生最大效应，使血清 PRL 水平达到 448 ± 64 μg·L^{-1}，0.2 mg·kg^{-1}则无效。对于多巴胺受体激动剂培高利特(pergolide)引起的 PRL 水平低下，SPD 5 mg·kg^{-1}有部分对抗作用，10 mg·kg^{-1}能够完全对抗。结论：SPD 是 D_2 多巴胺受体拮抗剂。

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Anxiogenic effect of naltrexone in social interaction test in rats[1]

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KEY WORDS naltrexone; animal behavior; morphine; fenclonine; 5-hydroxytryptophan; locomotion; anxiety disorders

AIM: To study the anxiogenic effect of naltrexone (Nal) on the emotional state of rats. **METHODS**: The duration of active interaction was measured in the social interaction test in rats. **RESULTS**: Without influence on the locomotor activity, Nal (0.1 − 50 mg·kg^{-1}) dose- and time-dependently decreased the duration of active interaction, which was antagonized by morphine (5 mg·kg^{-1}) or fenclonine (Fen, 150 mg·kg^{-1} × 3 d) and was enhanced by 5-hydroxytryptophan (5-HTP, 50 mg·kg^{-1}). **CONCLUSION**: Nal produced anxiety via its blockade of opioid receptors; central opioidergic neurons were involved in the regulation of anxiety through their tonic inhibitions in serotonergic neurons

The studies of endogenous opioid peptides (EOP) have been focused on their analgesia and dependence since they were discovered more than 20 years ago, whereas their effects on anxiety are still unknown. This is because: (1) Exogenous opioids can not cross over the blood-brain barrier and are degraded quickly by the pertinent peptidase, so it is difficult to observe behavioral effects; (2) The anxiety studied is mostly of the state one which is characterized by instantaneousness[1]. Fortunately, the function of EOP can be observed indirectly by opioid antagonists, through which the effects of EOP on stress and analgesia have been studied successfully. Naltrexone (Nal) is a potent antagonist of opioid receptors, which acts mainly at μ subtype. In contrast to naloxone, Nal is orally effective and lasts longer[2]. Although it antagonizes exogenous opioids powerfully, Nal is hardly effective when given alone. However, we found recently that Nal had an anxiogenic effect in Vogel's conflict test[3], which suggested that central EOP were involved in the regulation of anxiety. To verify such a result and explore its possible mechanism, we observed the effect of Nal in the social interaction test in rats.

MATERIALS AND METHODS

Fen, 5-HTP, and methyl-4-ethyl-6, 7-dimethoxy-β-carboline-3-carboxylate (DMCM) (Sigma, USA) were dissolved in 0.9 % NaCl, but the solution of Fen containing Na_2CO_3 125 mmol·L^{-1} (pH 9) while those of 5-HTP and DMCM containing HCl 800 mol·L^{-1} (pH 5). Nal hydrochloride (Institute of Pharmacology and Toxicology, Beijing, China), morphine hydrochloride (Qinghai Pharmaceutical Factory, Qinghai, China), and clonidine hydrochloride (Changzhou Pharmaceutical Factory, Jiangsu, China) were dissolved in 0.9 % NaCl. Drugs and vehicles were injected sc (for Nal and morphine) or ip, in a volume of 2 mL·kg^{-1} or 5 mL·kg^{-1} (for Fen and 5-HTP).

Male Wistar rats (Animal Center of Academy of Military Medical Sciences, Beijing, China) were grade-1 animals and weighed 250 ± s 25 g (n = 488). The rats were housed in a room with temperature of 20 - 25 ℃, lights on from 07:00 to 19:00. Experiments were carried out daily during 08:00 - 13:00, keeping the room quiet. Blind observation was used to make the results more reliable.

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Social interaction test The test was carried out as previously described[4], except that the arena was replaced by a Plexiglas box (50 cm × 50 cm × 32 cm) with a black wooden floor. The data were analyzed by one-way ANOVA followed by Dunnett's t-test.

Image motion test The system of Videomex-V image motion computer (Columbus Instruments Co, Ohio, USA) was used. It was composed of a main controller, a video monitor, an AST386 microcomputer, an image screen, and a printer. The video monitor was hanged vertically 86 cm above the arena so that the whole box could be monitored. Rats were placed in the center of the arena. The line formed by moving of the rat was shown on the image screen. The travelling distance (mm), the ambulatory time (s), and the resting time (s) of the rat within 10 min were recorded simultaneously by the computer. The data were analyzed by ANOVA.

RESULTS

In social interaction test, Nal (0.1 – 50 mg·kg^{-1}) dose- and time-dependently reduced the duration of active interaction under the high illuminance and unfamiliar condition ($P < 0.01$) (Fig 1), which was most effective 15 – 30 min after the injection and ineffective 60 min after the treatment (Fig 2).

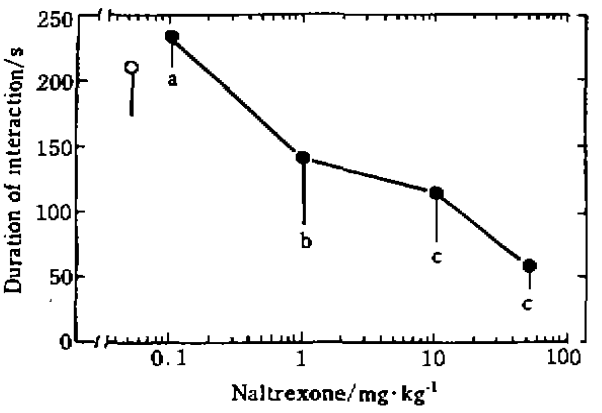

Fig 1. Effect of naltrexone (sc 30 min previously) on active interaction of rats in a high illuminance (380 lx) and unfamiliar arena. $n = 5 - 10$ pairs of rats, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ vs control (○).

With the decrease of intensity of anxiogenic stimuli, ie in high illuminance and familiar, low illuminance and familiar or unfamiliar conditions, little effect of Nal was seen ($P > 0.05$) (Tab 1).

Nal (1 mg · kg^{-1})-induced inhibition (the duration of interaction decreased from the control of 163 ± 22 s to 105 ± 24 s) was antagonized by the opioid agonist morphine (5 mg·kg^{-1}, the duration of interaction was 154 ± 48 s, $P < 0.05$ vs Nal). The classical anxiogenic agent DMCM (0.1 – 1 mg·kg^{-1}) also dose-dependently decreased the duration of interactoin ($P < 0.01$), which was enhanced by Nal (Fig 3).

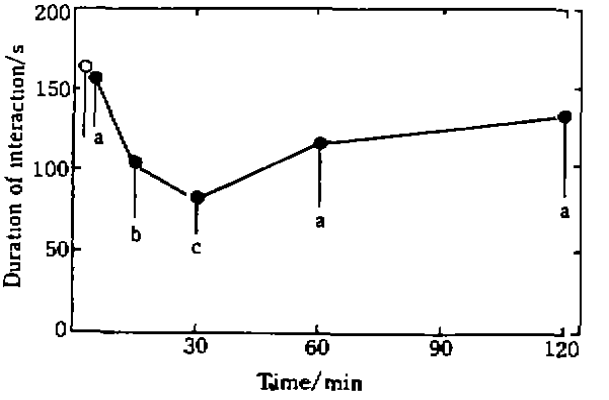

Fig 2. Effect of naltrexone (sc 1 mg · kg^{-1} 30 min previously) on active interaction of rats in a high illuminance (380 lx) and unfamiliar arena. $n = 5$ pairs of rats, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ vs control (○).

Tab 1. Effects of naltrexone (Nal) on duration of active interaction in social interaction test in rats under high illuminance (380 lx) and familiar (HF), low illuminance (35 lx) and unfamiliar (LU) or familiar (LF) conditions. Nal was sc 30 min before test.
$n = 5$ pairs of rats, $\bar{x} \pm s$. $^aP > 0.05$ vs control.

Nal/ mg·kg^{-1}	Duration of interaction/s HF	LU	LF
0	264 ± 28	196 ± 51	256 ± 62
1	228 ± 15^a	185 ± 10^a	236 ± 20^a
10	225 ± 47^a	160 ± 38^a	242 ± 68^a

The effect of Nal was blocked by Fen, an inhibitor of tryptophan hydroxylase, and was potentiated by 5-HTP, a precursor of 5-HT (Fig 4).

In the image motion test, clonidine, an agonist of α_2 receptor, reduced the travelling distance and the ambulatory time and increased the resting time simultaneously ($P < 0.05$). Nal (1 – 50 mg·kg^{-1}), however, did not affect these 3 indices ($P > 0.05$) (Tab 2).

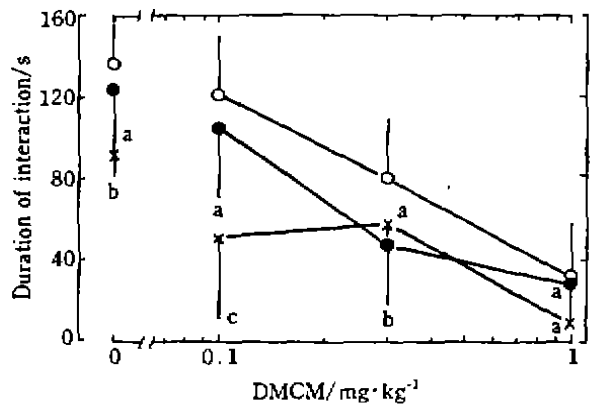

Fig 3. Potentiating effects of naltrexone (Nal) on methyl-4-ethyl-6, 7-dimethoxy-β-carboline -3-carboxylate (DMCM)-induced inhibition in duration of active interaction in social interaction test in rats in high illuminance (380 lx) and unfamiliar arena. Nal was sc 20 min prior to DMCM, which was ip 20 min before test. (○) Control (saline + saline or DMCM), (●) Nal 0.3 mg·kg^{-1} + saline or DMCM, (×) Nal 1 mg·kg^{-1} + saline or DMCM. n = 5 – 6 pairs of rats, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ vs corresponding control.

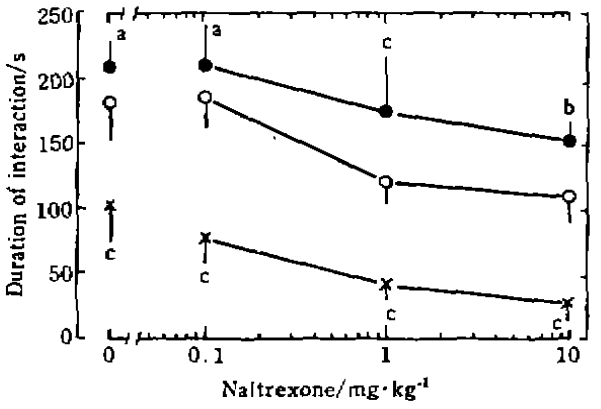

Fig 4. Effects of ip feuclonine (Fen, 150 mg·kg^{-1} × 3 d) on naltrexone (Nal)-induced inhibition in active interaction in rats under high illuminance (380 lx) and unfamiliar milieu. 5-HTP and the last dose of Feu was injected at 30 min and 18 h, respectively, prior to Nal, which was sc 30 min before test. (○) Control (saline + saline or Nal), (●) Fen + saline or Nal, (×) 5-HTP + saline or Nal. n = 5 – 6 pairs of rats, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ vs corresponding control.

DISCUSSION

In the social interaction test, Nal caused an obvious anxiety in rats in the high illuminant and unfamiliar environment, which was similar to that observed in Vogel's conflict test[3]. As shown in this study, the anxiogenic effect of Nal was related to the intensity of stimuli. Clonidine inhibited the locomotor activity of rats even in a low dose[5]. Its similar effect in the image motion test suggested that it was reliable to estimate locomotor activities of animals using such a model. Since Nal did not affect the locomotion of rats, the possible interference with locomotor activity was elimilated.

Tab 2. Effects of sc naltrexone and ip clonidine on locomotor activity within 10 min in image motion test in rats. Drugs were injected 30 min before test. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ vs control.

Drugs/ mg·kg^{-1}	n	Distance/ mm	Ambulatory time/s	Resting time/s
Control	6	5 350 ± 1 810	196 ± 51	256 ± 62
Nal				
1	7	5 160 ± 1 920^a	185 ± 10^a	236 ± 20^a
10	7	5 420 ± 3 230^a	160 ± 38^a	242 ± 68^a
50	6	3 470 ± 1 010^a	80 ± 24^a	469 ± 45^a
Clonidine				
0.1	7	2 350 ± 1 900^b	49 ± 37^b	514 ± 75^b

The effect of Nal was blocked by morphine, which suggested that Nal played a role in anxiety through its antagonism against opioid receptor, especially μ subtype, and that the central opioid system was tonically active, which was involved in keeping a normal state of emotion. Nal induced emotional imbalance and produced anxiety via its blocking of opioid neurons.

DMCM is an inverse agonist of the benzodiazepine (BDZ) receptor and produced anxiety even at low doses[6]. The result that Nal potentiated the anxiogenic effect of DMCM was consistent with that seen in the four-plate test[7]. So the involvement of GABA-BDZ-Cl^- complex in the anxiogenic effect of Nal could not be excluded.

As an inhibitor of tryptophan hydroxylase, Fen decreased the content of 5-HT in the presynapse of 5-HT nervous system and produced an anti-anxiety effect in the animal test[8]. 5-HTP is a precursor of 5-HT so that it increases the presynaptic content of 5-HT. The fact that Fen blocked, while 5-HTP potentiated, the effect of Nal indicated that the anxiogenic effect of Nal depended on the presynaptic 5-HT of the serotonergic neurons, which were

involved in the regulation of EOP in the emotion of anxiety.

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在大鼠群居相互接触模型上纳曲酮的致焦虑作用[1]

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关键词 纳曲酮；动物行为；吗啡；对氯苯丙氨酸；5-羟色氨酸；运动；焦虑症

目的：观察纳曲酮（Nal）对焦虑情绪的影响 方法：在群居焦虑模型上观察给予 Nal 等药后配对大鼠主动接触时间的变化 结果：Nal（0.1－50 mg·kg^{-1}）明显减少大鼠在强光不熟悉环境下的主动接触时间，且有剂量和时间依赖关系，并可被吗啡（5 mg·kg^{-1}）和 5-HT 合成抑制剂 Fen（150 mg·kg^{-1}×3 d）所拮抗，为 5-HT 合成前体 5-HTP（50 mg·kg^{-1}）所增强。而 Nal 对大鼠运动性活动无显著影响 结论：Nal 使动物产生焦虑状态；中枢阿片肽能神经通过其对 5-HT 能神经的紧张性抑制作用参与焦虑情绪的调控

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Effects of β-carotene on doxorubicin-induced cardiotoxicity in rats

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KEY WORDS β-carotene; doxorubicin; lipid peroxidation; superoxide dismutase; glutathione peroxidase; free radicals; electron spin resonance spectroscopy

AIM: To study the effects of β-carotene (Car) reducing the cardiotoxicity induced by doxorubicin (Dox). **METHODS**: The pathological changes of rat myocardium were observed with photomicroscopy. The malondialdehyde (MDA) value of rat heart was measured with thiobarbituric acid method. The pyrogallol autoxidation method was used for determination of superoxide dismutase (SOD) activity. The activities of glutathione peroxidase (GSH-Px) were quantitatived with DTNB method. Electron spin resonance (ESR) technique was used to measure the level of the semiquinone free radicals. **RESULTS**: Car 10 or 30 mg·kg^{-1}·d^{-1} ig reduced the cardiotoxicity induced by Dox, diminished the myocardial MDA production ($P < 0.01$), and protected the activi-

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