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The Effects of Ketamine on the Excitation and Inhibition of Dorsal Horn WDR Neuronal Activity Induced by Bradykinin Injection into the Femoral Artery in Cats after Spinal Cord Transection

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Background: It is now well established that wide dynamic range neurons (WDR) can possess widespread cutaneous inhibitory receptive fields, as well as excitatory receptive fields, in specific regions of the body. The ability of ketamine to depress the excitatory responses of spinal WDR neurons indicates that the analgesia produced by this agent may be a result, in part, of this spinal action. The primary purpose of this study was to investigate the effects of ketamine on the WDR propriospinal inhibitory mechanism that is induced by a bradykinin (BK) injection as a noxious test stimuli.

Methods: In decerebrate, spinal cord-transected cats (L1–L2), the effects of a low (0.5 mg · kg^{-1}, intravenous) and a high (10 mg · kg^{-1}, intravenous) dose of ketamine on the neuronal activity of spinal dorsal horn WDR neurons evoked by femoral artery injection of BK (10 μg) was examined. Extracellular activity was recorded from single WDR neurons that responded to noxious and innocuous stimuli applied to the cutaneous receptive fields on the foot pads of the left hind paw.

Results: After ipsilateral BK administration, the activity of the WDR neurons was found to be increased (excited) in all ten neurons that were examined. In contrast, the activity of these neurons was found to be decreased (inhibited) in five of these ten neurons after BK administration into the contralateral femoral artery. The 10 mg · kg^{-1} dose of ketamine significantly suppressed the excitatory activity observed in all 15 of the WDR neurons examined. A comparison of the effects produced by the 0.5-mg · kg^{-1} and the 10-mg · kg^{-1} intravenous doses reveals that the amount of suppression was dose-related. In addition, the inhibitory WDR neuronal activity induced by contralateral BK injection was also significantly reduced by both the 0.5- and the 10-mg · kg^{-1} doses of ketamine.

Conclusions: These results indicate that this reduction of excitatory and inhibitory responses of WDR neurons after noxious stimulation is likely to be the fundamental basis for the spinal cord component of ketamine-induced analgesia. (Key words: Anesthetics, intravenous: ketamine. Spinal cord: WDR neuron.)

THE class of dorsal horn neurons classified as WDR (wide dynamic range) neurons are excited by low-intensity innocuous, as well as high-intensity noxious, stimuli applied to specific regions of the body (the excitatory receptive fields). As such, these cells have been associated with the central processing of information about pain. The ability of anesthetics and opioids to depress the excitatory response of these spinal WDR neurons indicates that the analgesia produced by these agents may be a result, in part, of a spinal action.[1–4] However, it is also well established that the WDR neurons can possess widespread cutaneous inhibitory receptive fields, the presence of which depends on the applied stimulus (*i.e.*, innocuous or noxious).[5–8] However, the role of such an inhibitory mechanism cannot currently be stated with certainty. Moreover, the effects of anesthetics on the inhibitory WDR neuronal activity produced by noxious stimulation are also not well understood.

Although there is abundant clinical evidence for the potent analgesic action of ketamine,[9,10] the neuronal mechanisms responsible for this action are still unclear. It is indicated that ketamine depresses the excitation of spinal WDR neurons *via* two different mechanisms. The first is by a direct depressant effect of ketamine at the spinal level. Such an effect has been demonstrated

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by administering ketamine systemically into spinal cord-transected animals, eliminating the possibility of descending inhibitory control of dorsal horn neurons from supraspinal structures.[3,11] The other mechanism by which ketamine depresses spinal cord WDR neurons is indicated to occur supraspinally.[12] Although there are reports that a descending inhibitory pathway from the periaqueductal gray (PAG) to the spinal cord does not contribute to ketamine's antinociceptive action,[13] other reports have shown that ketamine does, in fact, activate a descending inhibitory system that originates from supraspinal structures, including that of the nucleus reticularis gigantocellularis.[14]

It should also be noted that, in addition to the depressant effects of ketamine (at 2.5–10 mg·kg^{-1} intravenous) on WDR neurons excited by noxious stimulation, it has been shown in intact, awake, and drug-free cats that the response of WDR neurons to innocuous, low-intensity tactile stimulation is not significantly altered by 10 mg·kg^{-1} of ketamine intravenous.[15]

Although there have been several reports on the action of ketamine on spinal WDR neurons, to our knowledge, there has been no investigation of the effect of ketamine on the inhibitory response of WDR neurons that is triggered by certain noxious and innocuous stimuli. The purpose of this study was to investigate the effects of ketamine on the WDR propriospinal inhibitory mechanism that is induced by BK injection as a noxious test stimuli. This initial study was done in spinal cord-transected cats and was undertaken to compare the magnitude of WDR neuronal response produced by injecting BK into the ipsilateral femoral artery (which passes through the appropriate excitatory receptive field), and comparing it with the response produced by BK injected into the contralateral field.

Materials and Methods

Seventy-four cats of either sex (3.0 kg) were used in these experiments. The experimental protocol was approved by the Institutional Animal Care and Use Committee. All surgical procedures were performed under halothane (0.5%)–nitrous oxide (60%)–oxygen anesthesia (see fig. 1 for a summary of animal preparation). A tracheostomy was performed, the right common carotid artery was ligated, the left common carotid artery was cannulated for continuous arterial pressure monitoring, and the left external jugular vein was also cannulated for intravenous administration of fluid and drugs. In the preliminary studies, both the left and right

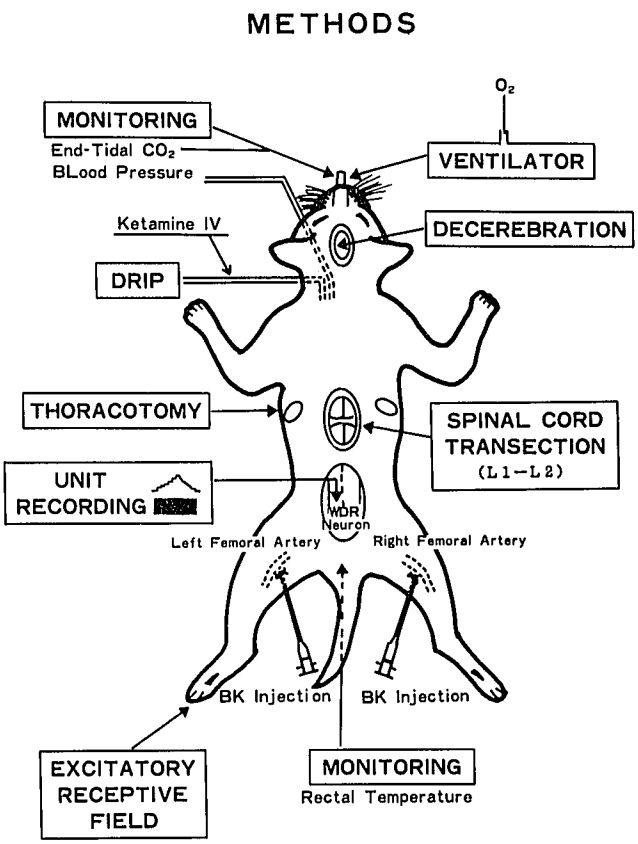

Fig. 1. A diagramatic representation of the experimental preparation. The spinal cord was transected at L1–L2. A thoracotomy was performed to avoid movement of the spinal cord resulting from mechanical ventilation.

femoral arteries were cannulated to allow for administration of BK (10 μg·ml^{-1} in saline; vol = 1 ml) *via* a polyethylene cannula, diameter 1 mm. In experiment 3, only the left femoral artery cannulation was done and, in experiment 4, only the right femoral artery cannulation was done. Each catheter was introduced into the femoral artery and fixed in such a manner that the tip was just distal to the bifurcation. The animals were paralyzed by a continuous infusion of pancuronium bromide and the lungs were ventilated mechanically (Shinano SN-480-5, Tokyo). A bilateral pneumothorax was routinely performed to minimize respiration-induced spinal cord movements. After stereotaxic fixation of the animals, a lumbar laminectomy was performed to expose the lumbar and sacral cord segments. The spinal cord was then transected at L1–L2 and the animal rendered decerebrate by a midbrain transection at the intercollicullar level. The dura was locally incised and the exposed spinal cord was bathed in 37° C liquid

paraffin to control the temperature. Carotid artery pressure was recorded continuously on a polygraph and most of the values of the systolic pressure were above 100 mmHg. Data collection was terminated when the systolic pressure decreased to less than 100 mmHg. Ventilation was controlled to keep the end-expiratory CO_2 concentration at about 4%. Rectal temperature was maintained in the range of 36° C to 37° C and, if necessary, the body was warmed with an infrared heat lamp. Lactated Ringers solution was administered at the rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$ through the intravenous catheter. When the surgical procedure was completed, anesthesia was discontinued and the lungs were ventilated with 100% oxygen.

Approximately 2 h after the anesthesia was discontinued, a tungsten microelectrode with 9–12 mohm impedance was advanced slowly, by a hydraulic micromanipulator (Narishige MO-10, Tokyo), into the spinal cord to record extracellular neuronal activity. Single-unit activity from the recording tungsten microelectrode was amplified (Nihon Kohden, MZ-4, Tokyo) and monitored with a memory osciloscope (Nihon Kohden, VC-11, Tokyo), and action potentials were counted (Yokokawa Hewlett Packard, 5330 A, Santa Clara, CA). Spike configuration and size were continuously monitored on the oscilloscope to confirm that the same cell was registered by the window discriminator (Nihon Kohden, PC-001S, Tokyo) throughout the experiment. This was found useful to ensure that orientation of the recording electrode to the target cell was maintained and to exclude the discharges of neighboring cells that were occasionally observed. Only WDR neurons that had their receptive fields on the foot pads of the left hind paw were selected. The WDR neurons were identified by a spontaneous firing pattern that consisted of a burst followed by steady firing, and by the evoked response to peripheral stimuli of several types: 1) air puff, 2) light touch, 3) light forceps pinch, and 4) strong forceps squeeze (fig. 2). Neuronal activity was quantified as the number of impulses per 5 s, and were recorded by polygraph (Sanei 2G66, Tokyo). The pulsatile spontaneous activity of isolated single units was counted electronically. Units were observed for 15 and 30 min after isolation to obtain a stable firing pattern and to control the effect of transient tissue distortion by the microelectrode.

The experiments were divided into four sections. 1: In the preliminary experiment after the control study, the magnitude of the WDR neuronal response produced by the administration of BK into the ipsilateral (left) femoral artery was compared with the response produced after BK injection into the contralateral (right)

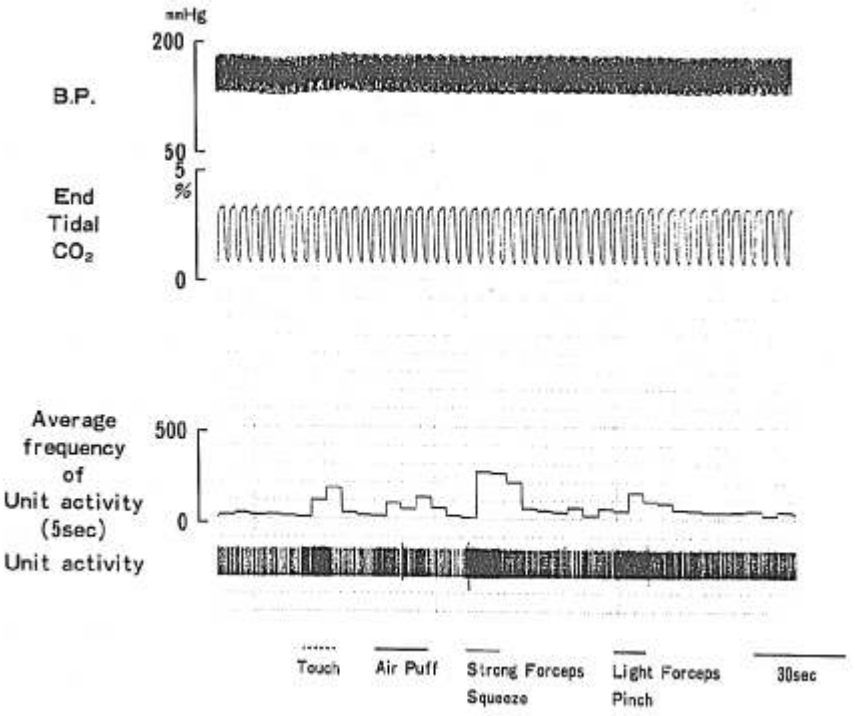

Fig. 2. An example of a response profile of a WDR neuron. Responses of WDR neurons to various stimuli at their excitatory receptive field of the footpad of the left hind paw are shown.

femoral artery. The activity of WDR neurons was recorded for 20 min after the ipsilateral BK injection and then for 10 min after the contralateral BK injection.

2: In the second experiment, ketamine hydrochloride (Ketalar, Parke-Davis Co., Sankyo, Japan; solution 10 $mg \cdot ml^{-1}$), either 0.5 or 10 $mg \cdot kg^{-1}$ intravenous, was administered and the effect of ketamine on the spontaneous activity of WDR neurons was monitored continuously for 70 min.

3: In the third experiment, the effect of ketamine, either 0.5 or 10 $mg \cdot kg^{-1}$ intravenous, on the activity of WDR neurons evoked by the ipsilateral intraarterial injection of BK was examined. After the recording of the control values during BK-induced activity, ketamine was administered intravenously and the neuronal responses were observed for 5 min after administration of the drug, after which the activity evoked by the ipsilateral BK injection was recorded for 20 min. The ipsilateral BK injections were repeated at 20-min intervals for a total of 65 min after ketamine administration. The BK-induced activity of the WDR neurons before ketamine administration was then compared with the BK-induced activity of those after ketamine administration.

4: In the fourth series of experiments, the effect of ketamine (0.5 or 10 $mg \cdot kg^{-1}$ intravenous) on the activity of WDR neurons evoked by contralateral BK injection was examined. As in the third experiment, ketamine was administered intravenously after recording the control values during BK-induced activity. The neuronal responses were observed 5 min after administration of the drug, after which the activity evoked by the contralateral BK injection was recorded for 20 min. The contralateral injections were repeated at 20-min intervals until 65 min after ketamine administration. The BK-induced activity as the control values of the WDR neurons before ketamine administration were compared with the BK-induced activity of those after ketamine administration.

The number of unit spikes of each neuron was counted for 60 s before and after each injection of BK in the third and fourth experiment. The magnitude of the excitatory and inhibitory activity induced by BK was determined by subtracting the spontaneous activity measured before each injection of BK from the peak (nadir) number of units discharged after the injection of BK. In addition, the duration of the excitatory and inhibitory responses produced by BK were measured in the third and fourth experiments.

Data Analysis

The changes induced by ketamine were expressed as the percent change from the control values, because the level of the neuronal activity differed with each experiment. The results are expressed as mean ± SEM. Statistical comparisons were performed with the use of a Student's *t* test. The time-course effects of ketamine were tested by one-way analysis of variance (ANOVA) and Newman-Keuls *post hoc* comparison for statistical analysis. Values of $P < 0.05$ were defined as significant.

Results

Data were obtained from WDR neurons in 74 cats. Each animal received only one dose of ketamine in experiments 2, 3, and 4. Innocuous cutaneous stimuli (light-touch stimuli) were routinely tested, but never produced inhibition in either hind limb.

Ipsilateral and Contralateral BK

The magnitude of evoked activity after the intraarterial injection of BK was compared in ten cats (fig. 3). After ipsilateral BK injection, WDR neurons were excited in all ten animals. Twenty minutes later, after the contralateral BK injection, the activity of the WDR neurons was inhibited in five of the ten cats, was slightly excited in one, and was not affected in four. Figure 3 presents the time course of the effects on the five WDR neurons that were inhibited by contralateral BK injection to compare the magnitude of the WDR neuronal response induced by BK into the ipsilateral femoral artery with that of the contralateral BK response. In addition, when the contralateral injection was first done, the neuronal activity was inhibited in two of the five WDR neurons examined (n = 5). Twenty minutes later, after an ipsilateral BK injection, the WDR neurons were observed to be excited in all five cats.

Ketamine and Spontaneous Activity

The spontaneous activity of cells before administration was 49.0 ± 18.2 spikes/5 s (n = 7) in the 0.5-$mg \cdot kg^{-1}$ intravenous group and 20.7 ± 8.4 spikes/5 s (n = 7) in the 10-$mg \cdot kg^{-1}$ intravenous group. Ketamine evoked a dose-dependent decrease in this spontaneous activity that lasted between 30 and 60 min with a mean decrease in activity of 74.8% in the 10-$mg \cdot kg^{-1}$ intravenous group and 33.1% in the 0.5-$mg \cdot kg^{-1}$ intravenous group.

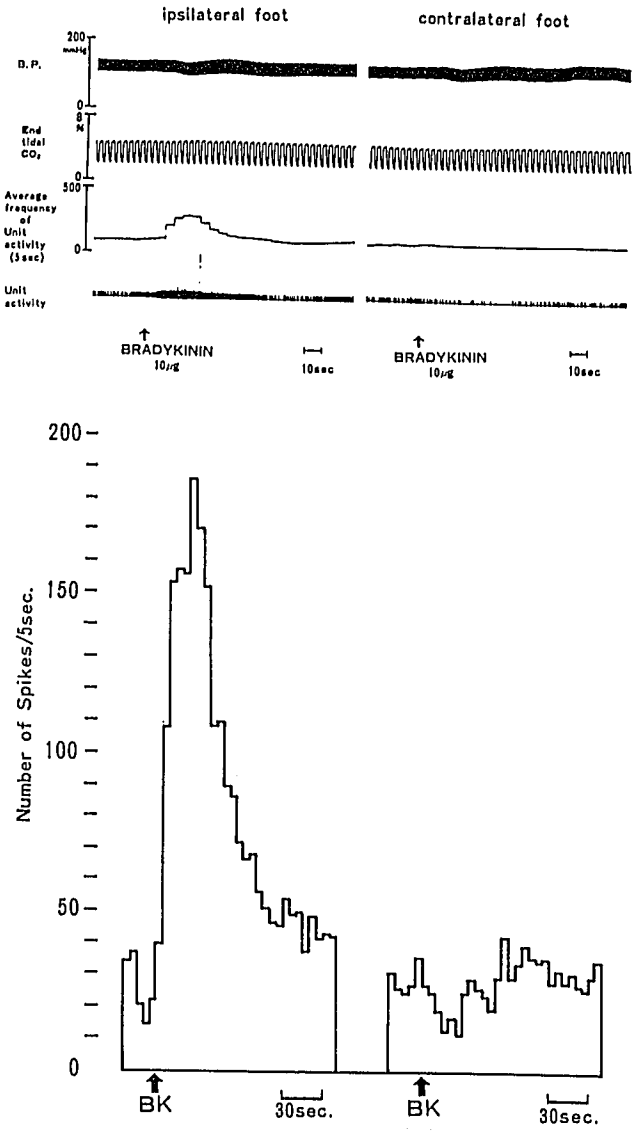

Fig. 3. Comparison of effects of ipsilateral and contralateral BK injection on the magnitude of the spinal WDR neuronal response. The upper panel shows typical results. The lower panels are the histograms, which were hand drawn after averaging from a spike integrator (n = 5). Bradykinin injections are made at the arrows. (The left is ipsilateral BK injection and the right is contralateral BK injection.)

Ipsilateral BK and Ketamine

All 15 WDR neurons examined were excited by ipsilateral BK injection (figs. 4 and 5). The spontaneous activity before drug administration was 30.7 ± 8.3 spikes/5 s in the 0.5-mg·kg^{-1} (n = 7) and 49.7 ± 8.6 spikes/5 s in the 10-mg·kg^{-1} group (n = 8), respectively. The magnitude of BK-induced neuronal firing rates was 155 ± 34 spikes/5 s in the 0.5-mg·kg^{-1} intravenous group and 184 ± 55 spikes/5 s in the 10-mg·kg^{-1} intravenous group. This magnitude was significantly depressed by 46.0, 65.0, 49.6, and 40.1% at 5, 25, 45, and 65 min after administration of ketamine 10 mg·kg^{-1} intravenous, respectively. However, within the ketamine 0.5-mg·kg^{-1} intravenous group, this magnitude was not significantly depressed at any time. The duration of BK-induced neuronal firing activity was 120 ± 31 s in the 0.5-mg·kg^{-1} intravenous group and 133 ± 23 s in the 10-mg·kg^{-1} intravenous group. This duration was significantly depressed by 35.2% only at 5 min after administration of ketamine 10 mg·kg^{-1}. Similar to the magnitude of BK-induced neuronal firing rate, this duration was not significantly depressed at any time after administration of ketamine 0.5 mg·kg^{-1}. The above results, therefore, indicate that ketamine produced a dose-dependent suppression of the excitatory effect of BK on WDR neurons.

Contralateral BK and Ketamine

After contralateral BK injection, the neuronal activity was inhibited in 16 of the 30 WDR neurons examined (figs. 6 and 7). The effect of ketamine on this inhibitory WDR neuronal activity is shown in figures 6 and 7. The spontaneous activity before drug administration was 52.8 ± 15.3 spikes/5 s in the 0.5-mg·kg^{-1} intravenous group (n = 9) and 38.1 ± 18.5 spikes/5 s in the 10-mg·kg^{-1} intravenous group (n = 7), respectively. The magnitude of BK-induced neuronal firing rates before ketamine administration was −45.4 ± 14.2 spikes/5 s in the 0.5-mg·kg^{-1} intravenous group and −32.1 ± 14.6 spikes/5 s in the 10-mg·kg^{-1} intravenous group. This magnitude was significantly depressed by 54.0% and 45.1% at 5 and 25 min after administration of ketamine 0.5 mg·kg^{-1}, respectively. In addition, this magnitude was significantly depressed by 82.4%, 60.6, 40.4, and 40.2% at 5, 25, 45, and 65 min after ketamine 10 mg·kg^{-1}, respectively. The duration of BK-induced neuronal firing activity before ketamine administration was 120.5 ± 20.3 s in the 0.5-mg·kg^{-1} intravenous group and 147 ± 39.4 s in the 10-mg·kg^{-1} intravenous group. This duration was significantly depressed by 45.3% at 5 min after ketamine 0.5 mg·mg^{-1} intravenous, but was significantly depressed by 84.2, 77.7, and 70.9% at 5, 25, and 45 min after ketamine 10 mg·kg^{-1} intravenous, respectively. The inhibitory neuronal activity was observed to be significantly depressed by 0.5 mg·kg^{-1} of ketamine. At 10 mg·kg^{-1}

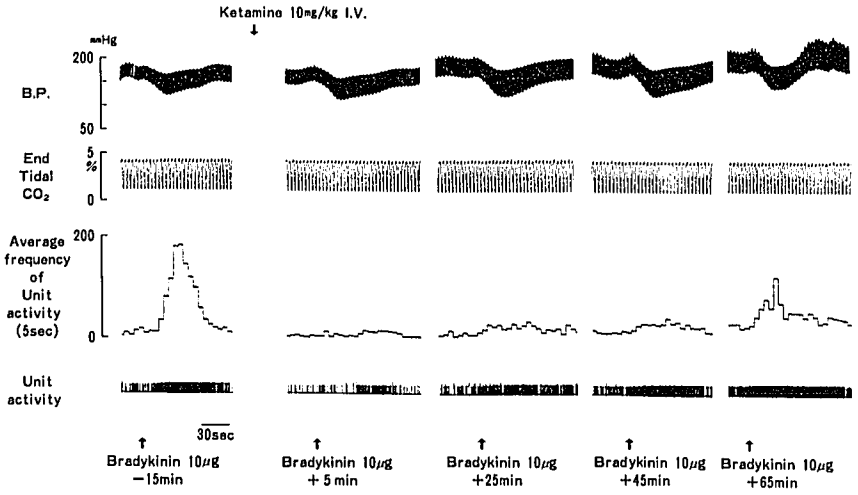

Fig. 4. An example of effect of ketamine (10 mg·kg^{-1} intravenous) on the excitatory neuronal activity induced by BK injection ipsilateral to the recording site. Polygraph records showing the blood pressure (BP) response (*top*) to a noxious chemical stimulus evoked by BK and histograms (*lower middle*) showing average frequency of unit activity per 5 s. The record, from left to right, shows the response measured before and 5, 25, 45, and 65 min after intravenously administered (intravenous) ketamine (10 mg·kg^{-1}).

ketamine intravenous, the spontaneous activity observed before BK injection was depressed as previously shown, and the inhibitory neuronal activity normally produced by BK injection was not evident at 5 min after ketamine administration.

Discussion

BK as a Noxious Stimulus

Although several groups have used BK to activate nociceptive neurons in the CNS to study their pharmacology, the significance of intraarterial administration of BK as a noxious stimulus remains controversial. Fjallabrant and Iggo (BK300–400 μg) and Beck and Handwerker (5–10 μg) stated that the effects produced by the intraarterial injection of BK are not strictly limited to nociceptors and that other receptors, supplied by fast-conducting fibers, are excited concomitantly.[16,17] Mense reported that, after administration of BK (26 μg), about one-half of group intravenous and two-thirds of group III muscle afferents could be activated, while group II and group I afferent units were usually not excited by BK.[18] Belcher recorded the responses of dorsal horn cells in cats and found that a small dose of BK (2.5–15 μg) given into the femoral artery activated the majority of nociceptive cells, although cells stimulated by innocuous stimuli were generally unchanged. Larger doses (30–70 μg) of BK were observed to be less specific and activated both cells stimulated by nonnociceptive stimuli, as well as cells stimulated by noxious stimuli.[19] Guilbaud *et al.* concluded that, at the dorsal horn level, peripheral A fiber activation by BK does not play an important role in nociceptive cell excitation, whereas C fiber activation always evoked a strong modification and that, within the C fibers of the sural nerve excited by BK, a large number could have been connected with nociceptors.[20] Our method of BK injection was identical to that of Guilbaud *et al.* and Belcher, and we chose our small doses according to their criteria.

As shown in figures 3, 4, and 6, the blood pressure response to BK was transiently decreased by 5–20 mmHg. The mechanism of the depressor response to intraarterial BK injection is unclear. Some investigators have reported variable pressor, depressor, and mixed arterial blood pressure responses to afferent nerve stimulation, especially BK intraarterial injection, in spinal cord-intact animals.[21,22] Intrafemoral artery injection of BK presumably activates the group III (A delta) fibers to a certain degree, and group IV (C) nerve fibers located in periphery. The afferents that are activated by BK produce the inhibitory or excitatory inputs to the spinal somatosympathetic reflex center in the spinal transected state. Nevertheless, it has been reported that the spinal reflex center plays a minor role in the central mediation of pressor and depressor responses.[23] In addition, it appears that autonomic reflex responses induced in the course of noxious stimulation not only depend on the site and intensity of the noxious stimulus, but also on the nature of the noxious stimulation.[21] In addition to the blood pressure changes produced by BK as a noxious stimulus, BK is also known to act locally to produce vasodilation, as well as pain.[24] It is possible, therefore, that this blood pressure-de-

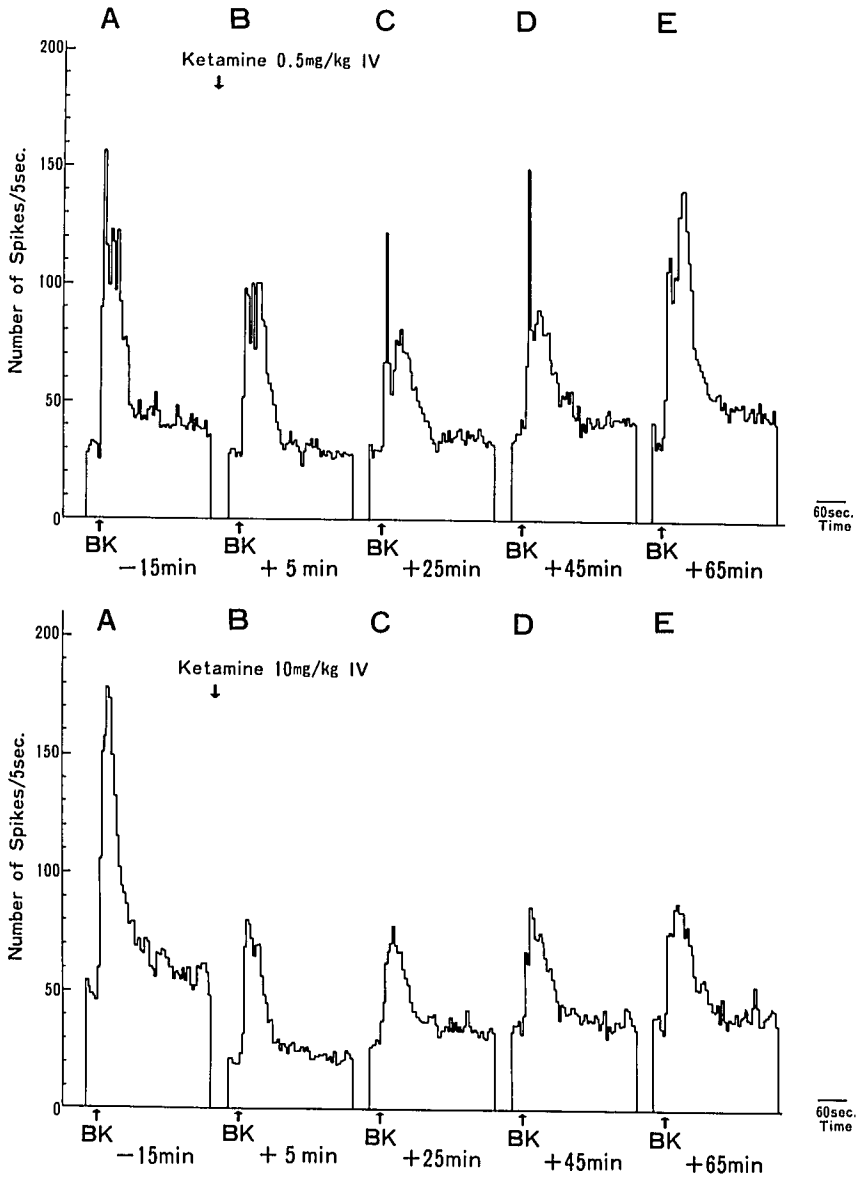

Fig. 5. Effect of ketamine on the excitatory neuronal activity induced by BK injection ipsilateral to the recording site. The histograms were hand drawn after averaging from a spike integrator. The upper histograph shows the results of ketamine 0.5 mg·kg^{-1} intravenous (n = 7). The lower shows the results of ketamine 10 mg·kg^{-1} intravenous (n = 8). Bradykinin injections are made at arrows in: (*A*) control; (*B*) at 5 min after ketamine intravenous; (*C*) at 25 min after ketamine intravenous; (*D*) at 45 min after ketamine intravenous; and (*E*) at 65 min after ketamine intravenous.

pressive response to BK may result from a local vasodilative action of BK, or a depressor autonomic reflex, or both.

Ketamine and the BK-Evoked Inhibitory WDR Neuronal Response

The results demonstrate that a clear inhibition of spinal WDR neuronal activity is produced by BK injection into the contralateral femoral artery in spinal cord-transected cats and that, in contrast, an excitatory response is produced by BK injection into the ipsilateral femoral artery. As this was observed in a spinal cord-transected preparation, this inhibition is produced to be a segmental phenomenon not involving pathways to and from the supraspinal structures. The results of the current study support the indication that contralateral inhibitory receptive fields are, functionally, mirror images of the ipsilateral excitatory receptive fields and may imply the presence of a local network involving connections within the cord.[7,8] In contrast with cord-intact animals, this crossed inhibition is weak.[25] Therefore, Le Bars *et al.* failed to find a pro-

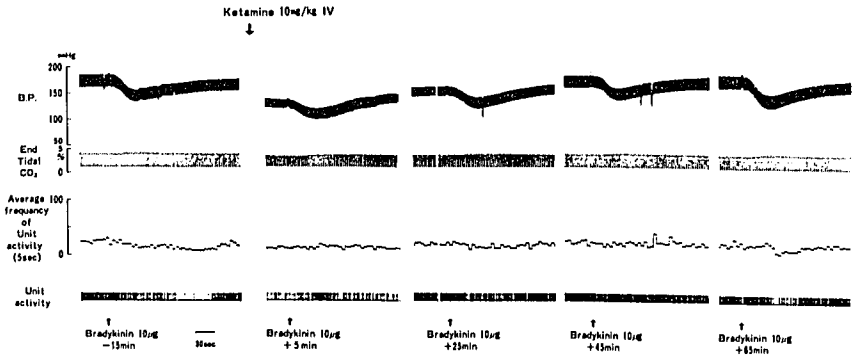

Fig. 6. An example of the effect of ketamine (10 mg·g^{-1} intravenous) on the inhibitory neuronal activity induced by BK injection contralateral to the recording site. Polygraph records show the blood pressure (BP) response (*top*) to a noxious chemical stimulus evoked by BK and histograms (*lower middle*) show average frequency of unit activity per 5 s. The record, from left to right, shows the response measured before and 5, 25, 45, and 65 min after intravenously administered (intravenous) ketamine (10 mg·kg^{-1}).

priospinal inhibitory phenomenon in 0.5% halothane-anesthetized rats after cervical section of the spinal cord.[26]

We have shown that the duration, as well as the magnitude, of the inhibitory responses were reduced by ketamine at either dose. We, therefore, conclude that ketamine attenuates the inhibitory activity evoked by BK. However, it is apparent that ketamine, at either dose, lowers the spontaneous activity of the WDR neuron recorded before BK injection. The absolute level of firing in response to BK falls to a lower value in the record only at 5 min after 10 mg·kg^{-1} ketamine, so that the relative inhibition from BK seems much diminished in ketamine-treated animals. This seems to put limits on the extent of BK-related inhibition that can be achieved during ketamine administration.

It seems unlikely that the reduced inhibitory influence on WDR neurons can contribute to ketamine "analgesia," because the intrinsic analgesic system is considered to result in an inhibition of the WDR neuron. These results, however, are not inconsistent with the scenario proposed by the "Diffuse noxious inhibitory control (DNIC) system" of Le Bars *et al.*[5] In this model, a wide variety of noxious stimuli applied to widespread areas of the body by mechanical, thermal, or chemical means may induce specific and powerful inhibition of the activities of spinal convergent neurons. The activity of this system is reduced by morphine.[27] These workers have proposed that "DNIC system" could improve the spatial and intensive contrast in the coding of the response to noxious stimulation.[28] Morphine analgesia could act on spinal WDR neurons by a reduction of

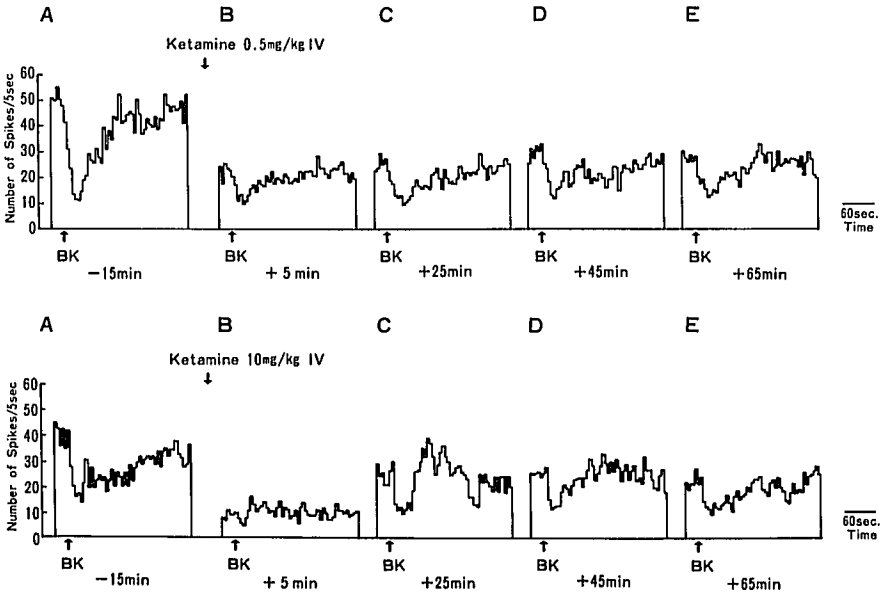

Fig. 7. Effects of ketamine on the inhibitory neuronal activity induced by BK injection contralateral to the recording site. The histograms were hand drawn after averaging from a spike integrator. The upper histograph shows the results of ketamine 0.5 mg·kg^{-1} intravenous (n = 9). The lower shows the results after ketamine 10 mg·kg^{-1} intravenous (n = 7). Bradykinin injections are made at the arrows in: (*A*) control; (*B*) at 5 min after ketamine intravenous; (*C*) at 25 min after ketamine intravenous; (*D*) at 45 min after ketamine intravenous; and (*E*) at 65 min after ketamine intravenous.

this contrast induced by the nociceptive message (excitatory response) and the somesthetic background activity (inhibitory response). Ketamine may also exert an effect on the "DNIC system" in a manner similar to morphine. However, because the relation between this noxious-induced inhibition and morphine was assessed using anesthetized cord-intact rats, further studies in cord-intact cats are required to study the possible interference of ketamine with this inhibitory mechanism.

The fact that the inhibitory influence studies could be demonstrated in a spinal preparation indicates the presence of a local spinal mechanism. Contralateral inhibition observed in the current investigation implies a connection between the contralateral and ipsilateral sides of the spinal cord. To influence the inhibitory interneurons, the primary afferents must, in part, be relayed by ipsilateral interneurons that project to the contralateral side. In addition, one could postulate that inputs from the ipsilateral hind limb could be mediated in part *via* primary afferent fibers crossing the midline and terminating on interneurons involved in the inhibitory pathway. Such a crossing primary afferent fiber is compatible with anatomical data obtained in the cat. Horseradish peroxidase (HRP) studies of dorsal horn projections in the cat have revealed a few smaller fibers (1–2 μm) crossing through the dorsal commissure to the contralateral dorsal horn (laminae I and V) in lumbar sections.[29] In addition, the ascending and descending fibers of the propriospinal tract consist of both uncrossed and crossed (at a variety of segmental level) fiber systems that give off their fibers bilaterally.[30] These connections may also contribute to the observed contralateral inhibition; however, it is not clear how substantial a role these connections may play.

Ketamine and the BK-Evoked Excitatory WDR Neuronal Response

In agreement with other investigators, we have observed the depressant effects of ketamine on both the excitatory response evoked by BK injection and on the spontaneous activity observed in spinal cord-transected animals.[3,11] On the basis of these results, spinal WDR neurons are postulated to be one of the sites of action for ketamine analgesia. In contrast, Headley *et al.* have recently reported that ketamine (5 $mg \cdot kg^{-1}$ intravenous) did not block the WDR neuronal activity evoked by mechanical noxious stimuli in spinal cord-transected cats.[31] The inability to block the response of feline WDR neurons to this type of mechanical stimulus (forceps) may be due, in part, to the use of inadequate doses of ketamine. Conseiller *et al.*[11] also used forceps to provide mechanical stimulation and reported a reduction in excitatory activity using 10 $mg \cdot kg^{-1}$ intravenous of ketamine. However, Kitahata *et al.*[3] found that only 2.5 $mg \cdot kg^{-1}$ intravenous of ketamine was required to depress the excitatory WDR neuronal activity produced when an alligator clamp was used as a noxious mechanical stimulus, indicating that both the dose of ketamine and the type of stimulus are important.

It has been proposed that an important component of ketamine analgesia is the activation of brain-stem neurons that project to the spinal cord and ultimately depress the spinal transmission of nociceptive information.[12] Because spinal cord-transected cats were used in our preparation, we cannot address this hypothesis at this time. The importance of spinal sites for ketamine analgesia has been discussed in experimental reports[3,11,15,32,33] and in several clinical reports of epidural use of ketamine for pain control.[34] Although it is possible that ketamine may exert significant effects on the sensitizing aspect of repetitive noxious input,[33,35] the evidence for "simple" analgesia mediated by a spinal action of ketamine is inconclusive.

The reports of ketamine as a spinal analgesic are controversial,[3,11,15,32–34] but would appear to correlate, in part, with the observation that ketamine, with an action limited to the spinal cord, can suppress at least neurons excited by ipsilateral BK. However, the relatively poor analgesic effects of spinally administered ketamine correlate with the inability of even large doses of ketamine to block the BK response completely. Recent studies by Woolf and Wall[36] suggest that a blockade of the facilitated flexion reflex evoked by prolonged repetitive stimuli (as generated by BK[37]) in the decerebrate, spinal cord-transected rat might represent the mechanism for the net WDR depressive effects of spinally administered ketamine observed in the current study. Schouenborg and Sjolund[38] have shown a clear relationship between C-fiber evoked wind-up of WDR neurons and the heightened excitability of the flexion reflex in response to repeated noxious stimuli. The wind-up in dorsal horn cells and the wind-up in the reflex response are dependent on the activation of NMDA receptors.[35,39] Glutamate, as well as substance P and calcitonin-gene-related peptide (CGRP), are likely to play a role in nociceptive transmission in the spinal cord.[40] These neuropeptides also appear to enhance the response of dorsal horn neurons to excitatory

amino acids.[40,41] The role of the NMDA receptor in the dorsal horn processing of afferent nociceptive traffic appears to be confined to its involvement in neuronal events mediating hyperalgesia.[42,43] In addition, ketamine at subanesthetic doses (5 $mg \cdot kg^{-1}$ intravenous) has been shown to selectively reduce WDR neuron excitation produced by NMDA in the spinal cord, but not excitation produced by mechanical noxious stimulation.[31] On the basis of the abovementioned study and other studies,[44,45] the action of ketamine anesthesia is closely associated with a blockade of NMDA receptors and ketamine analgesia appears to be more sensitive to hyperalgesic pain rather than simple pain at the spinal level.

Ketamine and Neurotransmitter Systems

The neurochemical mechanism of ketamine-induced depression of spinal nociceptive neurons in the spinal cord-transected animals is not clear. In addition to the NMDA neuronal system, some studies have demonstrated that ketamine acts, in part, as an agonist at opiate receptors and that it has the ability to recruit spinopetal noradrenergic and serotonergic neuronal pathways for its antinociceptive effect.[46] Furthermore, ketamine may affect some neurotransmitter systems in the CNS, including interactions with cholinergic receptors[47] and gamma-aminobutyric acid (GABA) receptors.[48] Therefore, several neuronal receptor systems may be involved in the depressant action of ketamine on WDR neurons of the dorsal horn of the spinal cord.

In conclusion, these results demonstrate that ketamine can reduce both the excitation and the inhibition of dorsal horn WDR neurons evoked by BK injection. Thus, ketamine-induced anesthesia appears to involve both a reduction of the excitatory and inhibitory responses produced by noxious stimulation and a decrease in the normal spontaneous activity of spinal WDR neurons.

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