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Effects of cysteamine on flexion reflex facilitation by C–primary afferents in cats[1]

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ABSTRACT Brief (20 s) conditioning stimuli at C–fiber intensity applied to the sural or gastrocnemius nerve evoked a facilitation of the flexor α–motoneurone discharges from small filaments of the posterior biceps semitendinosus nerve produced by subcutaneous stimulation of the plantar region in anesthetized spinal cats. Such C afferent–induced facilitation was blocked reversibly by cysteamine (50 mg · kg^{-1}), a somatostatin depletor, without affecting the basic mechanisms of flexor reflexes, suggesting an important role played by somatostatin in transmission and / or modulation of nociceptive information in the spinal cord

KEY WORDS nociceptors; spinal cord; cysteamine; somatostatin

Numerous immunohistochemical studies have demonstrated the presence of somatostatin in small dorsal root ganglion neurones and in the substantia gelatinosa of the spinal dorsal horn where nociceptive primary afferents terminate[1–3]. Some physiological evidences suggest that somatostatin may be involved in the transmission and / or modulation of nociceptive information[4–6]. Its functional role, however, is controversial[7,8].

Cysteamine (2–mercaptoethylamine) is a thiol reagent which has been found to be able to deplete selectively somatostatin–like immuno– reactivity in the CNS of the rat when administered systematically[1,9,10]. It therefore seems to be a useful tool for investigating the role of Somatostatin in nociceptive transmission in the spinal cord. The present work was designed to show the effects of cysteamine on a prolonged facilitation of the flexor withdrawal reflex produced by conditioning stimuli at C–fiber strength applied to peripheral nerves.

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METHODS

Twenty–two cats of either sex weighing 2.5–3.5 kg were used. As a routine, cats were anesthetized initially with sodium pentobarbitone (40 mg · kg^{-1}, ip) and paralysed with gallamine triethiodide (4 mg · kg^{-1}, iv). Artificial ventilation (with end–tidal CO_2 levels at 3.5–5.0%) was instituted throughout the experiment. An infusion pump delivered both pentobarbitone (2 mg · kg^{-1} · h^{-1}) and gallamine (4 mg · kg^{-1} · h^{-1}) continuously to the cat throughout the recording period. Blood pressure and body temperature were maintained within physiological range. The spinal cord was transected at the lower thoracic level. The averaged responses of flexor α–motoneurones recorded from the filaments of the nerve innervating the posterior head of the biceps femoris and semitendinosus (PBST) muscle were evoked by electric stimulation (1 mA, 0.2 ms, 0.5 Hz) through 2 stainless steel needles inserted subcutaneously into the plantar region of the ipsilateral hindlimb. The sural and gastrocnemius nerves were prepared for conditioning stimulation with intensity strong enough to activate C–fibers (5 mA, 0.5 ms).

RESULTS

C afferent–induced facilitation of flexor response of α–motoneurones Electrical

stimulation of the plantar region at non-noxious intensity at 0.5 Hz evoked a stable polysynaptic reflex with a short latency (10 ms) in PBST motoneurones. When a conditioning stimulus was applied to the sural for 20 s at intensity enough to activate C-fibers, polysynaptic reflexes were markedly facilitated from 43.3% ± SD 20% to 345% ± SD 153% (mean 139% ± SD 95%, $n=30$) of the control value for 4.6 ± 3 min. There was no change in the amplitude of the reflex following a A-fiber conditioning stimulus (1 Hz, 20 s) applied to the sural nerve (Fig 1). A similar increase from 46.7% ± SD 30% to 353.3% ± SD 254% (mean 133% ± 79%, $n=26$) of the control in polysynaptic reflex was also observed when a C-fibers conditioning stimulus was delivered to the gastrocnemius nerve (Fig 2).

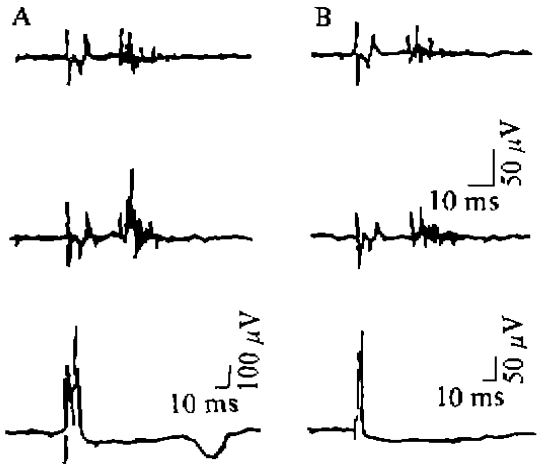

Fig 1. Effect of conditioning stimulation of sural nerve on PBST polysynatic reflex. Sural stimuli at 1 Hz for 20 s at C-fiber intensity (A) and at A-fiber intensity (B). Upper tracing: averaged control responses ($n=8$) evoked by electric stimulation of plantar region (1 mA, 0.2 ms, 0.5 Hz). Middle tracing: 10 s after conditioning stimuli. Lower tracing: compound action potential in the sural nerve by conditioning stimulus. Calibration: A) 100 μV, 10 ms; B) 50 μV, 10 ms.

Depression of facilitation in flexor α-motoneurones by cysteamine In 11 cats,

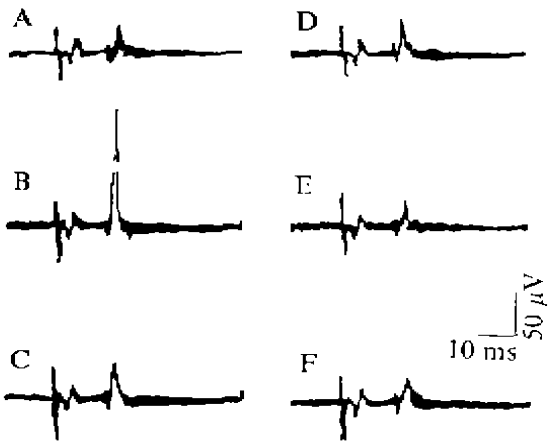

Fig 2. Facilitation of PBST polysynaptic reflex produced by conditioning stimulation of the gastrocnemius nerve at 1 Hz for 20 s at C-fiber intensity. A, Averaged control response ($n=8$) produced by stimulation of the plantar region. B – F indicate 10 s, 1, 3, 5 and 7 min respectively after conditioning stimuli. Calibration: 50 μV, 10 ms.

cysteamine (50 mg · kg^{-1}, iv) produced a reversible depression of C afferent-induced facilitation without affecting the level of the polysynaptic reflexes (Fig 3).

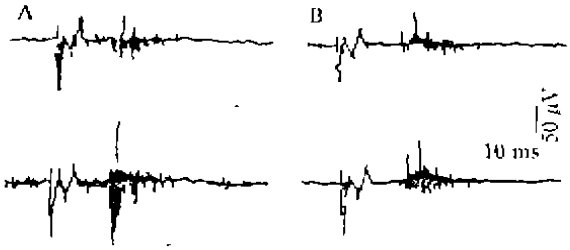

Fig 3. Inhibitory effect of cysteamine on sural-induced facilitation of the PBST polysynaptic responses. A) Before; B) 4 h after iv cysteamine 50 mg · kg^{-1}. Upper tracing: averaged control response ($n=8$); Lower tracing: sural-induced facilitation response showing abolition of facilitation. Calibration: 50 μV, 10 ms.

The degree of facilitation was profoundly reduced and the duration was shortened (Fig 4). The onset and the peak of cysteamine-induced depression were 1 h and 4 h,

respectively, after injection of cysteamine (50 mg • kg^{-1}) and the recovery time was over 8 h. When the dose of cysteamine was increased to 100 mg • kg^{-1}, no significant differences in the onset and the peak of the reduction were seen. The recovery time, however, was prolonged to 16 h or more. When cysteamine (2–5 mg) was intrathecally administered, a similar results were seen in 2 cats tested.

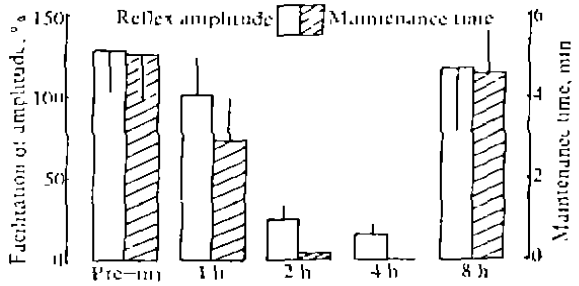

Fig 4. Facilitation of the PBST reflexes after iv cysteamine 50 mg • kg^{-1}.

DISCUSSION

The present experiments in cats tend to confirm the previous observations in rats that brief conditioning stimuli at C–fiber, but not A–fiber, intensity to peripheral nerves elicited a prolonged facilitation of the flexor α–motoneurones[11,12]. On the basis of involvement of the C polymodal nociceptors, associated dominantly with C fibers, in pain, it is reasonable to assume that such facilitation reflects pain hypersensitivity.

The present results have shown that cysteamine reduced the C afferent–induced facilitation without altering the amplitude of polysynaptic reflex in the absence of conditioning stimulus, indicating that the effect of this somatostatin depletor is highly selective to C–fiber mediated nociceptive transmission. It is consistent with our recent observation that cysteamine, when administered microelectrophoretically into the substantia gelatinosa where somatostatin–containing fibers terminate, could inhibit selectively nociceptive responses of dorsal horn neurons. Moreover, somatostatin was released in the spinal substantia gelatinosa produced by noxious peripheral stimuli[13] and the time course of reduction in C afferent–induced facilitation by cysteamine in this study was found to run in parallel with that of somatostatin depletion by cysteamine[14]. Taken together, it was therefore conceivable that selective depression of nociceptive responses by cysteamine might be resulted from somatostatin depletion in somatostatin–containing primary afferent neurons conveying nociceptive signals[9].

It is noteworthy that the time course of facilitation by activation of cutaneous C afferent (sural) is similar to that by muscle C afferent (gastrocnemius) in the cat, and that cysteamine non–selectively depresses both the cutaneous C and muscle C afferent–induced facilitations. These results provide a hint that somatostatin might act as a neurotransmitter or neuromodulator in a variety of C–induced facilitation associated with hyperalgesia, despite of possible involvement of different peptides in transmission of different modalities of pains *per se*[4].

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半胱胺对刺激猫 C 传入纤维引起的屈反射易化的阻抑作用

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提要 电刺激麻醉猫的膝肠或腓肠肌神经 C 纤维，可易化皮肤刺激引起的后二头半腱肌神经细束的反射性放电。生长抑素静空剂半胱胺(50 mg·kg^{-1}, iv)明显减小易化效应，而对多突触反射的振幅没有影响。提示生长抑素可能参与脊髓伤害性信息的传递和调制。

关键词 伤害性感受器；脊髓；半胱胺；生长抑素

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Effect of ubiquinone on ischemic arrhythmia in conscious rats[1]

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ABSTRACT Ubiquinone 6.2, 12.5 or 2.5 mg·kg^{-1} respectively twice iv 24 h and 30 min before coronary artery ligation, ameliorated the ischemic arrhythmia in conscious rats, and there was a close positive correlation between the ubiquinone concentration in myocardium and plasma and its anti–arrhythmic effect. Ubiquinone iv 3.1, 6.2, and 12.5 mg·kg^{-1} increased, while 25 mg·kg^{-1}

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