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L-Stepholidine Inhibits Methamphetamine Intravenous Self-administration Behavior in Rodents

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ABSTRACT

Methamphetamine (METH) is a powerful psycho stimulant. Chronic obsessive and compulsive usage of METH caused great harm to human health (physical and psychological) and social stability issues all over the world. Currently, no drugs have been used to treat and prevent METH addiction. L-Stepholidine (L-SPD) is a partial agonist of dopamine D1 receptor, meanwhile an inhibitor of dopamine D2 receptor. The unique neuropharmacological effects of L-SPD indicates that it might a agent which worthy of research and development targeting chronic and compulsive METH usage. In this research, rats were trained to establish stable intravenous self-administration (IVSA) behavior. Subsequently, the effects of different doses of L-SPD on METH IVSA under progressiveratio (PR) paradigm were tested. The behavior data shows that L-SPD (20 mg/kg, i.p.) attenuated METH IVSA behavior. This experimental data illustrates that L-SPD might be considered as a candidate chemical compound to treat chronic and compulsive METH usage.

Keywords: *L-SPD, Methamphetamine, Dopamine receptor, Self-administration*

1. INTRODUCTION

METH is a highly potent psychoactive substance which repeated use leads addiction [1]. Chronic use of METH contributes a societal burden by increasing health care costs and crime, psychomotor dysfunction and ultimately irreversible damage to human body [2]. What's more worrying is that, currently, no therapeutic agents have been approved to treat METH addiction. Thus, it has great actual meaning for finding and developing medications to treat and prevent METH dependence. The reinforcing characteristic of METH result from elevations in dopamine (DA) level in the mesocorticolimbic system [3]. The dopamine receptor blockers have been widely considered as promising drug candidates to treat and prevent METH dependence [4]. Unfortunately, the unpleasant side effects of specific dopamine receptor inhibitors limit their application [5]. Therefore, partial dopamine receptor agonist and antagonist have entered the vision of drug R & D personnel. L-SPD has dual effects targeting dopamine receptor system. It is a partial agonist of dopamine D1 receptor and an inhibitor of dopamine D2 receptor [6]. The unique neuropharmacological effects of L-SPD indicates that it very likely to become a new agent for the prevention of compulsive METH usage. We recently demonstrated that 3 and 6 mg/kg L-SPD attenuates METH IVSA seeking [7]. In order to further understand the attenuation action of L-SPD to METH IVSA seeking in rodents, we established METH IVSA model under a PR paradigm in rats. Subsequently, we evaluated the attenuation action of L-SPD on METH IVSA under PR paradigm.

2. MATERIALS AND METHODS.

2.1. Animals and drugs

Thirty two male SD rats (weighing 270 to 300 g) were

obtained from Wuhan rat Bailey Biotechnology Co., Ltd. All procedures were reviewed by the Jianghan University Animal ethics committee. METH (98%) was a gift from local Narcotics Control Committee. L-SPD was obtained from ApexBio Technology (Shanghai, China). Both compounds were dissolved in 0.9% sterile saline solution.

2.2. METH Self-administration training.

During the first ten days of acclimatization to the laboratory, all subjects were housed two per cage with ad libitum access to maintenance diet for rats. Subsequently, the subject was anesthetized by ketamine and xylazine (i.p.). A permanent-indwelling catheter (RJVR-10, SAI Infusion Technologies, USA) was surgically implanted into the left jugular vein, then extemalized between rat's mid scapular [8]. After the seven day recovery period, subjects were initially trained with METH (30 μg/kg per infusion) reinforcement under FR1 schedule in the SA chambers, as per Kai et al [8]. The training lasted for 14 days.

2.3. Effect of L-SPD on METH IVSA.

Following the last session of METH IVSA, the subjects were injected i.p. with various doses of L-SPD (0, 5, 10 and 20 mg/kg), and after 15 min they were tested in the chamber for METH IVSA under a PR schedule for 1 h. Each dose was studied in eight subjects and each subject was tested only once. The requirement (active nose poke) for getting an injection was determined by the formula 5(0.2 × infusion number) - 5 [9]. The last METH injection completed was considered as the breakpoint.

2.4. Statistical analysis.

The software GraphPad Prism 7 was employed. Data were exhibited as mean values ± S.E.M. of the number of nose poke and breakpoint. The METH IVSA under FR1 data were analyzed by repeated two-way ANOVAs to determine whether the stable SA behavior was established. For this analyze, the active or inactive responses was considered as a between-subject factor. The session was considered as a within-subject factor. The breakpoint data were analyzed by one-way ANOVA followed by Dunnett's tests of difference from control values. The p-value threshold was 0.05.

3. RESULTS

3.1. The METH IVSA under FR1 schedule.

METH IVSA responses are displayed in Fig.1. Statistical analysis indicated significant effects of nose poke (active or inactive) ($F_{1,2} = 6.91$, $p < 0.05$) and session over 14 days ($F_{13,26} = 3.06$, $P < 0.01$). When the numbers of active responses in the last session were compared with those in the first session of the experiment, a significant increase was observed ($p < 0.05$). The active responses were greater than the inactive responses ($F_{13,26} = 4.14$, $p < 0.01$).

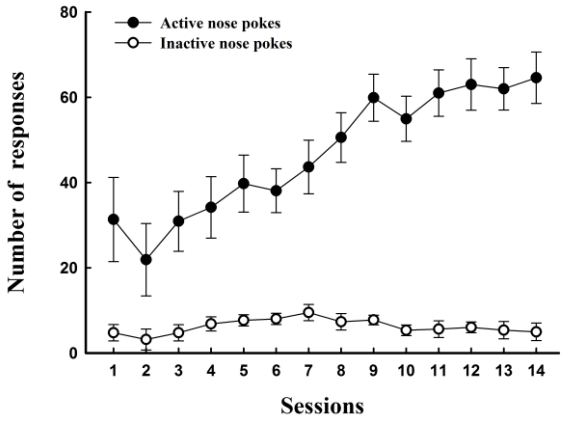

Figure 1 METH IVSA under FR1 schedule. Responses (active and inactive) during METH IVSA over 14 days. The filled and open symbols represent the active and inactive responses, respectively (mean ± SEM, n = 32).

3.2. Attenuation action of L-SPD on METH IVSA under PR reinforcement.

The attenuation action of L-SPD on METH IVSA under PR schedule are shown in Fig.2. The ANOVA indicated that treatment with L-SPD decreased the METH earned ($F_{3,28} = 3.12$, $p < 0.05$). Post-hoc indicated that the highest dose of L-SPD reduced the breakpoint of METH IVSA under PR schedule ($p = 0.03$).

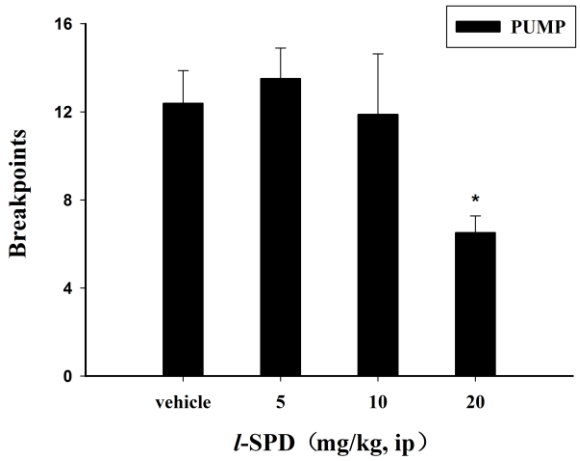

Figure 2 Attenuation action of L-SPD on METH IVSA under a PR schedule. The highest dose of L-SPD reduced METH earned. Data are presented as mean value ± S.E.M (n = 8).

4. CONCLUSION

In conclusion, we have demonstrated that L-SPD attenuates the METH IVSA under a PR schedule in rats. This experimental data illustrates that L-SPD might be considered as a candidate chemical compound to treat chronic and compulsive METH usage.

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