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Influence of tramadol on morphine discriminative behavior in rats[1]

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KEY WORDS tramadol; dependency (psychology); discrimination (psychology); reinforcement (psychology)

ABSTRACT

AIM: To study the potential of the psychological dependence of tramadol. **METHODS**: Rats were trained to discriminate 4.0 mg/kg morphine, and to discriminate 0.5 mg/kg methamphetamine (MA) from saline under a fixed-ratio (FR10) schedule of reinforcement. After they acquired the discrimination, different doses of tramadol were used to substitute for training dose of morphine and MA. Naltrexone was injected concomitantly with tramadol. **RESULTS**: Tramadol fully substituted morphine at a dose of 32 mg/kg or higher. The ED_{50} value of the discriminative effects of tramadol was 20.94 mg/kg, higher than that of morphine (2.04 mg/kg, $P < 0.01$). MA failed to generalize to tramadol at the doses tested. Naltrexone antagnized the discriminative respondse of tramadol. **CONCLUSION**: Tramadol can substitute for morphine in morphine discriminative rats. The discriminative stimulus effects of tramadol are mediated by a mu opioid mechanism.

INTRODUCTION

Tramadol is a centrally acting analgesic with weak opioid agonist properties, and effects on noradrenergic and serotonergic neurotransmission. It has been in clinical use in Germany since the late 1970s and became popular quickly for its fewer side effects and lower abuse potential than classical opioids[1,2]. However, there was evidence in recent years that tramadol was abused by opiate addicts in China[3].

The subjective effects of drugs in humans are considered to play a major role in determining whether a drug has a psychological dependence or not. If a drug has psychological dependence, there is a risk for it being abused. The action of drugs such as discriminative stimulus in animals is closely related to its subjective effects in human[5].

Tramadol has been reported to possess low opiate effects[1]. It is possible that its abuse in opiate addicts is based on its opioid mechanisms. The present experiments were designed to study the discriminative stimulus effects of tramadol in rats trained to discriminate morphine from saline in order to primarily evaluate the psychological dependence of tramadol.

MATERIALS AND METHODS

Subjects Male SD rats, weighing 300 - 320 g, were supplied by the Department of Laboratory Animal Science (Grade Ⅱ, Certificate № 01 - 3055), Beijing Medical University. All subjects were housed individually with free access to water. The rats were food deprived to 80 % of their free-feeding body weight and maintained at that weight.

Agents Morphine (Batch № 981101, Qinghai Pharmaceutical Plant, China), methamphetamine (National Narcotic Lab, China), naltrexone (Research Biochemical International, USA), and tramadol (Baoding Pharmaceutical Plant, China) were dissolved in 0.9 % saline.

Apparatus Experiments were conducted using the improved Skinner's operant chamber (Muromachi Kikai, Co, Ltd, Tokyo, Japan) enclosed in a sound and light attenuating box. A 28V-DC light provided illumination of the chamber during the session. There were two levers on wall of the chamber and a feeder delivered a 45-mg food pellet when the rat pressed the lever for the correct number of times. Data were recorded and sessions were controlled by an IBM personal computer pro-

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grammed with Med-PC Software.

Procedures The rats were trained in an alternation schedule of drug (D) and saline (N) administration (D,N,D,N...)[4]. On drug days, the rats were sc injected with either 4 mg/kg morphine 30 min before, or 0.5 mg/kg methamphetamine (MA) 10 min before the training session commenced and the rats were trained to press drug appropriate lever during the sessions. An equal volume of physiological saline was administered on non-drug days and the rats were trained to press non-drug appropriate lever. All injections were in a volume of 1 mL/kg.

Lever pressing was established under a fixed ratio (FR10) schedule of food reinforcement. That is the rats got a reinforcement when they pressed 10 times in continuation on the appropriate lever. A training session lasted for 30 min or until 100 food reinforcements had been achieved. Substitution testing was begun after the rats completed ten consecutive training sessions with an accuracy (the percentage of responses on the appropriate lever) equal to or greater than 80 %. Substitution testing sessions differed from training ones. The rats got a reinforcement when they produced 10 responses on either lever. The testing sessions terminate after the first reinforced delivery. During the test sessions, the rats were sc administered 0.56 – 10 mg/kg morphine or 3.2 – 56 mg/kg tramadol to substitute for the training dose of morphine. Naltrexone (0.01 – 0.5 mg/kg) was injected concomitantly with tramadol. On intervening days, the training was continued to maintain the baseline stimulus control.

Data analysis For each rat, the percentage of responses occurring on the drug lever (%) was calculated. The mean values were calculated for each measurement at each dose. The degree of substitution was determined by the maximum % for all doses of the test drug. "No substitution" was defined as 20 % or less, "partial substitution" was 20 % – 79 %, and "complete substitution" was 80 % or higher[5]. Data were expressed as $\bar{x} \pm s$. Statistical significance was determined by t-test. The ED_{50} values were calculated using computer software "SPSS 6.0".

RESULTS

Acquisition of baseline discrimination All rats trained with either morphine ($n=8$) or MA ($n=8$) acquired their baseline discrimination at the training doses (Fig 1, 2). The morphine discriminative rats produced (98.0 ± 2.6) % responses on morphine-lever with morphine administration and (2.5 ± 1.9) % of that with saline injection. The MA discriminative rats produced 100 % MA-lever responding with MA administration and no responding of that with saline injection.

Substitution tests The results of morphine substitution are shown in Fig 1 for the group mean. The training dose of morphine was substituted by 2.37 mg/kg and higher doses of morphine. The ED_{50} of morphine substitution was 2.04 (1.00 – 4.21) mg/kg.

When the training dose of morphine was substituted by tramadol at different doses, the discriminative effects of it were completely substituted by that of 32 mg/kg or higher doses of tramadol (Fig 1). The ED_{50} of tramadol substitution was 20.94 (11.00 – 39.08) mg/kg.

When tramadol was used to substitute MA, there was no selection on MA-lever (Fig 2), that is, tramadol failed to substitute for MA.

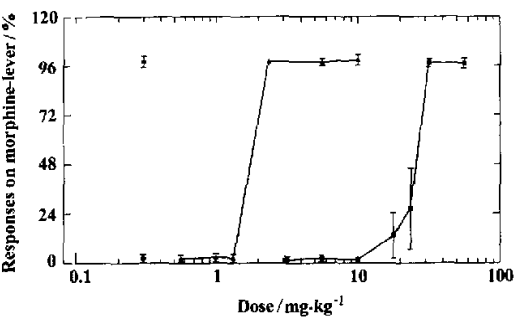

Fig 1. Substitution effects of morphine and tramadol in morphine discriminative rats. (●) Baseline response of morphine. (○) Baseline response of saline. (▲) Effects of morphine substitution. (■) Effects of tramadol substitution. $\bar{x} \pm s$. $n=8$.

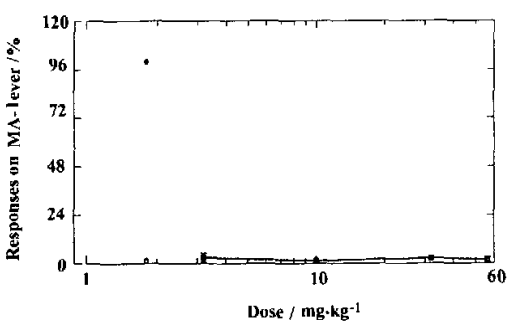

Fig 2. Effects of tramadol substitution in MA discriminative rats. (●) Baseline response of MA. (○) Baseline response of saline. (□) Tramadol substitution. $\bar{x} \pm s$. $n=8$.

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When naltrexone (0.01 – 0.5 mg/kg) was sc injected concomitantly with tramadol, it completely blocked the stimulus effects of tramadol at 0.1 and 0.5 mg/kg doses (Fig 3).

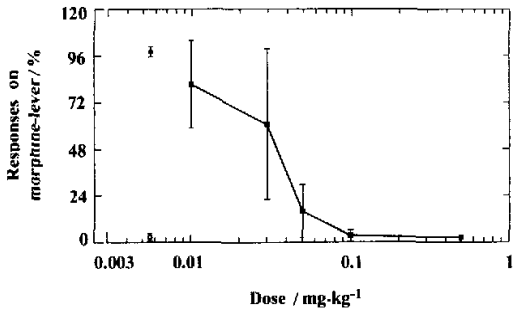

Fig 3. Effects of tramadol substitution in morphine discriminative rats pretreated with different doses of spiperone. (●) Baseline response of morphine. (○) Baseline response of saline. (□) Tramadol substitution effects 30 min after the rats were administered different does of spiperone. $\bar{x} \pm s$. $n = 8$.

DISCUSSION

In the present experiment, tramadol substituted for morphine in morphine dependent rats and the ED_{50} value of tramadol substitution was 10.3 times higher than that of morphine ($P < 0.01$). Accordingly, the initial conclusions which can be obtained are that tramadol can produce morphine-like subjective effects in human and has lower psychological dependence than morphine in absolute doses. That may explain, in part, why opiate addicts abuse tramadol. However, as we only employed the substitution procedure in the current experiments further verification is required.

The failure of tramadol to substitute for MA indicates that its discriminative stimulus differs from that of MA and the result suggests that the stimulus control of the tramadol has pharmacological specificity. That supports the fact that the drug discrimination procedure is specific for substances resembling the training drug.

The results of the naltrexone antagonization test demonstrate that naltrexone decreases the tramadol respond significantly at 0.1 and 0.5 mg/kg. This suggests that the discriminative stimulus of tramadol is mediated by mu opioid mechanisms.

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曲马朵对大鼠吗啡辨别行为的影响

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关键词 曲马朵；依赖性(心理学)；辨别(心理学)；强化(心理学)

目的：研究曲马朵的精神依赖性潜力. **方法**：采用固定比率(FR10)的食物强化法，训练一组大鼠辨别 4 mg/kg 的吗啡和生理盐水；训练另一组大鼠辨别 0.5 mg/kg 甲基苯丙胺和生理盐水. 辨别形成后，以不同剂量的曲马朵分别替代训练剂量的吗啡和甲基苯丙胺；纳曲酮与曲马朵联合给药，观察大鼠的辨别行为的变化. **结果**：32 mg/kg 或更高剂量的曲马朵可完全替代 4 mg/kg 吗啡；曲马朵替代效应的 ED_{50} 值为 20.94 mg/kg，高于吗啡的 ED_{50} 值 2.04 mg/kg ($P < 0.01$)；纳曲酮拮抗曲马朵的辨别效应. **结论**：高剂量的曲马朵可替代吗啡的辨别效应；mu 受体机制调节曲马朵的辨别效应.

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