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Effects of Ketamine on Nociceptive Cells in the Medial Medullary Reticular Formation of the Cat

Minako Ohtani, M.D., Ph.D., Hirosato Kikuchi, M.D., Ph.D.,* Luke M. Kitahata, M.D., Ph.D.,† Arthur Taub, M.D., PhD.,‡ Hidenori Toyooka, M.D.,* Kazuo Hanaoka, M.D.,* Shuji Dohi, M.D.**

Anatomic, physiologic and behavioral evidence suggests that the neurons in the nucleus reticularis gigantocellularis of the medial medullary reticular formation may act as a relay station for the transmission of nociceptive information from the spinal cord to higher brain centers. The nucleus reticularis gigantocellularis may also be the site of action of analgesic agents, such as ketamine hydrochloride. Utilizing extracellular microelectrodes in 23 decerebrate cats, the authors measured the effect of ketamine on neurons in the nucleus reticularis gigantocellularis that were excited by electrical stimulation of peripheral nerves. The frequency of spontaneous single-unit firing activity in the nucleus reticularis gigantocellularis was suppressed by 31 ± 11 ($\bar{x}$ ± 1 SE) and by 62 ± 7 per cent with ketamine, 1.0 and 2.5 mg/kg, iv, respectively. The frequency of evoked single-unit activity was suppressed by 57 ± 9 and 79 ± 5 per cent with ketamine, 1.0 and 2.5 mg/kg, respectively. Ketamine produces significant depression of single-unit activity of the cells in the nucleus reticularis gigantocellularis, suggesting that this may be an important site of its analgesic action. (Key words: Analgesia. Anesthetics, intravenous: ketamine. Brain: reticular formation.)

KETAMINE HYDROCHLORIDE is a potent analgesic and anesthetic agent both in animals and in man. Although there have been many neurophysiologic investigations related to the effects of ketamine on central nervous system activity,[1,2] its exact mechanism and site of analgesic action in the brain remain unclear. French *et al.*,[3] utilizing macroelectrode recording techniques, demonstrated that anesthetics such as ether and pentobarbital blocked the potentials conducted in the medial ascending pathway of the brain stem, leaving lateral pathways relatively unaffected. Fields *et al.*[4] have shown that the spinoreticular neurons relay information concerning noxious stimuli, and some investigators[5–7] have demonstrated that the nucleus reticularis gigantocellularis forms a relay in this spinoreticular pathway for somatic impulses between the spinal cord and higher brain centers. Furthermore, other investigators[8–11] have demonstrated a correlation between neuronal activity in the medial medullary reticular formation and escape behavior in animals. These studies indicate that the nucleus reticularis gigantocellularis may be a part of the nociceptive system and, hence, the site of action of analgesic agents such as ketamine.

Small-diameter myelinated A-delta and unmyelinated C-fiber activity is necessary for the transmission of nociception. Goldman *et al.*[12] have demonstrated that the stimulation of the small myelinated A-delta fibers of peripheral nerves produced significant responses in the neurons located in the nucleus reticularis gigantocellularis, while stimulation of A-alpha fibers produced no significant response in those neurons. Thus, one can identify the neurons in the nucleus reticularis gigantocellularis by their modality specificity, in that they may preferentially respond to either peripheral noxious stimuli or electrical stimulation at an intensity that evokes activity of A-delta or C-fibers in the peripheral nerve. Utilizing the electrical stimulation technique, the present investigation was undertaken to study the effect of ketamine on the spontaneous and evoked single-unit activity of neurons in the nucleus reticularis gigantocellularis.

Materials and Methods

Studies were made in 23 adult cats of both sexes, weighing 2.2–4.0 kg. During anesthesia with halothane, nitrous oxide, and oxygen, a tracheostomy was performed, and a femoral artery and vein were cannulated with polyethylene tubing for continuous arterial pressure recording and intravenous drug administration. After mounting the head in the Horsley-Clark stereotactic apparatus, electrolytic lesions were made in the midbrain reticular formation for supracollicular decerebration. General anesthesia was discontinued, and the lungs were ventilated with oxygen using a Harvard® pump. Gallamine triethiodide (0.1 per cent) in lactated Ringer's solution was infused intravenously at a rate of 5 to 7 ml/kg/hour to maintain paralysis. End-tidal CO_2 was held at 30–36 torr as measured by an infared gas analyzer. Care was taken to maintain systolic arterial blood pressure above 80 torr, and rectal temperature was maintained at 37 ± 1 C with a thermal servocontrolled warm mattress and an infrared heating lamp.

Bilateral pneumothoraces were made to decrease

* Postdoctoral Research Fellow.
† Professor and Chairman.
‡ Clinical Professor of Anesthesiology.

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Address reprint requests to Dr. Kitahata.

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the respiratory movement of the brain stem. A superficial radial nerve was isolated for the placement of two pairs of silver bipolar electrodes: the distal pair for recording and the proximal pair for stimulating. A paraffin film was placed beneath each nerve to shield it from the surrounding tissue. In addition, the occasional application of warm paraffin oil to the nerve protected it from cooling and drying out.

The snout of the animal was tilted downward 30 degrees from the horizontal plane. Following occipital craniectomy, the brain stem was covered with 4 per cent agar to decrease respiratory movement and to maintain normal body temperature. With the aid of a hydraulic micromanipulator, a tungsten microelectrode with a tip impedance of 9–12 MΩ was inserted into the brain-stem structures 1–2 mm lateral and 1–3 mm rostral to the tip of the obex, to a depth of 2–5 mm. The axis of the microelectrode was angled 18–20 degrees from the vertical line in order to advance the microelectrode tip cephalad.

The stimulation, consisting of a train of ten 1-msec square-wave impulses with an interstimulus interval of 9 msec, was applied to the superficial radial nerve. A stimulus of 1.0–1.5 volts was sufficient to produce supramaximal responses for A-delta excitation. The stimulus train was repeated at one-minute intervals. The neuronal impulses were transmitted through a differential AC preamplifier, displayed on a cathode-ray oscilloscope, and recorded on magnetic tape. The instantaneous frequencies of the spontaneous and evoked activity of a single unit were traced on a polygraph.

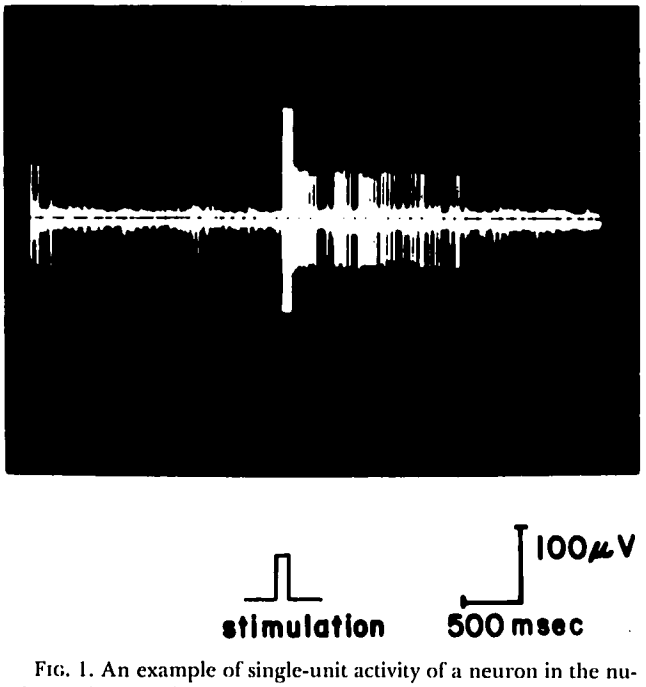

FIG. 1. An example of single-unit activity of a neuron in the nucleus reticularis gigantocellularis before and after electrical stimulation of the contralateral superficial radial nerve (a 100-msec train of ten evenly spaced 1-msec square-wave impulses sufficient to evoke A-delta action potential). Notice the marked increase in the burst of single-unit activity for a few seconds following stimulation.

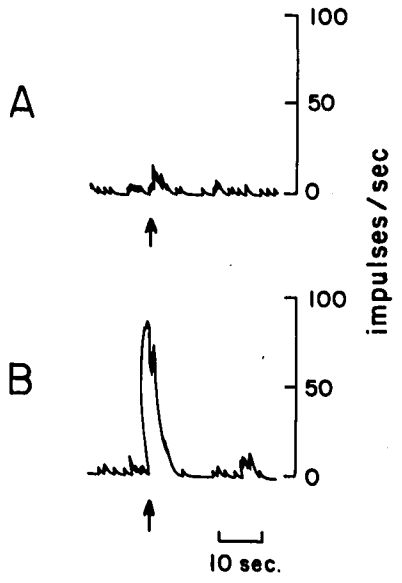

FIG. 2. An example of polygraph tracings of instantaneous firing frequency (impulses/sec) of single-unit activity in the nucleus reticularis gigantocellularis. A 100-msec train of ten pulses, each lasting 1 msec and separated from contiguous trains by 9 msec, was applied to the superficial radial nerve at: *A*, 0.3 volts, supramaximal to large myelinated A-alpha fibers; *B*, 1.3 volts, supramaximal to small myelinated A-delta fibers.

Following the control study, ketamine hydrochloride, either 1.0 or 2.5 mg/kg, was administered intravenously. Neuronal activity was monitored continuously to observe the effect of ketamine on the single-unit activity and to follow the recovery phase of the firing activity. At the end of the experiment, an electrolytic lesion was made by applying direct current through the recording microelectrode. The animal was then sacrificed by inhalation of 100 per cent nitrous oxide. The segment of brain stem with the microelectrode track was fixed in formalin (10 per cent). Frozen sections were cut in a thickness of 30–50 μm and stained with cresyl violet to identify the sites of the recordings. The location of each lesion within the nucleus reticularis gigantocellularis was verified histologically.

Data recorded on magnetic tape were analyzed off-line using a general-purpose digital computer (DEC PDP-11/40). The differences between mean values of spontaneous and evoked firing rates obtained during the control period, after the administration of ketamine, and during the recovery phase were assessed for significance by the Student *t* test.

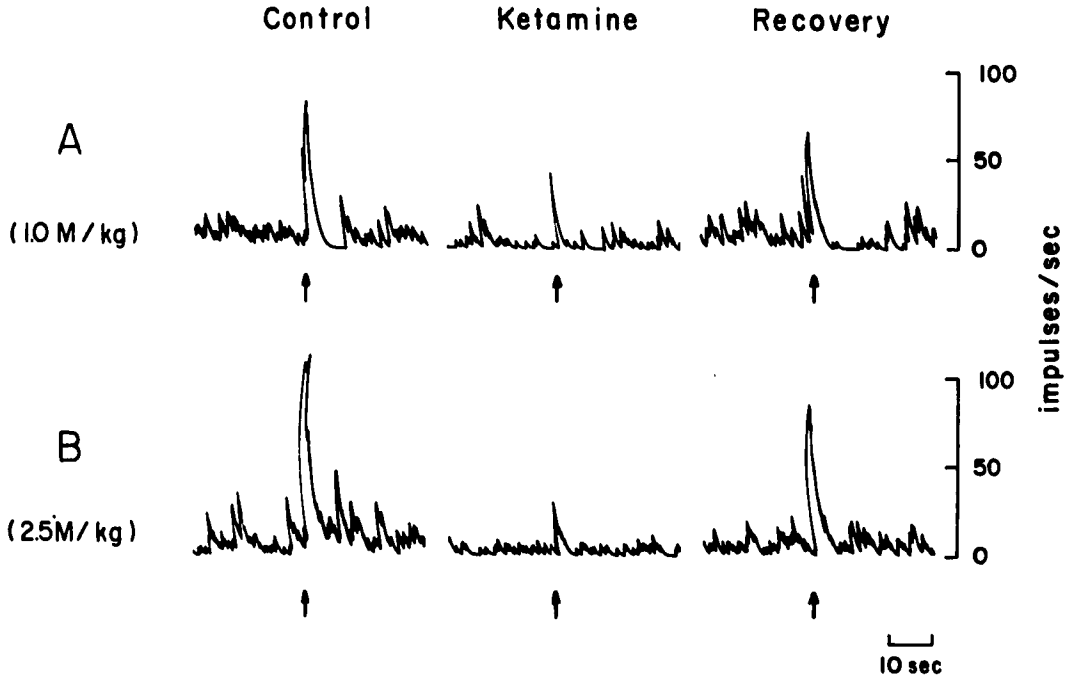

FIG. 3. An example of polygraph tracings of instantaneous firing frequency (impulses/sec) of single-unit activity in the nucleus reticularis gigantocellularis during the control period (*left column*), 5 min after administration of ketamine hydrochloride, 1.0 mg/kg (*A*), and 2.5 mg/kg (*B*), iv, and during the recovery period (*right column*). Activity in the nucleus reticularis gigantocellularis unit was evoked at the arrows by superficial radial-nerve stimulation with a 100-msec train of ten pulses at 1.0-volt intensity and 1-msec duration, with an interstimulus interval of 9 msec. Notice the graded suppression of spontaneous activity, as well as evoked activity, by increasing doses of ketamine hydrochloride.

Results

The 23 single units that responded to the A-delta stimulation of a superficial radial nerve were studied. The firing rate increased following electrical stimulation of the superficial radial nerve (fig. 1). The vast majority of neurons responded to electrical stimulation with an initial burst of spike activity, lasting 1–4 sec (fig. 2). The frequency of both spontaneous activity (11 ± 3 impulses/sec) and evoked activity (29 ± 4 impulses/sec) was suppressed by ketamine, 1.0 and 2.5 mg/kg (table 1). Full recovery occurred by 20 min. An example of these effects on the activity of a single neuron is shown in figure 3.

TABLE 1. Effects of Ketamine Hydrochloride, 1.0 and 2.5 mg/kg, Intravenously, on Spontaneous and Evoked Single-unit Activity of Neurons in the Nucleus Reticularis Gigantocellularis

Ketamine (mg/kg)	Number of Experiments	Maximum Suppression of Spontaneous Activity (Per Cent Decrease from Control)	Maximum Suppression of Evoked Activity (Per Cent Decrease from Control)
1.0	7	31 ± 11*	57 ± 9*
2.5	16	62 ± 7*	79 ± 5*

* Significantly different, $P < 0.01$.

Discussion

Kitahata *et al.*[13] have demonstrated that ketamine given intravenously suppresses preferentially both spontaneous and evoked single-neuron activity of cells in Rexed laminae I and V, which are associated with nociception, whereas it does not affect the activity of neurons in Rexed laminae IV and VI, which are not associated with nociception but are low-threshold mechanoreceptors and proprioceptors, respectively. The same manner of lamina-specific effects was also shown for nitrous oxide[14] and morphine.[15] This explains a probable mechanism at the spinal level for anesthetic agents.

Fields *et al.*[4] have shown that the spinoreticular pathway is a part of a somatosensory projection concerned with noxious stimuli, that it projects to the nucleus reticularis gigantocellularis, and that its cell bodies are located deep to lamina V of the feline spinal cord, and the nucleus reticularis gigantocellularis area was suggested to be an integral part of the central pain-perception mechanism.[10] Spencer *et al.*[16] reported that the evoked activity of single neurons in the nucleus reticularis gigantocellularis was suppressed by nitrous oxide, although the spontaneous activity showed variations in responses to it. With morphine, however,

spontaneous and evoked activities of the excitatory and inhibitory neurons in the nucleus reticularis gigantocellularis were suppressed.[17] The results of our study demonstrate that ketamine suppresses activity, both spontaneous and evoked, in single neurons in the nucleus reticularis gigantocellularis following high-intensity electrical stimulation of peripheral neurons. The extent of suppression of the nucleus reticularis gigantocellularis neurons by comparable doses of ketamine is greater than that in the dorsal horn of the lumbar spinal cord, since the spontaneous and evoked activity in Rexed lamina V was reported to be suppressed by 43 and 64 per cent, respectively, with ketamine, 2.5 mg/kg.[13] Thus, it may be concluded that since a greater effect of ketamine is seen in the nucleus reticularis gigantocellularis than in lumbar dorsal-horn cells, its total effect on activity in the nucleus reticularis gigantocellularis is more likely to be related to the analgesic action of the drug.

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