ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Jul; 22 (7): 603 - 608
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Effects of cysteamine on nociception in mice

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KEY WORDS cysteamine; pain measurement; analgesics

ABSTRACT

AIM: The present study was carried to study the effects of cysteamine on nociception in mice. **METHODS**: The pain assays were the hot plate and the tail flick test. **RESULTS**: When cysteamine, a drug well known as a somatostatin depletor, was administered 1 and 4 but not 24 h before the tests (hot plate, tail flick), the nociceptive threshold was elevated when the drug was administered at high doses (50 and 100 mg/kg) while at a lower dose (10 mg/kg), it was able to elevate the nociceptive threshold in the hot plate test only. In the hot plate as well the tail flick test cysteamine effects are reversed by naloxone administration and potentiated by morphine administration, whereas neither somatostatin nor cyclo-(7-aminoheptanoyl-Phe-D-Trp-Lys-Thr Bzl], a reported somatostatin antagonist, changes cysteamine effects. **CONCLUSION**: These results suggest that cysteamine effects on the nociceptive threshold in the hot plate and tail flick test may be mediated by cysteamine interference with the opioid system.

INTRODUCTION

Cysteamine (β-mercaptoethylamine) is a thiol compound whose biological activities have recently received great attention, and that can be found in animals when acetyl coenzyme A is hydrolized by pantethinase[1]. Clinically it has been used in the treatment of acetaminophen poisoning[2] and in the treatment of nephropathic cystinosis[3]. It was reported that cysteamine depletes somatostatin in the stomach, duodenum, pancreas, gut and hypothalamus of rats[4]. Cysteamine was also found to deplete somatostatin in the brain[5,6] and spinal cord[7]. This depletion is observed within minutes after administration, reaches maximal values 4 h after the administration, and is absent within 24 – 78 h after the administration[8]. Furthermore, assays performed on CSF and on cortical somatostatin levels in same animals showed that cysteamine induced depletion of cortical somatostatin was accompained by parallel increase in CSF levels of somatostatin[9]. The lack of cysteamine effects on other peptides such as luteinizing hormone-releasing hormone, arginine, vasopressin, substance P, β-endorphin, vasoactive intestinal polypeptide, thyrotropin releasing hormone, neuropeptide Y and cholecystokinin octapepetide[5,10-12] suggested that cysteamine may be a potentially useful pharmacological tool for understanding the role of somatostatin in the central nervous system. However, cysteamine also reduced pituitary prolactin levels[13] and, following administration of high dose, inhibited dopamine-β-hydroxylase activity, with cortical changes in norepinephrine and dopamine levels[9,14,15].

Few data are available on the effects induced by cysteamine on nociception in animals. Recently, we have demonstrated that cysteamine was able to modify the nociceptive response induced by chemical and electrical stimuli and that these effects may be mediated by somatostatin[16,17]. Previous studies performed in order to investigate the possible role exerted by somatostatin in nociception, indicated that cysteamine administration elevated the nociceptive threshold in the tests involving prolonged and inflammatory pain induced by chemical stimuli, but did not change the nociceptive response induced by acute stimuli[7,18]. In this report we further investigate the effects induced by cysteamine on the nociceptive threshold by using hot plate and tail flick tests. Furthermore, since Haroutunian *et al* (1987) suggested that some effects of cysteamine may be attributed to cysteamine induced somatostatin depletion or alternatively, to the non-physiological release of somatostatin in CSF, in our experiments we investigated the possibility that somatostatin or cyclo [7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr(Bzl)]-a reported somatostatin antagonist[19] may interfere with

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Received 2000-10-09 Accepted 2001-04-05

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Jul; 22 (7)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

cysteamine effects on the nociceptive threshold. In addition we also investigated the possible involvement of the opioid system in cysteamine induced effects.

MATERIALS AND METHODS

Animals Male CD-1 mice (Charles River Italy) weighing 25 g – 30 g were used in the experiments. The animals were housed in colony cages (5 mice each) with free access to food and water prior to the experiments. They were maintained in a climate and light controlled room (22 ℃ ± 1 ℃, 12/12 h dark/light cycle with light on at 07:00) for at least 7 d before testing. Testing took place during the light phase. The animals were brought to the test room for at least three hours before testing. Each animal was used only in one experimental session. In all experiments attention was paid to the ethical guidelines for investigations of experimental pain in conscious animals[20] and all the procedures were approved by the Animal Care Committee of the Istituto Superiore di Sanità.

Hot plate test Mice were tested with the hot plate in accordance with the methods described previously[21] which were later modified[22]. The device (Ugo Basile, Italy) consisted of a metal plate (25 cm × 25 cm) heated to a constant temperature, on which a plexiglass cylinder (20 cm diameter and 16 cm height) was placed. The hot plate was set to a plate temperature of 55.0 ℃ ± 0.5 ℃. The time of hind paw licking was recorded, and the measurement was terminated if the licking exceeded the cut-off time (60 s). Each mouse was tested 60 and 30 min before drug administration in the baseline latency determination and only once after drug administration.

Tail flick test Tail flick latency[23,24] was obtained using a tail flick unit (Ugo Basile, Italy) consisting of an infrared source (100 W bulb) whose radiant light with adjustable intensity was focused by an aluminized parabolic mirror on a photocell. Radiant heat was focused on a blackened spot 1 – 2 cm from the tip of the tail, and the latency until the mouse flicked its tail was recorded. Beam intensity was adjusted to give a tail flick latency of 2 – 3 s in control animals. The animals were restrained during the trials by means of a plexiglass cylinder 4 cm in diameter and 8 cm long. Each mouse was tested 60 and 30 min before drug administration for the baseline latency determination and only once after administration. The measurement was terminated if latency exceeded the cut-off time (10 s) to avoid tissue damage.

Drugs and administration routes On the day of testing all drugs used in the experimental sessions were dissolved in saline for the administration. Drugs were injected in a volume of 5 mL/kg for ip and sc administrations whereas for intracerebroventricular (icv) and intrathecal (it) administrations, they were injected in a volume of 2.5 μL/mouse.

Cysteamine solution was neutralized to pH 7.2 ± 0.2 using NaOH 1 mol/L. The injection was performed using a modification of the method of Haley and McCormick[25] as described by Porreca *et al*[26]. The it injection was administered according to the method of Hylden and Wilcox[27] using a 10-Hamilton syringe with a 27-gauge needle. At the end of the experimental session, the injection site was verified by using 1 % methylene blue and examining the distribution of the dye in the cerebrum and the spinal cord. Cysteamine (Sigma, Chemical, USA) was administered ip at doses of 10, 50, 100, and 200 mg/kg; morphine hydrocloride (Carlo Erba, Italy) was administered sc at doses of 0.5 or 1 mg/kg; naloxone hydrocloride (Sigma Chemical, USA) was administered sc at the dose of 1 mg/kg; somatostatin (Sigma Chemical, USA) was administered icv and it at the dose of 0.1 μg/mouse; cyclo(7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl) (Sigma, Chemical, USA) was administered icv and it at the dose of 0.1 μg/mouse.

The doses of cysteamine, naloxone, and morphine were calculated as the weight of the base; peptide purity was not checked, and the concentrations were calculated according to the purity quoted from the source.

Experimental protocol Since previous works indicate that in the mouse, cysteamine causes time-dependent somatostatin depletion (see Introduction), in preliminary experiments we investigated whether cysteamine injected 1, 4 and 24 h before the tests might be able to change the response to nociceptive stimuli. Following these experiments, the effects of somatostatin, cyclo-(7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl), naloxone, and morphine on cysteamine-induced antinociception were investigated in cysteamine pretreated animals that received cysteamine 1 and 4 h before the tests according to following experimental schedule: a) sc injection of naloxone or morphine 30 min before the nociceptive assay. b) icv or it injection of somatostatin or cyclo-(7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl) 15 min before the nociceptive assay.

Statistical analysis All data are expressed as

$\bar{x} \pm S_{\bar{x}}$ and were analyzed by Newman-Keuls analysis of variance, or by Student's t-test when the analysis was restricted to two means. Significance was assumed at $P < 0.05$.

RESULTS

Cysteamine effects on gross behavior Within 20 – 30 min after cysteamine administration at the dose of 200 mg/kg, most animals exhibited immobility and trembling and when handled, myoclonus appeared. Immobility as well as trembling disappeared 1 – 2 h after cysteamine administration whereas myoclonus lasted for 3 – 4 h after the administration. Some animals treated with cysteamine at the dose of 100 mg/kg exhibited trembling that almost completely disappeared 1 – 2 h after cysteamine administration. When the same animals were handled, no myoclonus were observed. Mice treated with cysteamine at lower doses (10 and 50 mg/kg) did not show any behavioral changes (data not shown).

Mice treated with saline icv or it or with somatostatin, and cyclo-(7-aminoheptainoyl-Phe-*D*-Trp-Lys-Thr-Bzl) icv or it did not show gross behavioral change (data not shown).

Cysteamine effects on nociceptive threshold Since cysteamine administered at a higher dose (200 mg/kg) significantly impaired motor performace, we performed the nociceptive assay with the lower cysteamine doses (10, 50, and 100 mg/kg). Statistical analysis revealed that cysteamine administered 24 h before the tests at the doses of 10, 50, and 100 mg/kg did not change the response to nociceptive stimuli in either of these tests [hot plate: $F(3,51) = 0.19$, not significant (ns); tail flick: $F(3,51) = 2.94$, ns]. In the hot plate test, a lower cysteamine dose (10 mg/kg) increased the nociceptive threshold 1 h after administration (Fig 1), however it was ineffective in the tail flick (Fig 2). Higher cysteamine doses (50 and 100 mg/kg) administered 1 and 4 h before the tests prolonged the response to nociceptive stimuli in the hot plate and tail flick (Fig 1 and Fig 2). After these experiments, we investigated whether morphine, naloxone, somatostatin and cyclic-(7-aminoheptanoyl-Phe-*D*-Trp-Lys-ThrIBzII)' administered at doses that did not change the response to nociceptive stimuli, might be able to modify the cysteamine effects. Morphine administered at low doses in animals pretreated with cysteamine at the dose of 10 mg/kg potentiates cysteamine effects in the hot plate (Fig 1) and in the tail

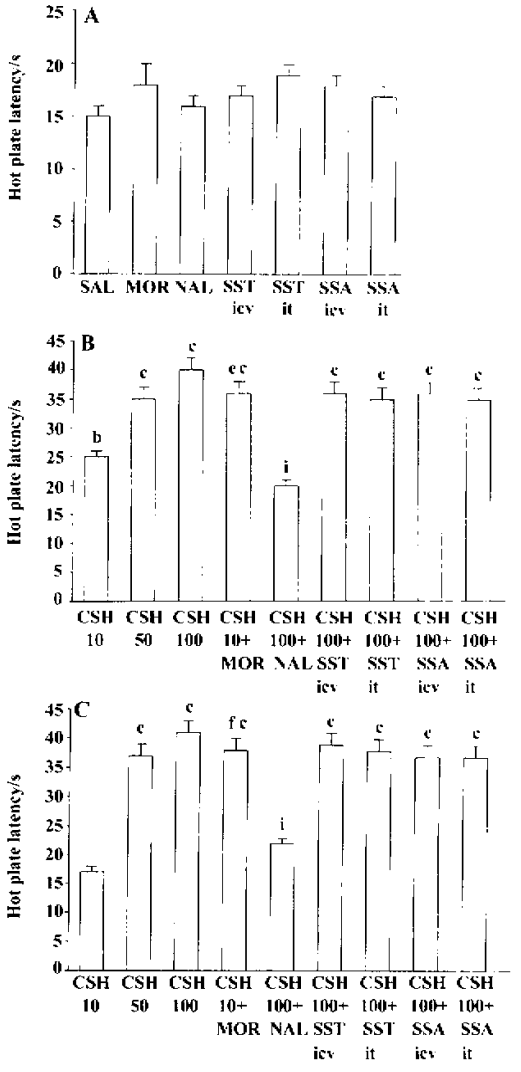

Fig 1. Panel A: effects induced by saline (SAL, 5 mL/kg, ip), morphine (MOR, 1 mg/kg, sc), naloxone (NAL, 1 mg/kg, sc), somatostatin (SST, 0.1 g/mouse icv or it), and cyclo (7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl) (SSA (0.1 μg/mouse icv or it) in the hot plate test in mice. Panel B and C: effects induced by cysteamine (CSH 10, 50, and 100 mg/kg ip) and the effects induced by MOR (1 mg/kg, sc), NAL (1 mg/kg, sc), SST (0.1 μg/mouse, icv or it), and SSA (0.1 μg/mouse, icv or it) in animals pretreated with cysteamine. In panel B the hot plate test was performed 1 h after cysteamine administration, in panel C the hot plate test was performed 4 h after cysteamine administration. $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* saline. $^{e}P < 0.05$, $^{f}P < 0.01$ *vs* animals pretreated with cysueamine at the dose of 10 mg/kg. $^{i}P < 0.01$ *vs* animals pretreated with cysteamine at the dose of 100 mg/kg.

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Jul; 22 (7)
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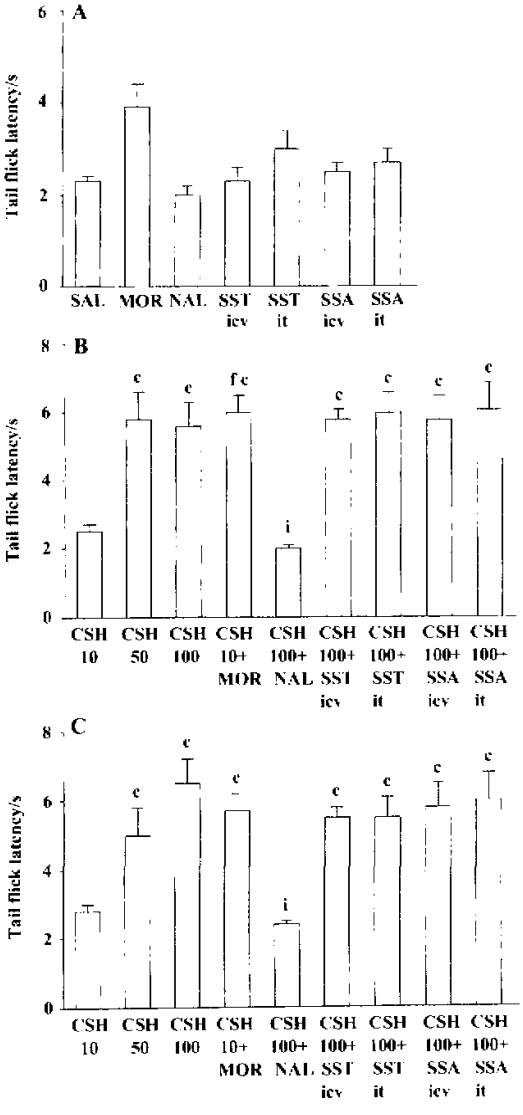

Fig 2. Panel A: effects induced by saline (SAL, 5 mL/kg, ip), morphine (MOR, 1 mg/kg, sc), naloxone (NAL, 1 mg/kg, sc), somatostatin (SST, 0.1 μg/mouse icv or it), and cyclo-(7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl) (SSA, 0.1 μg/mouse icv or it) in the tail flick test in mice. Panel B and C: effects induced by cysteamine (CSH 10, 50, and 100 mg/kg, ip) and the effects induced by MOR (1 mg/kg, sc), NAL (1 mg/kg, sc), SST (0.1 μg/mouse, icv or it), and SSA (0.1 μg/mouse, icv or it) in animals pretreated with cysteamine. In panel B the tail flick test was performed 1 h after cysteamine administration, in panel C the tail flick test was performed 4 h after cysteamine administration. $^{c}P<0.01$ *vs* saline. $^{f}P<0.01$ *vs* animals pretreated with cysteamine at the dose of 10 mg/kg. $^{i}P<0.01$ *vs* animals pretreated with cysteamine at the dose of 100 mg/kg.

flick test (Fig 2) both when cysteamine was administered 1 h and 4h before the tests. Naloxone administered in animals pretreated with 100 mg/kg of cysteamine 1 h and 4 h before the test, was able to revert the cysteamine induced effects, both in the hot plate (Fig 1) and the tail flick test (Fig 2). When somatostatin was administered icv or it in animals pretreated with 100 mg/kg of cysteamine somatostatin was not able to change the cysteamine effects in the hot plate and tail flick test, both when cysteamine was administered 1 h and 4 h before the test (Fig 1 and Fig 2). When somatostatin antagonist, cyclo (7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl), was injected icv or it, it did not change cysteamine 100 mg/kg effects in the hot plate and tail flick test both when cysteamine was administered 1 h and 4 h before the tests (Fig 1 and 2).

DISCUSSION

The results obtained in this work indicate that cysteamine is able to modify the nociceptive threshold in nociceptive assays involving acute stimuli in mice. In fact, cysteamine administration at doses that did not significantly change locomotor activity and reported as not interacting with dopamine-β-idrossilase activity, or did not change the cathecolamine content in the brain[9,15,16], prolonged the response to acute heat stimuli in the hot plate and tail flick test.

In disagreement with the present results obtained with the hot plate or tail flick test, Ohkubo *et al*[17] have reported that cysteamine administered it was not able to change the response in the tail pinch and hot plate tests in mice.

The same results were reported by Dalsgaard *et al*[18] who found that cysteamine it administration did not change to the hot plate in rat.

These results may reflect the difference in the experimental procedures used by Ohkubo *et al*[17] and Dalsgaard *et al*[18] and by us, ie, the different modality for cysteamine administration, but it also may suggest that cysteamine effects on the response to nociceptive stimuli may depend on the effects that cysteamine exerts on the different pain modulator system and/or pain neurotransmitter. Many authors indicate different kinds of pain activate different pain modulator systems or different pain neurotransmitters[28-30]. One of them is the well known system involving the endogenous opioids[31] and recent evidence indicated that somatostatin also may modulate pain response.

Somatostatin is widely distrbuted in the central nervous system[32] and has been found in higher concentrations in the dorsal root ganglia and in the primary sensory neurons[33,34]. In addition, it has been shown that iontophoretic application of somatostatin caused depression of the dorsal horn neurons[35] and that noxious stimuli produce an increase in somatostatin release in cerebrospinal fluid[36]. Behavioral data also indicate that somatostatin administration modifies the response to nociceptive stimuli[37-39] and in man, somatostatin has been reported as a potent antinociceptive agent[40]. Therefore, all these data support a possible involvement of somatostatin as neuromodulator and/or neurotransmitter for some type of pain. Although we did not perform analysis on the somatostatin levels after cysteamine administration, many data are available in literature on the effects exerted by cysteamine on somatostatin levels[9,16,41-43]. These data indicate that cysteamine at the doses used in our experiments induces a time-dependent elevation of the somatostatin concentration in CSF and a time-dependent somatostatin depletion in the brain as well as the spinal cord. In contrast to our previous paper[17], we found that in hot plate and tail flick cysteamine effects are reverted by naloxone and potentiated by morphine, whereas both somatostatin and antagonist somatostatin did not modify cysteamine effects. These data suggest that cysteamine effects in tests involving acute stimuli may be mediated by the opioid system or at least that the cysteamine may interfere with this pain system.

The absence of effects after somatostatin or cyclo(7-aminoheptanoyl-Phe-*D*-Trp-Lys-Thr-Bzl) administration in cysteamine pretreated animals performing the hot plate or tail flick test may suggest that in the hot plate and tail flick test, neither the cysteamine induced somatostatin depletion (that somatostatin administration may revert) nor the elevation of the somatostatin antagonist somatostatin levels in the CSF (that the somatostatin antagonist administration may antagonize) cysteamine participate in the cysteamine induced effects.

If cysteamine effects on nociception are the results of interferences with different pain modulator systems, the lack of effects in the tests involving acute stimuli obtained by Ohkubo *et al*[7] and Dalsgaard *et al*[18] who administered cysteamine it, may be caused by an interference that cysteamine exerts on somatostatin levels at the levels of the spinal cord and that may mediate the responses that are induced by pain stimuli as well as by formalin or acetic acid, but not by the hot plate and tail flick. Furthermore, data available on the effects induced by centraly administered drugs on the hot plate or tail flick test[37-39] are obtained with high somatostatin doses than that are reported in the CSF after administration. In addition no effects[43] are reported after somatostatin administration at higher doses in tests involving acute pain stimuli.

Given the evidence mentioned above it is of interest that cysteamine may be able to modify the nociceptive response induced by acute pain stimuli, and that these effects may be mediated by different pain modulator systems.

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ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Jul; 22 (7)
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半胱胺对小鼠疼痛感受的影响

关键词 半胱胺；疼痛测定；镇痛药

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