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Differential effects of ketamine and MK-801 on A-fiber and C-fiber responses of spinal wide dynamic range neurons in the cat

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Abstract

Purpose. To clarify whether ketamine suppresses both A-fiber- and C-fiber-mediated pain and to compare the effects of ketamine with those of MK-801.

Methods. Experiments were performed on urethane/chloralose-anesthetized cats. Glass capillary microelectrodes were used to record extracellular single unit activities from wide dynamic range (WDR) neurons in the spinal dorsal horn. Responses evoked by electrical stimulation of the superficial peroneal (SP), posterior tibial (PT), or both nerves were analyzed. The responses to successive electrical stimuli were displayed on a personal computer using a raster-dot processing program.

Results. A subanesthetic dose of intravenous ketamine suppressed both A- and C-fiber responses of WDR neurons in a dose-dependent manner without affecting A-fiber response of low-threshold mechanoreceptive (LTM) neurons. The C-fiber response was more markedly suppressed than the A-fiber response. Intravenous administration of MK-801, a specific *N*-methyl-D-aspartate (NMDA) antagonist, selectively suppressed the C-fiber response of WDR neurons.

Conclusion. Intravenous ketamine may suppress both A- and C-fiber-mediated pain at a subanesthetic dose. This finding could be a scientific basis for the usefulness of ketamine during clinical procedures such as dressing changes or débridement of the burned patient.

Key words: Ketamine, Analgesia, MK-801, NMDA antagonist, Wide dynamic range neuron

Introduction

During ketamine anesthesia the muscles are not relaxed, and the limbs may move involuntarily, but reflexes to noxious stimuli are attenuated [1]. Ketamine in subanesthetic concentration inhibits acute nociceptive pain in humans [2–4]. Data from controlled trials [5–7] show that ketamine relieves pain and hyperalgesia in some patients with neuropathic pain.

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist [8,9] and suppresses transmission of nociceptive impulses carried by peripheral C-fibers within the spinal dorsal horn [10]. Whether ketamine also suppresses transmission of A-fiber impulses within the spinal dorsal horn is still uncertain.

The present study was undertaken to study the effects of intravenous ketamine on A- and C-fiber-evoked responses of wide dynamic range (WDR) neurons in the dorsal horn of the cat spinal cord, in comparison with effects of intravenous MK-801, a selective NMDA antagonist [11], on the same responses.

Materials and methods

Experiments were performed on 50 adult cats weighing 2.4 to 3.5 kg. They were supplied by the Laboratory Animal Institute of our university, and the protocol was approved by our Animal Care and Use Committee. The animals were initially anesthetized with ether. The right cephalic vein was cannulated for drug administration, and anesthesia was maintained with an intravenous dose (3.5 ml·kg^{-1}) of urethane/chloralose solution (urethane 125 mg·ml^{-1} and chloralose 10 mg·ml^{-1}), supplemented as required. The right femoral artery was cannulated for continuous monitoring of blood pressure.

The left superficial peroneal (SP) and posterior tibial (PT) nerves were dissected free from the surrounding tissues at the level of the ankle joint. A pair of platinum stimulating electrodes was applied to each nerve. The lumbar enlargement was exposed by laminectomy from L3 through L6.

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During exploration, muscle paralysis was maintained with pancuronium bromide (0.2–0.4 mg·kg^{-1}·h^{-1}). The animal was respired with room air, and the expiratory CO_2 was maintained between 27 and 34 mmHg.

Glass capillary microelectrodes filled with 2% pontamine sky blue in 0.5 M sodium acetate were used to record extracellular single unit activities. Electrical stimulation of the SP and PT nerves served to identify the dorsal horn neurons to be studied. The stimulus intensity was 3 V (0.1 ms), so all of the Aβ-fibers and a large number of the Aδ-fibers were excited. The cutaneous receptive field was mapped with natural stimuli. Forms of natural stimuli used included displacement of hairs, stroking and probing the skin, firm but innocuous pressure exerted by picking up a fold of skin with flattened forceps or an arterial clip, and a noxious pinch with a small serrated forceps or an alligator clip. WDR units with SP or PT input (or both) were then tested for additional C-fiber excitation with 0.5 Hz stimuli at various intensities up to 20–30 V. The duration of each pulse was 1 ms.

Responsiveness to noxious radiant heat stimulation was tested in four units. A precisely controlled skin temperature (50°C) was obtained by a quartz halogen lamp focused with a condenser lens onto either the large hind paw pad or a toe pad in the center of the unit's peripheral receptive field as determined by mechanical stimulation. The current to the lamp was controlled by feedback from a thermistor in contact with the skin. The duration of each noxious heat stimulation was preset at 20 s.

Responses of spinal dorsal horn neurons to electrical and natural stimuli were displayed on an oscilloscope, and its output was fed to a window discriminator. The window discriminator output was in turn fed to a spike counter, the output of which was used to reconstruct a peristimulus time histogram. The responses to 60 successive electrical stimuli were displayed on a personal computer using a raster-dot processing program, QP-130J, which we developed in cooperation with the Nihon Kohden Co. (Tokyo, Japan) and printed out after the experiment.

The recording sites were marked by an electrophoretic injection of pontamine sky blue from the microelectrode tip, passing a negative current of 5 μA for 10 min. At the termination of each experiment, the spinal cord was cleared of blood and fixed in situ by perfusing 1000 ml of normal saline through the beating heart, followed by 3000 ml of 10% formal saline. After at least 1 week, the spinal cord was frozen and cut into 50-μm serial sections. Dye marks were identified in cresyl violet-stained sections.

Mean values were presented as mean ± standard error (SEM). The non-parametric Mann-Whitney U-test was used to evaluate the results obtained from paired data. $P < 0.05$ was considered to be statistically significant.

Results

A total of 49 WDR units were subjected to the present study. They had a low-threshold center of receptive field in the hind paw pad. They showed a graded response to touch, pressure, and noxious pinch (Fig. 1B, a) applied to this center (black area in Fig. 1A) and responded best to the noxious pinch. Outside this zone (cross-hatched area in Fig. 1A), they were unresponsive to low-intensity mechanical stimuli but differentially responded to pressure and the noxious pinch (Fig. 1B, b). Finally, the latter area was surrounded by an area (shaded area in Fig. 1A) in which only the noxious pinch resulted in spike discharges (Fig. 1B, c). They showed a C-fiber response (Fig. 1C). In addition, six low-threshold mechanoreceptive (LTM) units were examined. They had a receptive field in the hind paw pad and responded maximally to brushing the receptive field.

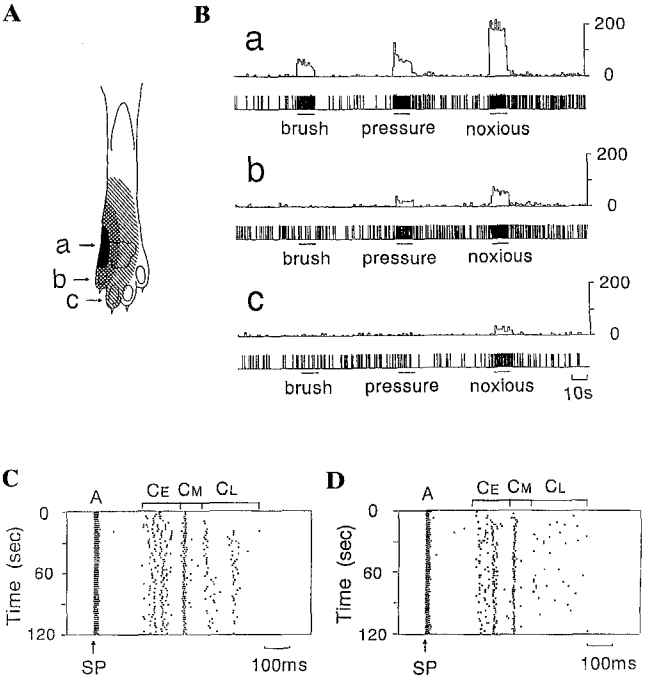

Fig. 1. Effects of intravenous ketamine (5 mg·kg^{-1}) on a wide dynamic range (WDR) unit. **A** Receptive field. **B** Responses to stimulation of corresponding three points indicated by arrows in **A** are shown as *a*, *b*, and *c*. **C** Raster-dot display from top down showing responses of the unit to 60 successive electrical stimuli applied to the superficial peroneal (*SP*) nerve at 0.5 Hz. The stimuli were 16 V in strength and 1 ms in duration. The top trace shows the initial response, while the bottom trace the 60th response. *A*, C_E, C_M, and C_L indicate A-fiber, early C-fiber, middle C-fiber, and late C-fiber responses, respectively. **D** Responses to SP stimulation 20 min after ketamine injection

The WDR units were located in laminae IV–VI of the L7 dorsal horn, whereas the LTM units were in lamina III–IV of the same segment.

Effects of intravenous ketamine on C-fiber response of WDR neurons

The effects of intravenous ketamine on responses evoked by electrical stimulation of C-fiber in the SP/PT nerves were studied in 18 WDR units. The C-fiber response consists of three components: early (CE), middle (CM), and late (CL). The minimum latency of the CE range is 182–236 ms, the CM range is 268–328 ms, and the CL range is 352–440 ms [12].

The total number of spikes evoked by 60 successive C-fiber stimulations was determined, and changes in this value produced by intravenous ketamine were expressed as percentages and pooled. An example is shown in Fig. 1C. The minimum latencies of CE, CM, and CL were 183–296 ms, 322–391 ms, and 400–583 ms, respectively. Following intravenous administration of ketamine 5 mg·kg^{-1}, all three components were reduced. Twenty minutes after the injection (Fig. 1D) the CE was reduced by 9.5%, the CM by 15.4%, and the CL by 64.0%. The mean time courses of inhibition in six units produced by intravenous ketamine (2.5, 5, or 10 mg·kg^{-1}) are plotted in Fig. 2. At 2.5 mg·kg^{-1} the CE was unaffected, but the CM and CL were significantly reduced. At 5 and 10 mg·kg^{-1}, all three components were reduced, with the order of inhibition CL > CM > CE. The inhibition of each component was dose-dependent.

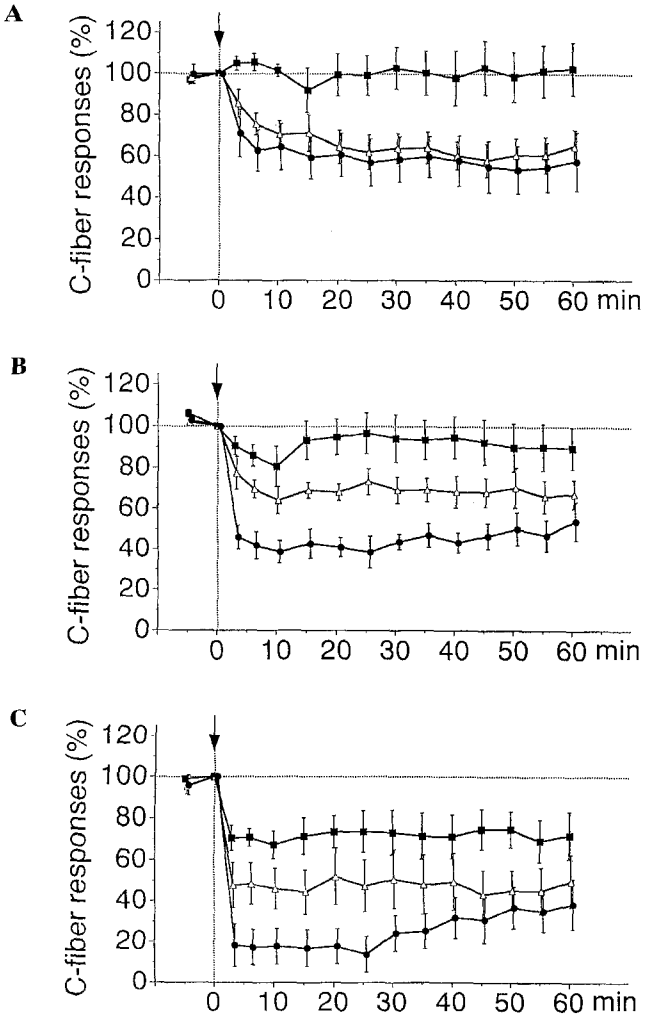

Fig. 2. Time courses of changes in C-fiber responses of wide dynamic range units after ketamine administration (*arrow*): 2.5 mg·kg^{-1} (**A**); 5.0 mg·kg^{-1} (**B**); 10 mg·kg^{-1} (**C**). Each curve represents results in six units. Mean and SE are plotted. *Square*, CE (early component); *triangle*, CM (middle component); *circle*, CL (late component)

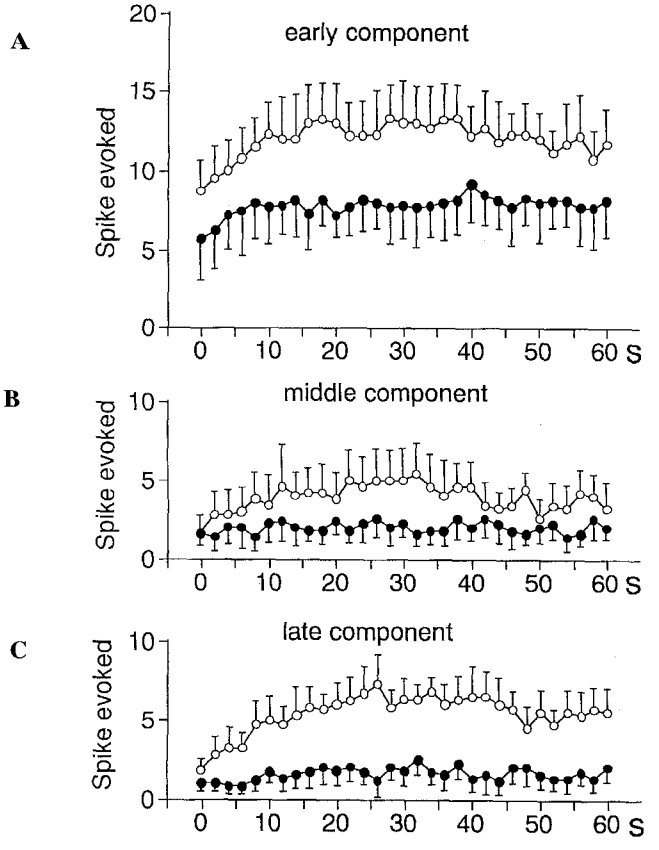

Fig. 3. Effects of intravenous ketamine (10 mg·kg^{-1}) on windup of each component of C-fiber response in WDR units. **A** CE. **B** CM. **C** CL. The number of spikes per stimulus is plotted against time for 30 successive stimuli trials (one stimulus per 2 s). *Open circles*, controls; *solid circles*, postketamine results (10 mg·kg^{-1} 10 min after administration)

C-fiber stimulation at 0.5 Hz produces a progressive increase in the total number of spikes evoked by each stimulus (the phenomenon of windup) [13]. We have examined the effects of intravenous ketamine on the initial C-fiber response evoked by the first stimulus and on the windup. Data are presented graphically as the number of spikes per stimulus in Figs. 3 and 4. Both CE and CL of the C-fiber response showed a windup, which tended to plateau by about 20 s. The initial response was measured as the number of spikes evoked by the first stimulus of each train of 60 successive stimuli at 0.5 Hz and the windup as the mean number of spikes evoked by each stimulus during the plateau period (20–40 s) minus the initial response. The effects of intravenous ketamine ($10\,mg \cdot kg^{-1}$) on the windup of each C-fiber response component are shown in Fig. 3. In CE, shown in Fig. 3A, the initial response and windup were reduced, but the windup remained. In both CM (Fig. 3B) and CL (Fig. 3C), the windup was virtually abolished. The effects of three doses of intravenous ketamine (2.5, 5, and $10\,mg \cdot kg^{-1}$) on the windup of the overall C-fiber response are shown in Fig. 4. The plateau and windup of the overall C-fiber response were significantly reduced by intravenous ketamine. Inhibition of the plateau was dose-dependent.

Effect of intravenous ketamine of A-fiber response of WDR neurons

Changes in the A-fiber response following intravenous administration of ketamine (2.5 and $10\,mg \cdot kg^{-1}$) were

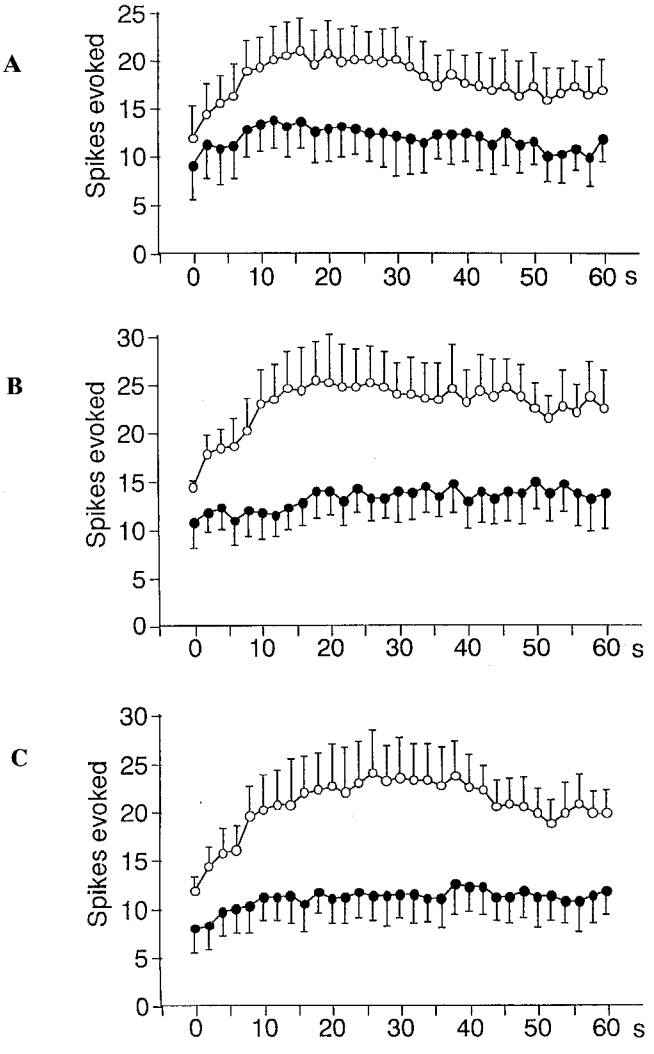

Fig. 4. Effects of intravenous ketamine on overall C-fiber responses of WDR units. **A** Ketamine $2.5\,mg \cdot kg^{-1}$. **B** Ketamine $5\,mg \cdot kg^{-1}$. **C** Ketamine $10\,mg \cdot kg^{-1}$. The total number of spikes per stimulus is plotted against time for 30 successive stimuli (*solid circles*, one stimulus every 2 s). *Open circles*, controls

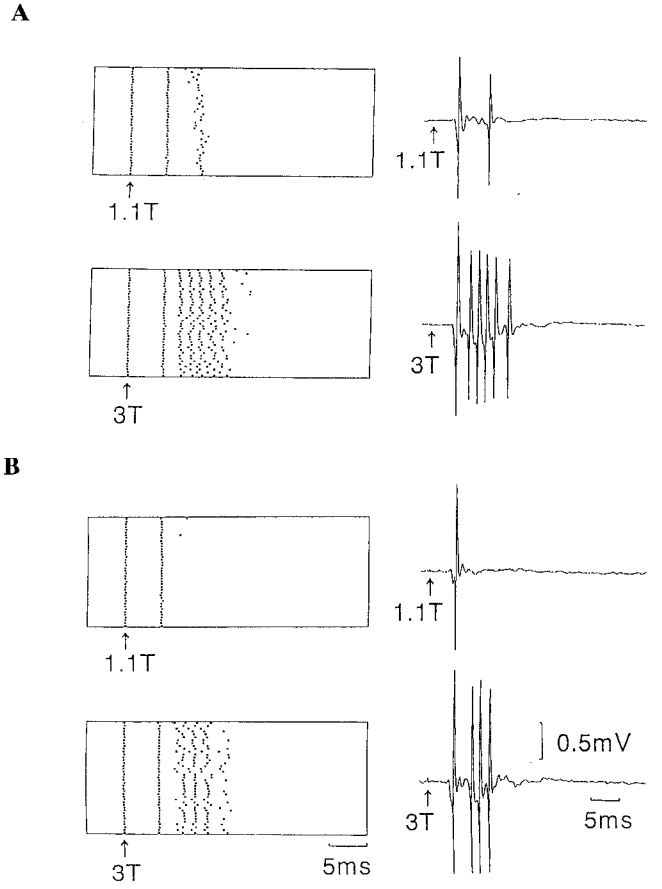

Fig. 5. Effects of intravenous ketamine ($10\,mg \cdot kg^{-1}$) on A-fiber response of a WDR unit. **A** Prior to injection. **B** At 20 min after injection. *Left panels*: Raster-dot displays of responses of the unit to 60 successive electrical stimuli at 1 Hz. *Right panels*: Representative records of spike discharges. Stimulus intensity was either 1.1 or 3.0 times threshold for spike discharges. The duration of each stimulus was 0.1 ms

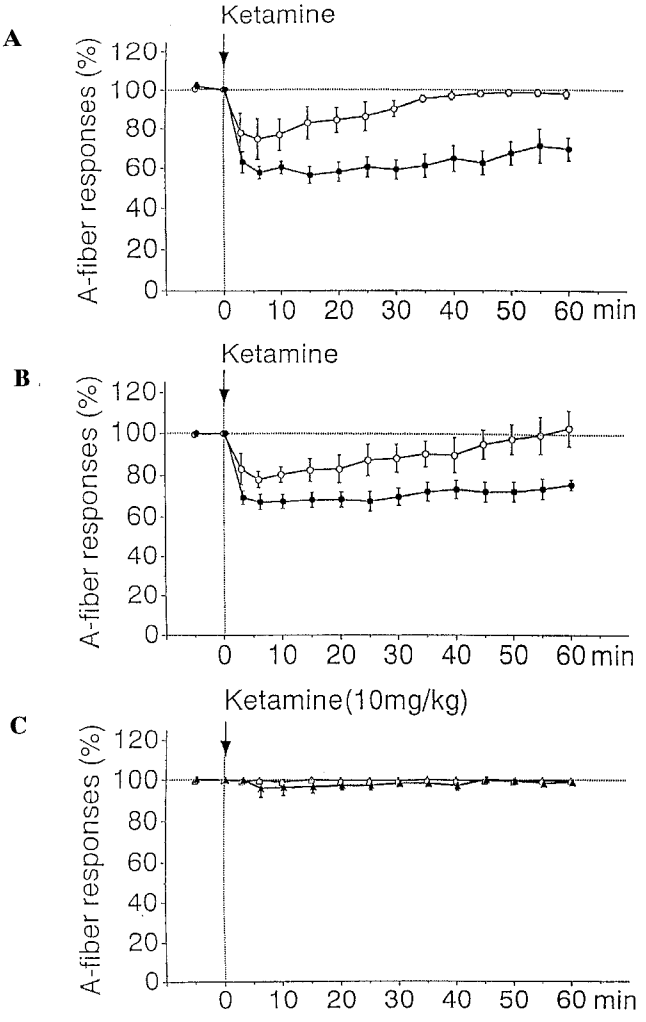

Fig. 6. Mean time courses of changes in A-fiber responses of WDR and low-threshold mechanoreceptive (LTM) units after ketamine administration. **A** Effect of ketamine on A-fiber responses of WDR units evoked at 1.1 times threshold. **B** Effect of ketamine on A-fiber responses of WDR units evoked at three times threshold. **C** Effect of ketamine 10 mg·kg^{-1} on A-fiber responses of LTM units evoked at 1.1 or 3.0 times threshold. Each curve represents results obtained in 5 to 8 units. **A, B** *open circles*, ketamine 2.5 mg/kg; *solid circles*, ketamine 10 mg/kg. **C** *open triangles*, 1.1 T; *solid triangles*, 3.0 T

studied in 13 WDR units. Effects were tested at 1.1 and 3.0 times threshold (1.1 T and 3.0 T) for spike discharges evoked by stimulation of the SP/PT nerves. The total number of spikes evoked by 60 successive stimulations at 1 Hz was measured. At the end of each experiment, the compound action potentials evoked by stimulation of the SP/PT nerves were recorded from an L7 dorsal root filament, and it was confirmed that 1.1 T only Aβ fibers were activated, whereas both Aβ and Aδ fibers were excited at 3.0 T.

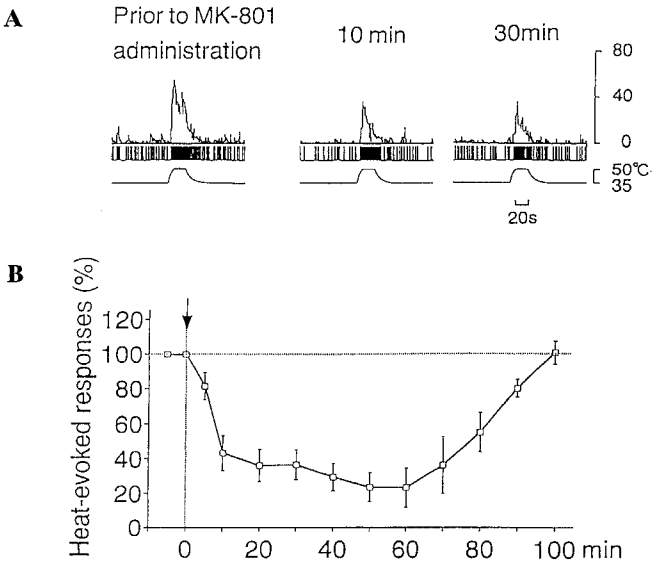

Fig. 7. Effects of intravenous MK-801 on heat-evoked responses of WDR units. **A** Data obtained from a WDR unit. *Top trace*, peristimulus time histogram; *middle trace*, spike discharges; *bottom trace*, skin temperature. **B** Mean time course in four units showing changes in the total number of spikes evoked by noxious heat stimulation (50°C) following intravenous MK-801 (*arrow*) (1 mg·kg^{-1})

An example is illustrated in Fig. 5. At 1.1 T, single, double, or triple spikes of 4.4–10.6 ms latency were elicited. At 3.0 T the number of spikes evoked by each stimulus increased to five to seven. At 20 min after intravenous administration of ketamine 10 mg·kg^{-1} the number of spikes evoked at 1.1 T was reduced by 47.5%, whereas at 3.0 T they were reduced by 24.3%. The mean time courses of inhibition of A-fiber response in six or seven units are plotted in Fig. 6A,B. Responses to both 1.1 T (Fig. 6A) and 3.0 T (Fig. 6B) stimulation were significantly inhibited. The inhibition was dose-dependent.

Effects of intravenous ketamine on responses of LTM neurons

Effects of intravenous ketamine on A-fiber response were studied in six LTM units. The total number of spikes evoked by 60 successive stimuli was counted and pooled. Results are summarized in Fig. 6C. The A-fiber response was unaffected by intravenous ketamine.

Effects of intravenous MK-801 on A-fiber and C-fiber responses of WDR neurons

Effects of intravenous MK-801 on heat-evoked responses were studied in four WDR units that had the

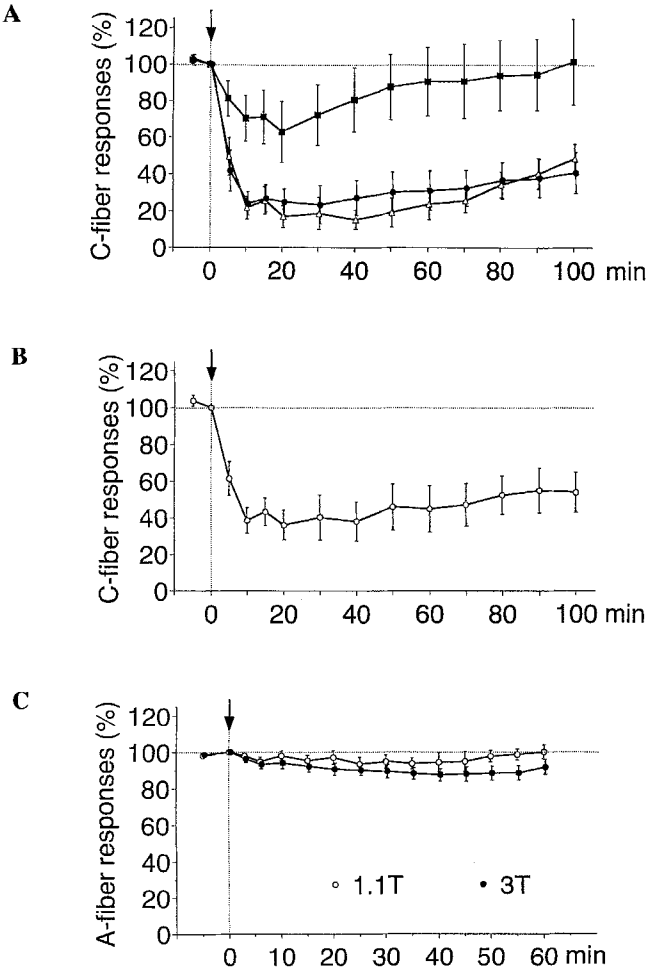

Fig. 8. Mean time courses of changes in A-fiber and C-fiber responses of WDR units after MK-801 administration (*arrows*) (1 mg·kg^{-1}). **A** Each component of C-fiber response (9 units). **B** Overall C-fiber response. **C** A-fiber response (five units). **A** *Solid squares*, CE; *Open triangles*, CM; *Solid circles*, CL. **C** *Open circles*, 1.1 T; *solid circles*, 3.0 T

center of peripheral receptive field in the hind paw pad. Noxious heat stimulation at 50°C was applied to the center for 20 s, and the total number of spikes evoked by the stimulation was counted. An example is illustrated in Fig. 7A, and the results are summarized in Fig. 7B. The heat-evoked response was reduced after intravenous administration of MK-801 (1 mg·kg^{-1}). Suppression was 56.8 ± 10.0% at 10 min after administration and remained around this level for 60 min.

Effects of intravenous MK-801 on A- and C-fiber responses after 60 successive stimulations were studied in 14 WDR units. The results are summarized in Fig. 8. CM and CL were significantly reduced. The maximum inhibition of CE, CM, and CL was 37.1 ± 16.8%, 84.8 ± 5.2%, and 76.8 ± 10.4%, respectively (Fig. 8A). The inhibition of overall C-fiber response was 65.0 ± 8.2% (Fig. 8B). In contrast, the A-fiber response was little affected. Thus the maximum reductions of the A-fiber response tested at 1.1 and 3.0 T were 6.5 ± 3.5% and 13.2 ± 2.7%, respectively (Fig. 8C). These changes were not statistically significant.

The effects of MK-801 on the windup are summarized in Fig. 9. During each component of the C-fiber response, the windup was virtually abolished following MK-801 administration. The changes in the initial response evoked by the first stimulus were not statistically significant.

Discussion

In the present experiments, intravenous ketamine reduced both A- and C-fiber responses of WDR neurons without affecting the A-fiber response of LTM neurons. The intravenous dose of ketamine required to suppress A- and C-fiber responses of WDR neurons was considerably less than the 20 mg·kg^{-1} needed for surgical anesthesia in the cat [14]. In contrast, MK-801 selectively suppressed the C-fiber response of WDR neurons. These results support the clinical argument that ketamine is too nonspecific and not sufficiently potent as an NMDA antagonist to serve as a probe for NMDA receptor-related functions [3,15].

Cutaneous A-fibers include both Aβ- and Aδ-fibers. The Aβ-fibers conduct neural information transduced by nonnociceptive mechanoreceptors. Cutaneous Aδ-fibers in the cat carry signals derived from mechanoreceptors or thermoreceptors (or both). Mechanoreceptive Aδ-afferents can be divided into two major classes on the basis of their adequate stimulus. They are highly sensitive D-hair receptors and high-threshold mechanoreceptors or nociceptors that are some times also responsive to noxious heat. Within the spinal cord, nociceptive and thermoreceptive Aδ-afferents project mostly to laminae I, IIo, and V, whereas D-hair afferents project mostly to laminae IIi and III [16]. WDR neurons in the spinal dorsal horn may receive monosynaptic input from nociceptive Aδ afferents. Furthermore, a significant proportion of WDR neurons subjected to the present study had the low threshold center of peripheral receptive field in the hairless paw pad. Hence the Aδ response of these neurons is likely to represent a nociceptive response.

Nonmyelinated C-fibers in the cat also supply either low- or high-threshold mechanoreceptors together with thermoreceptors. Most of the high-threshold mechanoreceptive C-fibers are polymodal nociceptive fibers. Low-threshold mechanoreceptive C-fibers in the spinal nerve project only in the dorsal column, whereas high-

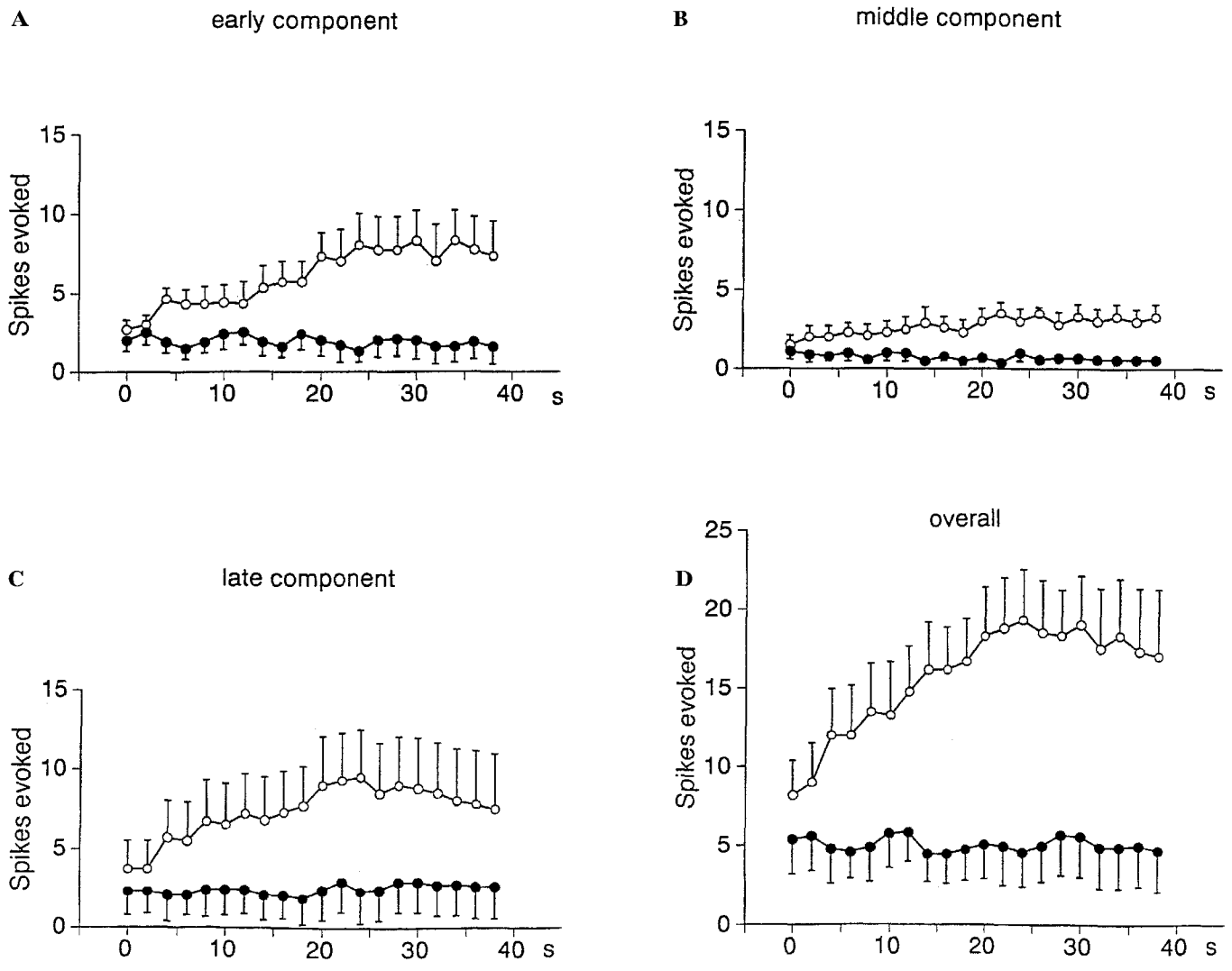

Fig. 9. Effect of MK-801 (1 mg·kg^{-1}) on windup of C-fiber response in WDR neurons. **A** Ce. **B** Cm. **C** Cl. **D** Overall C-fiber response. The total number of spikes in each component or overall C-fiber response per stimulus is plotted against time for 20 successive stimuli trials (one stimulus every 2 s). *Open circles*, controls; *Solid circles*, post-MK-801 results (10 min after administration)

threshold mechanoreceptive C-fibers project through Lissauer's tract or the dorsal column [17]. Peripheral C-fibers are the major primary afferent constituents of Lissauer's tract [18]. It follows that C-fiber input to WDR neurons in the spinal dorsal horn is primarily nociceptive. Hence the present data suggest that ketamine reduces both Aδ- and C-fiber-mediated nociceptive responses of WDR neurons in the spinal dorsal horn.

The C-fiber response of WDR neurons to stimulation of the SP nerve consists of three component: early, middle, and late components [12]. Because the percentage decrease in latency due to a decrease in conduction distance is constant in all three components, separation into three components is due to asynchronous volleys in three classes of C-fibers with different conduction velocities in the SP nerve [12]. The present study showed that the middle and late components are more susceptible to inhibitory action of intravenous ketamine than the early component, suggesting that responses evoked by more slowly conducting C-fibers are more susceptible to the effects of ketamine. Alternatively, residual excitatory effects of the earlier C-fiber response may facilitate later C-fiber responses. Thus inhibition of the late component by ketamine may be exaggerated by inhibition of the early component.

A remarkable property of WDR neurons is the phenomenon of windup, first described by Mendell [13]. Repeated electrical stimulation of nerve fibers innervat-

ing the peripheral receptive field at frequencies higher than 0.3 Hz and at a strength great enough to excite C-fibers causes a progressive increase in the number of spikes evoked in the WDR neuron by each stimulus. The phenomenon appears to originate centrally, as it occurs in the absence of any increase in the size of the incoming volley and has been suggested as the basis for central sensitization [19,20]. It has already been reported that iontophoretic or intravenous ketamine attenuates the windup [10]. The present experiments showed that MK-801 eliminates the windup. It is likely that NMDA receptors contribute to the windup. It has been postulated that the long-lasting excitatory postsynaptic potentials (EPSPs) evoked by each successive C-fiber volley summate to induce gradual depolarization, which progressively relieves the voltage-dependent blockade of NMDA receptors by Mg^{2+} and allows increased transmission via NMDA receptors [10]. The windup is observed in human psychophysical studies [21] and has been suggested to be critical for allowing prolonged firing of central neurons to C-fiber inputs even as these afferent inputs are starting to fail [22].

The NMDA receptor antagonists and NMDA channel blockers modify nociception at the spinal level in experimental animals [23–25]. The present experiments confirmed that MK-801 reduces heat-evoked nociception. Receptors responding to noxious heat stimulation have been reported to occur frequently in the C-fiber group, and nociceptive afferents sensitive to noxious heat are primarily C-fibers in the nerves supplying the hind paw pad in the cat [26].

Both ketamine and MK-801 bind to the phencyclidine (PCP) site of the NMDA receptor-gated ion channel and block NMDA receptors noncompetitively in a use-dependent manner [25]. NMDA receptors primarily mediate C-fiber responses rather than A-fiber responses [10]. Hence both ketamine and MK-801 were expected to selectively suppress C-fiber responses of WDR neurons without affecting the A-fiber responses. In the present experiments, however, ketamine suppressed not only C-fiber but also A-fiber responses of WDR neurons.

Most natural pain involves stimulation of multiple fiber populations. Both Aδ- and C-fiber nociceptors are activated during injury along with other sensory receptors that are not necessarily nociceptive. Persistent clinical pain states associated with past injury consist of ongoing signals on which brief signals evoked by exogenous disturbances are imposed. For example, the recovering burned patient experiences a resting pain presumably mediated by C-fibers, but movement that stretches an injured skin or débridement of the wound causes immediate, short-lived cutaneous pain, which is probably mediated for the most part by Aδ-fibers [27]. Alternatively, the movement-induced pain may be partly due to an allodynia in which even Aβ-fibers can mediate pain. In the present experiments the A-fiber response of WDR neurons was little affected by MK-801 in a dose sufficient to considerably reduce the C-fiber response. It is likely that pain mediated by A-fibers does not involved NMDA receptors. Nevertheless, low-dose ketamine has been used in burn units for dressing changes, débridement, and skin grafting procedures in children [28,29] and adults [30]. Suppression of A- and C-fiber responses by intravenous ketamine, as observed in the present study, may account for this clinical experience.

Antagonists of the NMDA subtype of glutamate receptor (e.g., MK-801) are potentially useful for relieving pain. The present results support this theory. However, some NMDA receptor antagonists cause neurotoxic side effects consisting of pathomorphological changes in neurons of the cingulate and retrosplenial cerebral cortex. MK-801 is no exception. It is more neurotoxic than PCP [31]. Clinical use of MK-801 is limited because of this side effect.

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