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Changes in Analgesia-Producing Mechanism of Repeated Cold Stress Loading in Mice

YUJI OMIYA, KAZUHIRO GOTO, ATSUSHI ISHIGE AND YASUHIRO KOMATSU

Kampo and Pharmacognosy Laboratories, Tsumura & Co., Ibaraki 300-1192, Japan

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OMIYA, Y., K. GOTO, A. ISHIGE AND Y. KOMATSU. *Changes in analgesia-producing mechanism of repeated cold stress loading in mice.* PHARMACOL BIOCHEM BEHAV **65**(2) 261–266, 2000.—Functional changes in opioid receptors involved in analgesia of repeated cold stress (RCS)-loaded mice were investigated. The antinociceptive potency of morphine (4 mg/kg, PO) was not affected in normal mice by norbinaltorphimine (10 mg/kg, SC), but treatment with this agent resulted in a lower level of morphine-induced antinociception in RCS-loaded animals. The antinociceptive activity of U-50488H (3 mg/kg, SC) was increased in RCS-loaded mice. In contrast to hypersensitivity to U-50488H (1 and 10 μg, IT) noted in RCS-loaded mice, the antinociception induced by DAMGO (0.1 and 1 μg, ICV) was reduced compared to that of normal animals. Diazepam (1 mg/kg/day SC) was given during RCS loading, and this agent prevented the development of hyperalgesia and the decrease in the antinociceptive activity of DAMGO (1 μg, ICV) in RCS-loaded mice, but there was no effect on the enhancement of the antinociceptive potency of U-50488H (10 μg, IT). These results indicate that the RCS-loaded mice were hyposensitive to supraspinal μ-opioid receptor-mediated antinociception, whereas their antinociceptive activities through κ-opioid receptor in the spinal cord were increased. Hypofunction of the supraspinal μ-opioid receptor due to anxiety may explain the mechanism involved in the lowering of the nociceptive threshold in RCS-loaded animals. © 2000 Elsevier Science Inc.

Repeated cold stress Hyperalgesia μ-Opioid receptor κ-Opioid receptor Antinociception

THE reactivity of animals to noxious stimulation is decreased by various stressors including a cold environment (14,22), fear (2,28), electrical shock (10,16), and swimming (1,26). Such phenomena are known as stress-induced analgesia. Other stressors have been reported to increase the sensitivity of animals to noxious stimulation. These stressors are called repeated cold stress (RCS), or specific alteration of rhythm in environmental temperature (SART) stress (14,15). Considerable attention has recently been paid to the decrease in the nociceptive threshold for pressure stimulation in animals exposed to cold temperature (4°C) and room temperature (24°C) at alternating 30-min intervals during the day over a few days, as a unique model of prolonged hyperalgesia with no apparent inflammation in the periphery. It was previously reported that various drugs exhibit marked antinociceptive effects in animals with pain sensitivity enhanced by RCS-loading (17,20). It was also reported that hypofunction of the pain inhibitory monoaminergic systems and enhancement of synaptic transmissions mediated by substance P and by calcitonin gene-related peptide in the spinal dorsal home were present in RCS-loaded animals (20,25). These changes are thought to cause an increase in the sensitivity to noxious stimulation, but the mechanism of this phenomenon induced by RCS has yet to be elucidated.

We recently clarified that processed *Aconiti* tuber, a crude drug exhibited more marked antinociceptive effects in RCS-loaded animals than in normal animals, and changes in spinal κ-opioid receptors were related to the etiology of this phenomenon (21).

It was previously reported that opiate receptor mechanisms altering by the type of loading stresses are initiated during the establishment of stress-induced analgesia (28). However, there have not been any reports indicating that such changes in opiate receptors are related to stress-induced hyperalgesia. Therefore, we evaluated whether intracerebral or intraspinal opiate receptors were involved in the mechanism causing decreases in the nociceptive threshold in RCS-loaded animals to clarify the etiology of marked antinociceptive potency in RCS-loaded animals. Moreover, it was indicated that hyperalgesia and various abnormal behaviors induced by RCS loading might be related to anxiety (7,19). Therefore, to clarify the correlation between anxiety induced by RCS loading and the

Requests for reprints should be addressed to Y. Omiya, Kampo and Pharmacognosy Laboratories, Tsumura & co., 3586 Yoshiwara, Ami-Machi, Ibaraki 300-1192, Japan.

subsequent decrease in nociceptive threshold, we evaluated the influence of the anxiolytic drug diazepam on functional changes in opiate receptors.

METHOD

Animals

Male ddY mice weighing 20–25 g at the beginning of the experiment were used. Four animals were housed per cage under a 12-h light and dark cycle (lights on between 0700–1900) and had free access to food and water throughout the experiments.

Repeated Cold Stress (RCS)

Kuraishi et al. (15) reported that sufficient and constant decreases in the nociceptive threshold were induced 3 days after initiation of RCS loading. In our experiment, the nociceptive threshold was also decreased 3 days after initiation of RCS-loading (Fig. 1).

Animals were exposed to a cold environment (4°C) from 1630–1000 h and then alternately to 24°C and 4°C at 30-min intervals from 1000 to 1630 h. The RCS schedule started at 1630 h on day 0 and stopped at 1000 h on day 3 (15). The nociception test was carried out between 1000–1800 h on day 3.

Drugs

Morphine (Takeda Chemical Industries, Ltd., Osaka) was dissolved in distilled water (10 ml/kg). [d-ALA^2, *N*-Me Phe^4, Gly-ol^5] enkephalin (DAMGO; Sigma Chemical, Co., St. Louis, MO), [D-Pen^{2,5}] enkephalin [DPDPE; Research Biochemicals International (RBI), Natick, MA], trans-(±)-3, 4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl] benzeneacetamide (U-50488H; RB1) and norbinaltorphimine (nor-BNI; RBI) were dissolved in saline (10 ml/kg). Nor-BNI was injected 2 h before the morphine treatment. Diazepam was administered using Cercine® injection (Takeda) (1 ml of Cercine® injection is comprised of 5 mg of diazepam, 0.015 ml of benzyl alcohol, 0.4 ml of propylene glycol, 0.1 ml of absolute ethanol and 42.8 mg of benzoic acid). The SC injection of diazepam was performed once a day from day 0 to day 2 of RCS loading, and the final injection was completed 1 day before the nociception test.

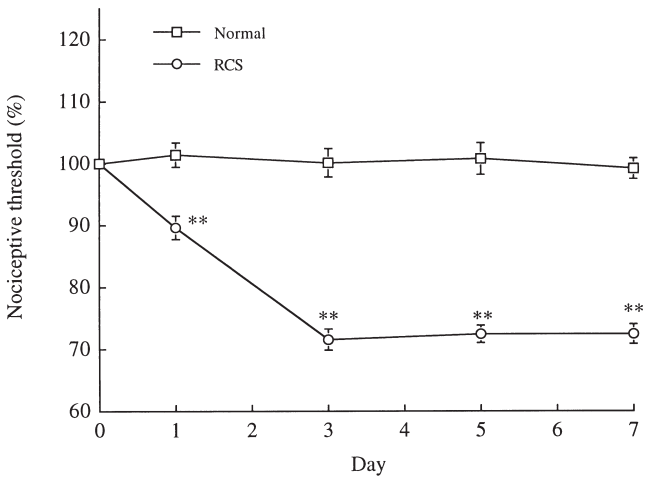

FIG. 1. Decreases in the nociceptive threshold in response to pressure stimulation in RCS-loaded mice. The nociceptive threshold was measured by the tail-pressure test as described in the text. Each point represents the mean ± SEM of seven to nine animals. $^{**}p < 0.01$ compared with normal mice (Student's *t*-test).

Intracerebroventricular and intrathecal injection

Intracerebroventricular (ICV) and intrathecal (IT) injections were carried out using a 10 μl Hamilton syringe according to procedures of Haley and McCormick (6) and Hylden and Wilcox (8), respectively. The saline and drug solutions were administered in a volume of 5 μl for both injections.

Nociception Test

Antinociceptive responses were evaluated by a tail-pressure test using a pressure analgesimeter (Ugo Basile, Milan, Italy) as described earlier (20).

Mice were subjected to pressure on the tail at a point 1 cm distant from the root. The force applied to the tail was increased at a constant rate of 16 g/s, the threshold for struggling behavior was measured. To avoid tissue damage, pressure was limited to a maximum of 250 g unless the animals started to bite or vocalize before this weight was reached. Changes in the threshold induced by drugs were monitored until 3 h after their administration, at 30-min intervals. In the experiments in which the opiate agonist was injected intracerebroventricularly or intrathecary, the threshold 10 min following the injection was also measured. The ratio of the pressure threshold after treatment to that before treatment was defined as the nociceptive threshold (%).

The antinociceptive effects were calculated as the area under the time exposure curve (AUC) by plotting the increase in the nociceptive threshold on the ordinate and the time interval (hour) on the abscissa. AUC is the area of the nociceptive threshold at each time point between 0 and 3 h.

Statistical Analysis

The results are presented as means ± SEM. The significance of differences was determined by Student's *t*-test or one-way analysis of variance (ANOVA) followed by Scheffé's test. For all cases, significance of differences was accepted at $p < 0.05$.

RESULTS

Effects of nor-BNI on the Antinociceptive Action of Morphine in RCS-Loaded and Normal Mice

The antinociceptive effect of morphine (4 mg/kg, PO), was not affected by RCS loading. Pretreatment with nor-BNI (10 mg/kg, SC), a highly selective antagonist of κ-opioid receptors, did not influence the antinociceptive effects of morphine in the normal (untreated) mice, whereas it reduced the potency of morphine-induced analgesia to 51% of that in the saline-treated group in RCS-loaded mice (Fig. 2).

Effects of RCS Loading on the Antinociceptive Activity of U-50488H

The antinociceptive activity of U-50488H (3 mg/kg, SC), a κ-opioid agonist, in the RCS-loaded mice was 2.0 times higher than that in normal mice (Fig. 3).

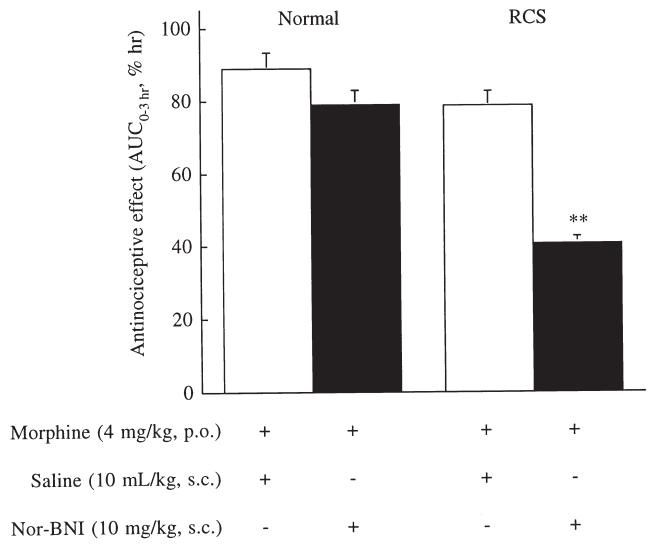

FIG. 2. Antagonism by nor-binaltorphimine (nor-BNI) of morphine-induced analgesia in RCS but not in normal mice. Nor-BNI (10 mg/kg, SC) was given 2 h prior to morphine (4 mg/kg, PO) administration. Antinociceptive activity was measured by the tail-pressure test every 0.5 hr after morphine injection for 3 h, and expressed as the area under the curve (AUC). Each column represents the mean ± SEM of 7–10 animals. $^{**}p < 0.01$ compared with the saline-treated group in RCS-loaded mice (Student's *t*-test).

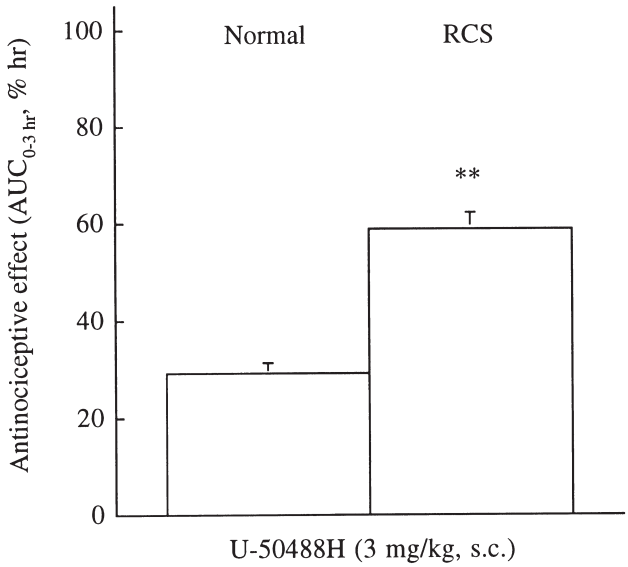

FIG. 3. U-50488H-induced antinociception in RCS-loaded and normal mice. The data are shown in the same way as in Fig. 2. Each column represents the mean ± SEM or 10–14 animals. $^{**}p < 0.01$ compared with normal mice (Student's *t*-test).

Functional Changes in μ- and κ-Opioid Receptors of RCS-Loaded Mice

The antinociceptive activities following the ICV administration of 0.1 and 1 μg of DAMGO, a μ-opioid agonist, to the RCS-loaded mice were 37 and 49% of the respective activities in normal mice. Analgesic effects of ICV administration of DPDPE, a δ-opioid agonist at 1 and 5 μg and IT, administration of DPDPE at 0.5 and 1 μg did not change in either RCS-loaded or normal mice. The antinociceptive activities of IT administration of U-50488H at 1 and 10 μg to RCS-loaded mice were 2.7 and 2.6 times higher than those in normal mice, respectively; however, the effects of the ICV-injected drug at 10 and 50 μg were not different (Table 1).

Effects of Diazepam on Functional Changes in μ- and κ-Opioid Receptors by RCS Loading

The lowering of the nociceptive threshold level by RCS loading was repressed by consecutive administration of diazepam (1 mg/kg/day, SC), an anxiolytic drug (Fig. 4).

TABLE 1

ALTERATIONS IN ANTINOCICEPTIVE POTENCY OF DAMGO AND U-50488H BUT NOT DPDPE IN RCS MICE

		Antinociceptive Potency (AUC)			
		ICV		IT	
Treatment	(μg)	Normal	RCS	Normal	RCS
Saline		6.2 ± 4.2	8.6 ± 2.8	7.8 ± 2.4	12.0 ± 1.9
DAMGO	0.1	65.8 ± 4.1	24.3 ± 4.5*	75.1 ± 9.0	58.0 ± 4.4
	1	217.9 ± 13.9	106.5 ± 7.2*	211.4 ± 18.7	218.7 ± 11.8
DPDPE	0.5	N.S.	N.S.	57.3 ± 5.3	76.0 ± 4.2
	1	42.4 ± 4.5	51.3 ± 2.9	83.5 ± 7.0	76.0 ± 4.7
	5	80.1 ± 5.1	90.2 ± 3.5	NS	NS
U-50488H	1	NS	NS	32.5 ± 2.2	88.6 ± 2.4*
	10	48.2 ± 4.0	36.9 ± 3.9	48.6 ± 6.1	124.7 ± 10.0*
	50	64.5 ± 3.9	55.6 ± 5.7	N.S.	N.S.

Mice were injured with the opiate agonist. The antinociceptive activities were measured by the tail-pressure test from 10 min to 3 h after the injection and were expressed as the area under the curve (AUC). Each value represents the mean ± SEM of 7–13 animals.

$^{*}p < 0.01$, compared to corresponding normal mice (Student's *t*-test). NS = not study.

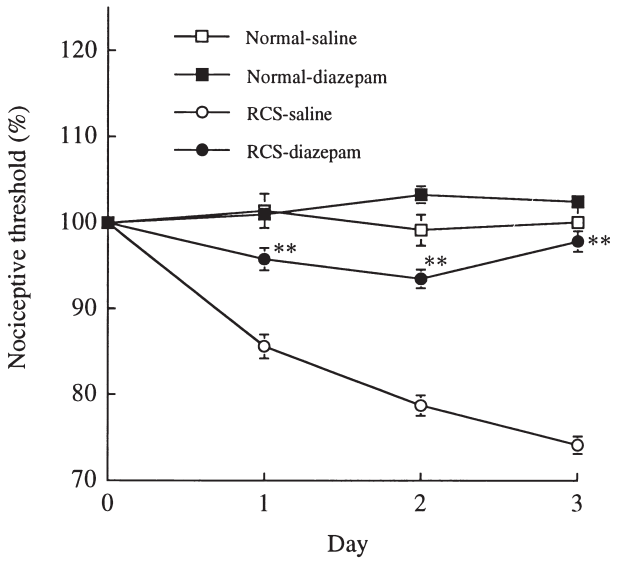

FIG. 4. Diazepam (1 mg/kg/day, SC) inhibited the decrease in the nociceptive threshold for pressure stimulation in RCS mice. RCS was started at 1630 on day 0, continued for 2 days, then stopped at 1000 h on day 3. See details in the text. Each point represents the mean ± SEM of seven to nine animals. $^{**}p < 0.01$ compared with the saline-treated group in RCS-loaded mice (Student's *t*-test).

The decrease in the antinociceptive activity of DAMGO (1 μg, ICV) caused by RCS loading was inhibited by diazepam while the enhancement of the antinociceptive activity of U-50488H (10 μg, IT) was not [ANOVA $F(3, 29) = 21.528$, $p < 0.0001$ for DAMGO; $F(3, 31) = 57.117$, $p < 0.0001$ for U-50488H] (Fig. 5).

Diazepam treatment did not influence the antinociceptive activity of the opioid agonist in normal mice.

DISCUSSION

This study is the first report demonstrating hyporesponsiveness of the supraspinal μ-opioid receptors and the enhancement of the spinal κ-opioid receptor-mediated antinociception in RCS-loaded animals.

The antinociceptive activity of morphine was decreased by pretreatment with nor-BNI in RCS mice, indicating that nearly half of the activity might be mediated by κ-opioid receptors in those animals. The increase in the antinociceptive activity of U-50488H in RCS-loaded mice supported that the role of κ-opioid receptors is very important in the morphine antinociception observed in RCS-loaded animals. In our study, the analgesic activity via κ-opioid receptors was increased in RCS-loaded mice, but such activity due to morphine was not significantly increased in those animals. This appears to have been caused by hypofunction of opioid-receptors but not κ-opioid receptors.

Both supraspinal and spinal opioid-sensitive structures are essential for the production of antinociception by systemic administration of morphine (23,24,32). Here, the antinociceptive effects ICV or IT administration of DAMGO, DPDPE, and U-50488H were compared between normal and RCS-loaded mice. The RCS-loaded mice were found to be hyposensitive to supraspinal μ-opioid receptor-mediated antinociception, but their spinal K-opioid receptor-mediated analgesic system was enhanced.

Several clinical and experimental studies have suggested that both diabetes and hyperglycemia alter pain sensitivity (3,11). Kamei et al. (12,13) suggested that diabetic animals become hyperresponsive to supraspinal δ_1-opioid receptor-mediated antinociception, whereas they also suggested that there was not a functional alteration of κ-opioid receptors, but rather a dysfunction of supraspinal μ-opioid receptors in diabetic animals. This phenomenon was considered the cause of selective alteration of the nociceptive threshold for noxious mechanical stimuli observed.

Supraspinal μ-opioid receptors are well known to play an important role in the functional regulation of the descending pain inhibitory system (30). It is likely that hypofunction of the pain inhibitory monoaninergic systems in RCS-loaded animals (20) is caused by the lowering of supraspinal μ-opioid receptor functions. On the other hand, Millan (18) concluded that dynorphin and κ-opioid receptors in the spinal cord can only partially counteract hyperalgesia. Indeed, both inflammation and ligation of the sciatic nerve induce hypersensitivity of the paw to noxious stimulation in rats, though dynorphin biosynthesis in the spinal dorsal home is enhanced under these conditions (4,9). This might be the reason why nociceptive sensitivity of RCS-loaded mice was increased despite hyper-

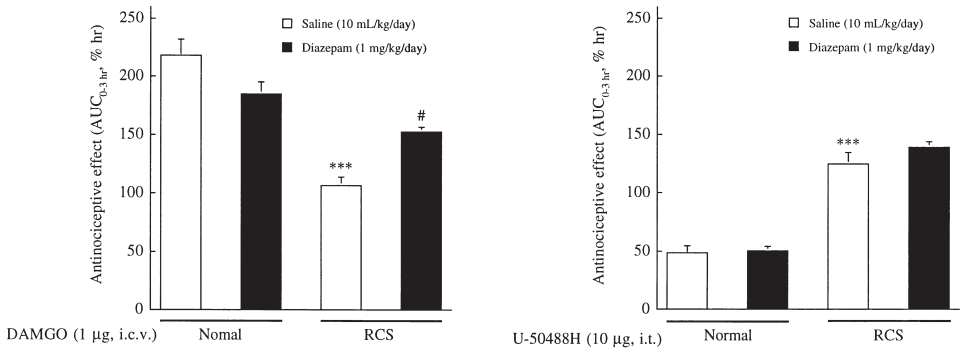

FIG. 5. Diazepam inhibited hyposensitivity to supraspinal μ-opioid receptors-mediated but not hypersensitivity to spinal κ-opioid receptors-mediated antinociception. The animals were treated repeatedly once each day (days 0–2) with saline 10 ml gl/kg or with diazepam 1 mg/kg. Each column represents the mean ± SEM of seven to nine animals. $^{**}p < 0.001$, compared with the saline-treated group in normal mice. $\#p < 0.05$, compared with the saline-treated group in RCS-loaded mice (Scheffé's test).

responsiveness to the antinociception mediated by the spinal κ-opioid receptors.

The present finding that hyperalgesia caused by RCS loading was suppressed by diazepam treatment is consistent with findings of the previous study (19). Because behavioral changes observed in RCS-loaded mice was improved by treatment with diazepam, Hata et al. (7) indicated that anxiety might be induced by RCS loading. The results of the present study supported the possibility that anxiety was related to the decreased nociceptive threshold in RCS-loaded animals. Because the marked reduction of antinociception induced by ICV administration of DAMGO was inhibited by diazepam in the present RCS-loaded mice, it is thought that the changes in the nociceptive threshold for noxious mechanical stimulation in RCS-loaded animals might be closely related to the functions of supraspinal μ-opioid receptors. Interactions between μ- and κ-opioid receptors have recently been demonstrated. For example, the activation of κ-opioid receptors suppressed the development of antinociceptive tolerance to morphine (29,31). It has also been reported that dynorphin inhibits [^{3}H] dihydromorphine (μ) binding through a noncompetitive mechanism (5). The presence of interactions between μ- and κ-opioid receptors has been suggested in an identical area, but the present results indicated hypofunction of μ-opioid receptors in supraspinal sites of RCS-loaded animals and hyperfunction of κ-opioid ones at spinal sites. Further, the enhancement of opioid analgesia mediated by κ-opioid receptors in the spinal cord was not suppressed in RCS-loaded animals of which hyposensitivity to supraspinal μ-opioid receptor-mediated antinociception was abolished by diazepam treatment. Therefore, hypofunction of μ-opioid receptors in RCS-loaded animals was probably not caused by interaction with κ-opioid receptors, suggesting that hypofunction of the supraspinal μ-opioid receptors is attributable to anxiety.

Neuropharmacological studies of the mechanisms of the analgesic effects caused by an environmental stressor have revealed the presence of stress-induced analgesia mediated by κ-opioid receptors (28). However, psychological stress-induced analgesia, which is assumed to be mediated by κ-opioid receptors in the spinal cord, was abolished by diazepam treatment (27). Meanwhile, the functional alterations of the κ-opioid receptors resulting from RCS loading were not affected by diazepam treatment, contrary to those in the μ-opioid receptors. The mechanism by which RCS loading induces changes in κ-opioid receptors and/or the extracellular levels of dynorphin in the spinal cord remains unknown at present. Further study is necessary to elucidate the mechanism of changes in receptor types involved in opioid analgesia induced in RCS-loaded animals, and quantitative and/or qualitative changes in μ- and κ-opioid receptors should be investigated.

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