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DL-Tetrahydropalmatine Inhibits Heroin Self-Administration in Rats

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ABSTRACT

DL-Tetrahydropalmatine is a Chinese herbal medicine used for analgesic purposes, whose main active compounds isolated from Corydalis. We investigate the effects of male Sprague-Dawley rats on heroin self-administration(SA) to examine the role for DL-THP. Rats were trained to intravenous injection heroin by self-administration for 12 consecutive days, then received DL-THP (5.0-20.0 mg/kg) on day 13. Our results showed that DL-THP (5.0 and 10.0 mg/kg) attenuated heroin self-administration without affect locomotion. The result showed that DL-THP inhibits heroin reinforcement.

***Keywords*:** *DL-THP, Heroin, Dopamine receptor, Self-administration*

1. INTRODUCTION

Heroin addiction is a highly addictive psychostimulant[1, 2]. However, currently there are no effective therapeutic agents for heroin addiction. Dopamine (DA) in the corticomesolimbic circuitry plays an important role in heroin reward[3]. We recently demonstrated L-stepholidine, attenuated heroin SA as well as cue-induced reinstatement[4]. DL-Tetrahydropalmatine (DL-THP) is an active component isolated from corydalis[5]. The effects of DL-THP on heroin SA behavior using a continuous-FR1 schedule of reinforcement was investigated. Moreover, locomotor activity was also in our study to assess possible motor effects.

2. MATERIALS AND METHODS

2.1 Subjects

The subjects were Male Sprague-Dawley rats (270–300 g, purchased from the Animal Center of the Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China) that were housed individually in home cages in a temperaturecontrolled ventilated colony room with a reversed 12-h light/dark cycle (lights onset 21:00 h, offset 09:00 h). Food and water were freely available except when specified.All procedures were reviewed by the Jianghan University Animal ethics committee.

Diacetylmorphine HCl (heroin) was obtained from the Hubei Public Security Bureau and was dissolved in 0.9% NaCl. DL-THP was acquired from the Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China). DL-THP was dissolved in 0.1 M H2SO4 and then diluted and adjusted to a pH of 5.0 with 0.1 M NaOH.

2.2 Heroin self-administration

The operative methods of intravenous intubation in rats are described in the literature[4,6,7]. Subjects were placed in self administration chambers during daily 4-h experimental sessions in which subjects were initially trained with responses producing heroin injections under a FR1-response schedule (each active one nose poke produced a 0.05 mg/kg/injection of heroin), and followed by a 15-s

timeout. Inactive nose pokes of rats which has been chioce in SA were recorded but produced no consequences. The acquisition sessions within 14 days.

2.3 Effects of DL-THP on Heroin SA Under FR1 Procedure

Thirty-two rats that meets the standards of SA model whice showed a stable pattern of heroin influsions. The animals were injected with various doses of DL-THP (0, 5, 10 and 20 mg/kg, n=7-9, i.p.), After 30 minutes, the experiment sessions started.

2.4 Locomotor test

After the heroin SA test is over, the test of locomotor activitystarts immediately, Thirty-one rats were participated in this test. Rats were then injected with DL-THP (0 mg/ kg, 5.0 mg/ kg, 10.0 mg/ kg and 20.0 mg/kg), injection method adopted methods of intraperitoneal injection and then put it in the test cage (Fig. 1), record the 120-minute horizontal movement distance.

Figure 1 Automated photocell system (AnilabSoftware & Instrments Co.,Ltd,China)

2.5 Statistical analysis

The data were expressed as the mean ± SEM. The differences in total active responses, inactive responses and locomotor activity were analyzed by one-way analyses of variance (ANOVA) followed followed by the Tukey test. All statistical analyses were carried out using SPSS for Windows (version 11.5; SPSS Inc., Chicago, Illinois, USA). The level of significance was set at P value less than 0.05.

3. RESULTS

3.1 Effect of DL-THP on drug-heroin IVSA

DL-THP with various doses significantly attenuation action of rats in this experiment about active nose-pokes numbers ($F_{3,28} = 15.89$, $P < 0.01$. **Fig. 2**). Comparisons showed significant differences in the numbers of SA-rats active nose-pokes about DL-THP treatment group at four doses ($P < 0.05$). ANOVA showed that doses of 10.0 mg/kg DL-THP produced significantly more intense effects than the 5.0 mg/kg dose ($P < 0.01$). In contrast, no significant differences in the number of inactive responses ($F_{3,28} = 2.65$, $P > 0.05$).

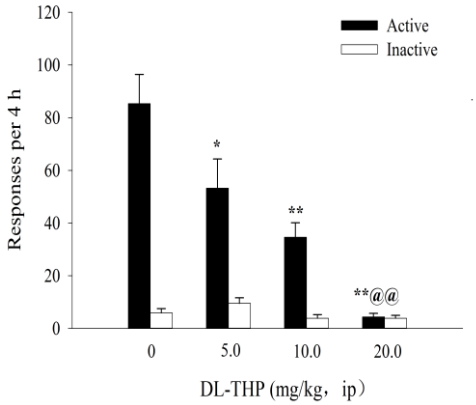

Figure 2 Acute effects of DL-THP on heroin self-administration. Each data point is means±SEM. DL-THP attenuated heroin self-administration under a fixed-ratio 1 schedule of reinforcement in rats. *P < 0.05, **P < 0.01, treatment significantly different from the 0 mg/kg DL-THP pretreatment group, respectively. @@P < 0.01, treatment significantly different from the 5.0 mg/kg DL-THP pretreatment group.

3.2 Effect of DL-THP on locomotor activity

Significant main effect of DL-THP treatment on locomotion activities ($F_{3,27}=6.60$, $p=0.002$, **Fig.3**) by One-way ANOVA statistical method and multiple comparisons showed that DL-THP treatment only at doses of 20.0 mg/kg significantly decreased the locomotion activities ($p<0.05$).

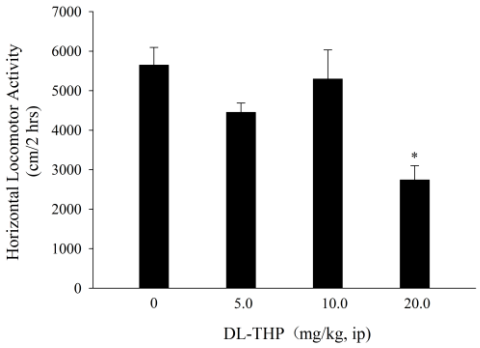

Figure 3 Effects of DL-THP on locomotion activity in the absence of heroin. Value of total distance (mean±S.E.M.). Rats (n=7-8) were put in chambers for 2 h, then injected with DL-THP (0, 5.0,10.0 or 20.0 mg/kg i.p.) and the total distance was recorded for 2 h. ** $p<0.05$ compared with the 0 mg/kg DL-THP.

4. CONCLUSION

In this study, we found that 5.0-20.0 mg/kg of DL-THP decreased the total amount of active nose-pokes. We also found that DL-THP at lower doses (5 and 10 mg/kg) had no effect on locomotor activities test. This result indicate that DL-THP have impact on attenuated drug SA under FR1 procedure without affecting the rats locomotion activities.

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