrasting results. Although Hao et al. found that ketamine produced a dose-dependent inhibition of flexor reflexes in spinal transected animals, Crisp et al., using the tail-flick test, observed that the spinally mediated analgesic effect of ketamine was suppressed by bilateral sectioning of the dorsolateral funiculi. They suggested that descending antinociceptive systems must be intact to allow the analgesic effects of ketamine in this model. Our results confirm a site of action of ketamine that is independent of supraspinal influences.

A dose-dependent inhibition of spontaneous neuronal activity, as well as a dose-dependent reduction of responses to the stimulation of convergent CRFs, was also observed after systemic ketamine in our preparation. Ketamine, in a range of doses similar to that used in our study, inhibits the spontaneous activity of wide dynamic range neurons in decerebrate, spinal cord–transected cats. The presence of convergent CRFs in spinal cord neurons is an important feature of visceral nociception. Increases of convergent CRFs of spinal cord neurons have been observed in cats after the repeated presentation of mechanical visceral stimuli. Kolhekar and Gebhart observed an increase of the size of convergent CRFs of spinal cord neurons excited by colorectal distension after the intrathecal administration of NMDA, an effect that was reversed by the NMDA receptor antagonist APV. There is an important clinical correlation between the observation of changes in CRFs of spinal cord neurons excited by visceral mechanical noxious stimuli and the increase of areas of superficial referred pain after repeat bladder and colorectal distensions in human experimental visceral pain. In our study, we used the mechanical distension of the bladder as a search stimulus, and all of the neurons studied here received 10 or more UBDs before pharmacologic manipulation. Because only neurons with reliable and consistent baseline responses to UBD were selected for pharmacologic manipulation, we did not formally study the effect of repeat UBDs on CRF size. We presume that an increase of CRF sizes occurred during initial UBDs because we have consistently observed such phenomena as part of an ongoing study. Thus, the contraction of the convergent CRFs after the intravenous administration of ketamine might represent the return of the CRFs to their prestimulus status. Another interesting finding in our study is the greater inhibition produced by ketamine on the neuronal activity evoked by nonnoxious cutaneous stimuli compared with the inhibition observed on neuronal responses evoked by noxious cutaneous stimuli. This inhibition must be produced by the effect of ketamine either peripherally or centrally on neuronal inputs from low-threshold (Aβ) afferents. These afferents have been related to the clinical symptom of allodynia, observed in many clinical scenarios, for example, in postoperative pain. Ketamine has been shown to be effective in reducing the mechanical punctuate hyperalgesia of the surgical incision after renal surgery, along with a short-lasting effect on pain scores and morphine consumption after surgery. An NMDA receptor antagonist effect of intravenous ketamine in this study was proposed to explain the results. Although changes in spontaneous neuronal activity and convergent CRFs produced by ketamine in our study might be explained by an antagonism effect of the NMDA receptor, the lack of effect of the other two NMDA receptor antagonists on these responses does not support that assumption, although differences in affinity for the NMDA receptor and other pharmacokinetic differences could contribute to the differences. Because of the complexity of the actions of ketamine in the central nervous system, other mechanisms such as opioid receptor interactions or local anesthetic effects may also explain these results.

The spinally transected preparation used in the current study may eliminate the potential for supraspinal effects but does not rule out possible peripheral effects of ketamine. It is therefore notable that effects of NMDA receptor antagonists have been proposed recently in models of somatic inflammatory and visceral pain. McRoberts et al. reported that the NR1 subunit of the NMDA receptor can be immunohistochemically identified on primary afferent nerves in the colon, and the NMDA receptor antagonist memantine inhibits the electrophysiologic responses of these afferents to colonic distension. Similar studies of bladder afferents have not been reported. We did not measure tissue concentrations of ketamine after its intravesical administration and therefore cannot rule out peripheral effects of the drug, but the minimal effect of the intravesical administration of the ketamine on responses to UBD that we observed in the current study suggests that bladder afferents may differ from colonic afferents. At the very least, these data demonstrate that such a route of administration is not practical as a method for producing antinociception. The use of NMDA receptor antagonists that do not penetrate the central nervous system but that can be administered systemically would allow one to assess potential peripheral effects of this class of drugs. At present, their role in the control of bladder pain must be purely speculative.

The role of the NMDA receptor antagonists in models of somatic pain is still not wholly defined, but most literature supports a role of the NMDA receptor in the
development and maintenance of spinal cord hyperexcitability after repeated C-fiber electrical stimulation (“wind-up”), inflammation, or nerve injury, rather than a role in the acute, direct, nociceptive transmission.\textsuperscript{36,37} In visceral models of pain, this topic is also controversial,\textsuperscript{35} but the role of NMDA receptor antagonists in acute visceral nociceptive transmission appears more relevant.\textsuperscript{2,5} We recently characterized the effect of ketamine on cardiovascular and visceromotor responses to UBD, and a direct effect of ketamine on acute nociception as opposed to a “preventive” effect on the development of hyperalgesia was observed.\textsuperscript{7} The current study is consistent with those results.

Although there is extensive experimental clinical data about the analgesic effect of ketamine, it is still not known if these actions are via the properties of ketamine as an NMDA receptor antagonist. The NMDA antagonist effect of ketamine is not in dispute, but this agent also appears to interact with many receptors and circuits related to nociceptive transmission, which may be related to its analgesic effects.\textsuperscript{6,8,38} By comparing the effect of ketamine with the effect of two other NMDA antagonist agents on neuronal activity evoked by UBD, we were able to demonstrate many qualitative similarities. We found an inhibition of the neuronal activity evoked by UBD (60 mmHg, 20 s) with a similar reduction of the slope of the stimulus-response functions to graded UBD (20–80 mmHg) after the intravenous injection of memantine. Interestingly, dextromethorphan produced quantitatively and qualitatively similar results on type I neurons but had no effect on type II neurons. The time frame of the effect of dextromethorphan was similar to that observed using the reflex responses to UBD in a previous study.\textsuperscript{7} This more selective effect of dextromethorphan on type I neurons but had also been observed after all doses of ketamine, reaching statistical significance at 3 and 10 mg/kg. Memantine also produced greater inhibition of type I neurons. It would appear that NMDA receptor antagonists have a selective effect on a specific group of neurons, characterized by the inhibitory effect of a nonsegmental noxious stimulus (type I neurons). Similar to the observations in colorectal distension studies, the current findings support the existence of at least two separate populations of spinal dorsal horn neurons that encode for the stimulus of UBD at noxious intensities. The precise role of these two different populations of spinal neurons excited by UBD in the nociceptive transmission remains unknown, but the differential effect of ketamine and the other two NMDA receptor antagonists on two different subgroups of neurons excited by UBD supports the assertion that bladder nociception is processed through a dual pathway. We recently observed a greater inhibition of these drugs on the electromyographic responses to UBD in comparison with the effect observed on the cardiovascular responses.\textsuperscript{7} It is possible that this more profound effect of NMDA receptor antagonists on the visceromotor responses might be linked with the greater inhibition observed with these drugs on the neuronal responses in type I neurons, although the neurophysiologic complexity of reflex responses precludes a definitive mechanism.

In conclusion, ketamine inhibits, in a dose-dependent manner, spinal neuronal responses to the acute noxious stimulus of distension of the urinary bladder. This effect is likely caused, in part, by NMDA receptor antagonist actions of ketamine, because other drugs with such pharmacologic properties produced a qualitatively similar inhibition. A selective inhibitory effect of ketamine and the other two clinically available NMDA receptor antagonists on a group of neurons subject to counterirritation (type I neurons) was observed. Using the spinalized decerebrate preparation coupled with intravesical and systemic administration of ketamine, we were able to demonstrate that a site of action of the drug appears to be localized to the spinal cord. This confirms previous observations using the cardiovascular and visceromotor responses to UBD in anesthetized animals.

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