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Ketamine-induced peripheral analgesia in rats

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KEY WORDS ketamine; electric stimulation; electromyography; pain measurement; analgesia; naloxone

AIM: To examine whether ketamine may directly act at peripheral nociceptors to produce analgesia. **METHODS:** Wistar rats were anesthetized with urethane. As a nociceptive flexion reflex (FR), C responses from the posterior biceps semitendinosus (PBST) muscle was evoked by electrical stimulation (2 ms, 80 V, 2-3 pulses, 0.5 Hz) via a pair of stainless steel needles inserted subcutaneously applied to the two toes of ipsilateral hindpaw. **RESULTS:** Subcutaneous injection of ketamine (36 mmol·L^{-1}, 5 μL) into the ipsilateral hindpaw produced an inhibition of C responses. At 9 min after application of ketamine, injection of naloxone (1 %, 5 μL) into the same area annulled ketamine-induced inhibition. **CONCLUSION:** Ketamine as a dissociate anesthetic acts on peripheral nociceptors to produce analgesia, which is related to activity of peripheral opioid receptors.

Ketamine as a dissociate anesthetic at very low dose (0.2 mg·kg^{-1}) produces analgesic effect in clinic[1]. Since ketamine is a selective channel antagonist for *N*-methyl-*D*-aspartate (NMDA) receptor, the central mechanism of ketamine-induced analgesia may be attributed to blockade of NMDA receptor-mediated spinal transmission of nociceptive information[2,3]. However, in our previous study[4], it has been shown that topical application of ketamine to the peripheral nerve powerfully blocked nerve conduction, suggesting that peripheral mechanism might be involved in analgesic effect of ketamine. The aim of this work was to analyze the peripheral analgesia of ketamine.

MATERIALS AND METHODS

Wistar rats (n = 15) weighting 278 ± s 24 g (Shanghai Animal Center, Chinese Academy of Sciences) were anesthetized with urethane (1.1 g·kg^{-1}, ip, initially) and fixed in a stereotaxic frame. Body temperature, the color of the plantar region, and blood pressure were maintained within normal limits.

As a nociceptive flexion reflex (FR), the firing of electromyography (EMG) from the posterior biceps semitendinosus (PBST) muscle was evoked by electrical stimulation (2 ms, 80 V, 0.5 Hz, 2-3 pulses, at 5-min intervals) via a pair of stainless steel needles inserted subcutaneously to the two toes of ipsilateral hindpaw[5]. To obtain a stable recording, urethane was supplemented to keep a stable anesthesia. The firing of EMG was averaged at 5-min intervals and a stable baseline was established for at least 20 min before medication. The drugs were injected sc into the paw between the two hind-toes stimulated. The effect of ketamine on FR was expressed as the change in the reflex magnitude compared to baseline. The data were expressed as $\bar{x} \pm s$ and analyzed by t test.

RESULTS

The firing of EMG in PBST reflex by electric stimulation of hind-digits exhibited two components, the A response with a short latency and C response with a long latency (Fig 1), which were evoked by A- and C-afferent input, respectively[5]. In this study, nociceptive C component in the flexion reflex was tested.

Ketamine injected into the ipsilateral hindpaw produced a marked inhibition of C responses in FR. Five minutes after injection of ketamine (36 mmol·L^{-1}, 5 μL), the averaged C responses were reduced by 40 % ± 7 % (n = 4), which returned to normal level 30 min after injection of ketamine. In contrast, ipsilateral injection of saline or contralateral injection of ketamine at the same dose failed to produce inhibition of C response. When a high dose of ketamine (180 mmol·L^{-1}, 5 μL, sc) was ipsilaterally injected, C responses in FR were significantly reduced by 85 % ± 7 % (n = 4). The inhibition lasted over 30 min (Fig 2).

During the maximal inhibition by ketamine, 1 % naloxone (5 μL) was injected sc into the same

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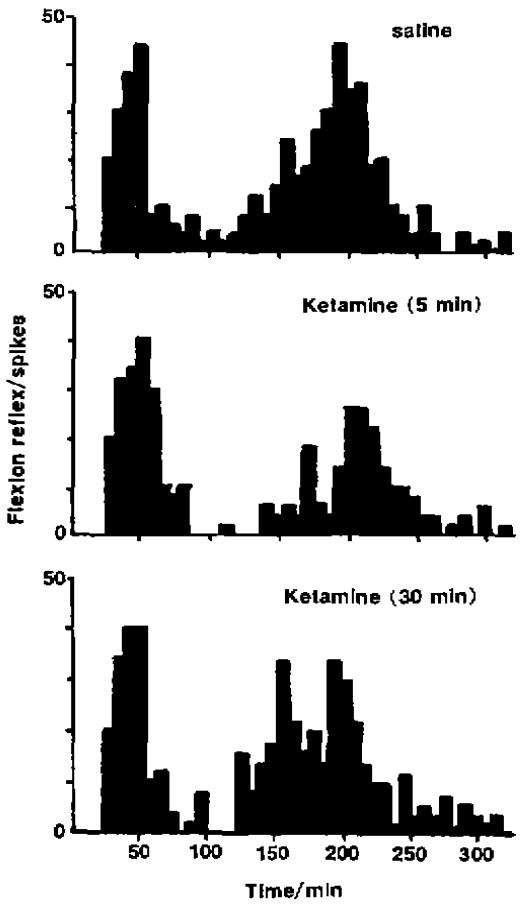

Fig 1. Inhibition on C response of flexion reflex by ketamine (36 mmol·L^{-1}, 5 μL). $\bar{x}$ of 4 responses.

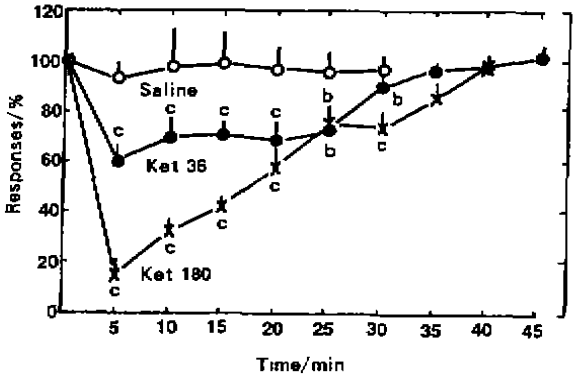

***Fig 2.* Effect of ketamine on C responses of flexion reflex (n = 4) by injection of 5 μL of saline or ketamine 36 or 180 mmol·L^{-1}. $^bP<0.05$, $^cP<0.01$ *vs* saline.**

area. Ketamine-induced inhibition was completely annulled 10 min after injection of naloxone, whereas there was no effect of injection of saline on ketamine-induced inhibition. When ketamine (180 mmol · L^{-1}) was applied to the contralateral hind toes, less inhibition of C responses was obtained (36 % ± 8 %, n = 5). The recovery time was 20 min, which was shorter than that of ipsilateral injection-induced inhibition (Fig 3).

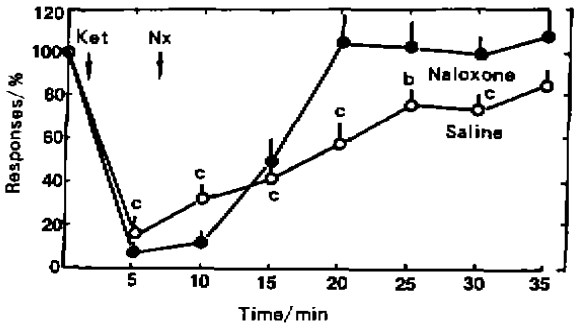

***Fig 3.* Effects of 5 μL of saline or 0.1% naloxone injected sc 9 min after ketamine-induced inhibition of C responses of flexion reflex. n = 4 rats. $\bar{x} \pm s$.**
$^bP< 0.05$, $^cP<0.01$ *vs* control (Ctr).

To test local anesthetic effect, ketamine (180 mmol · L^{-1}) produced a complete inhibition of C responses were selected in the 4 rats. When the current intensity of stimulation was enhanced (from 80 V, 2 pulses to 100 V, 5 pulses) during the period of inhibition, C responses were still evoked. In contrast, when C response was inhibited by procaine (1 %, 5 μL) instead of ketamine, increasing current failed to evoke C response.

DISCUSSION

The results first demonstrated that ketamine directly act on the peripheral receptive field, where there exist abundant nociceptors, to produce analgesia. As ketamine is a central anesthetics, an involvement of the central action in inhibition of C responses would be considered due to the diffusion of drugs. If this case occurs, there would be no difference between ipsi- and contra-lateral application of drug. However, ketamine-induced inhibition at a low dose (36 mmol · L^{-1}) was produced only by its ipsilateral application. Although the contralateral application of ketamine at a high dose (180 mmol · L^{-1}) also produced an inhibition of C responses, suggesting its central actions, the inhibition by ipsilateral application was

much powerful than that by contralateral. These data show ketamine-induced peripheral analgesia.

The mechanisms of ketamine-induced peripheral analgesia remain unclear. In the earlier *in vitro* studies[6,7], both sodium and potassium channels were affected by ketamine in the myelinated axons, suggesting that ketamine-induced blockage of conduction of the peripheral nerve probably resulted from non-synaptic inhibition of Na^+ current. Since there was no effect of ketamine on inactivation of Na^+ current[6], ketamine seems to differ from the local anesthetics. The facts that there exists a difference between ketamine- and procaine-induced effects and naloxone reverses ketamine-induced inhibition in our study support this view.

The opioid receptors are densely distributed in the peripheral nerve terminals and are implicated in antinociception[8]. In the present study, reversal of ketamine-induced peripheral analgesia by naloxone strongly suggests that the action of ketamine is closely related to activity of peripheral opioid receptors.

As mentioned in introduction, ketamine as a NMDA receptor antagonist produces inhibition of nociceptive responses of pain-sensitive neuron in the spinal cord[2]. A recent report showed that glutamate, aspartate and arginine concentrations in rat knee joint cavity were increased with inflammatory pain[9]. Therefore, it should be considered whether NMDA receptor might be contributed to ketamine-induced peripheral analgesia.

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氯氨酮引起的大鼠外周镇痛作用

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关键词 氯氨酮; 电刺激; 肌电描记术; 测痛; 镇痛; 纳络酮

目的: 研究氯氨酮是否可以直接作用于外周伤害性感受器而产生镇痛. **方法**: 一对不锈钢针插入尿酯麻醉的大鼠一侧后肢的两足脂皮下, 施加强电流(2 ms, 80 V, 2 - 3 脉冲, 0.5 Hz)作为伤害性刺激, 在同一后肢的后二头半腱肌记录肌电反应, 电刺激引起的长潜伏期 C 成分, 作为伤害性屈反射的指标. **结果**: 在邻近刺激电极的距部皮下注射氯氨酮(36 mmol·L^{-1}, 5 μL)可明显抑制 C 反应, 注射氯氨酮后 9 分钟, 在同一部位注射 5 μL 的 1 % 纳络酮, 可翻转抑制效应. **结论**: 氯氨酮可直接作用外周伤害性感受器产生镇痛, 并提示可能与外周阿片受体的激活有关.