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Research paper

Effects of environmental enrichment during induction of methamphetamine dependence on the behavioral withdrawal symptoms in rats

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HIGHLIGHTS

- METH-induced behavioral withdrawal symptoms include stereotypic behaviors, depression and anxiety.
- The 14 days of environmental enrichment during induction of METH dependence reduces METH-induced stereotypic behaviors and rearing in rats.
- The 14 days of environmental enrichment during induction of METH dependence reduces depression in METH withdrawn rats.

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ABSTRACT

This study was designed to examine the effect of environmental enrichment during METH administration on the behavioral withdrawal symptoms after drug abstinence in rats. Rats reared in standard (SE) or enriched environment (EE) during induction of METH dependence with bi-daily injections of METH (2 mg/kg, at 12-h. intervals) for 14 days. Then, rats were evaluated for behavioral withdrawal symptoms, and also for anxiety (elevated plus maze-EPM) and depression (Forced swim test-FST) over a ten day period of abstinence. The results showed that stereotypic behaviors score and the number of rearing were significantly lower in METH/EE rats compared to the SE group during 1–4 days. Also, The METH/EE group exhibited more weight gain during 6–10 days of abstinence. The METH/EE rats exhibited lower levels of immobility after METH abstinence than control group in the FST. EE had no effect on anxiety-like behavior. This study showed that exposure to EE diminished the severity of withdrawal symptoms and depressive-like behavior during spontaneous withdrawal from METH.

1. Introduction

Methamphetamine (METH) is a potent psychostimulant for dependence [23] with neurotoxic properties [7]. METH dependence is associated with a number of withdrawal symptoms after METH cessation including depression and anxiety after 2–3 days of abstinence in human [19] and animal models of anxiety using the EPM [22] and depression using the FST [24], stereotyped behavior, locomotor activity such as vertical rearing behavior in rats [10] and weight loss in humane [9]. The acute withdrawal symptoms last 7–10 days, and chronic phase associated with neurotoxicity effects may persist for several months. The severity of withdrawal signs are related to the dosage and duration of methamphetamine use [7]. Stereotypies is defined as repetitive and invariant behavior patterns with no obvious goal or function [29], include head and forelimb movement and oral behavior such as repetitive chewing [1]. Stereotyped behaviors are associated with an imbalance in serotonergic and dopaminergic axis [2]. These signs might be due to METH-induced dependence and neurotoxicity [20], which causes the depletion of presynaptic monoamine stores and down-regulation of receptors [7]. Thus, the reversal or prevention of METH-induced dependence and neurotoxicity could be a useful method for the treatment of METH dependence and withdrawal. In previous studies, environmental enrichment (EE) has shown rewarding effects [30] and useful results in animal models of drug addiction [27]. The EE consists of a big cage which covered with fiber and physical stimuli, which stimulate exploration behavior in laboratory animals [26]. In our previous study, we have

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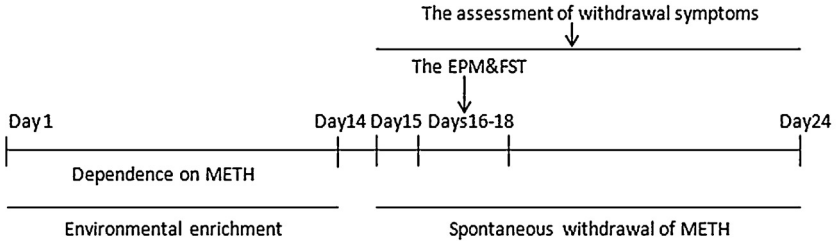

Fig. 1. Timeline of experiment (see Section 2 for details).

found that 30 days of exposure to enriched environment during METH withdrawal is associated with a decrease in anxiety and depression in METH withdrawn and intact rats [11]. It has been shown that enriched environment could improve neurotransmitters activity after drug abuse [12,31], also ameliorate stereotyped behaviors [29]. Thus, a more important question would be whether EE could blunt the deleterious effects of chronic administration of METH during dependency. Therefore, the aim of this study was to investigate whether exposure to EE during induction of METH dependence would attenuate behavioral withdrawal symptoms in rats. In previous studies, 10 and 14 days of exposure to the enriched environment reduced depressive symptoms [14] and cognitive deficits [17], respectively. Thus, with regard to the 14-days period to induce the development of methamphetamine dependence, we examined the effects of 14 days of environmental enrichment during induction of METH dependence.

2. Material and method

Male wistar rats (210 ± 10 g) were housed in a 12-h light/dark cycle at 22–24 °C, with food and water ad libitum. All of the experimental procedures were conducted in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize the number of animals and their suffering. Methamphetamine hydrochloride (Sigma-Aldrich, M 8750) was dissolved in 0.9% saline. The rats were chronically treated with subcutaneous injections of METH (2 mg/kg), twice per day at 12 h intervals, for 14 days, as described previously [11]. Control rats were similarly injected with saline. Rats were placed in their home cages (standard or enriched environment) for 14 days during induction of METH dependence (n = 7–8 rats per cage). The standard environment was (SE) consisted of standard plastic cages (42 × 34 × 15 cm). The enriched environment (EE) was consisted of large cages (96 × 49 × 38 cm), and the animals could play by plastic tunnels, rope, swing, balls, ramp, ladder, shelters, step, cube and running wheel, which were cleaned and changed every 2–3 days to stimulate exploratory behavior in rats [11].

Rats were divided into four groups (n = 7–8 per group): saline-standard environment (Sal/SE), saline-enriched environment (Sal/EE), METH-standard environment (METH/SE), and METH-enriched environment (METH/EE). The EE groups were allowed to freely exercise, play and explore their environment during induction of METH dependence (14 days). Then, all rats were transferred to standard cages on day 15. From day 15 to 24, stereotypic behavior, locomotor activity and body weight were recorded daily for 10 days in METH (n = 7–8 per group) and saline (n = 4 per group) groups. Also, on days 16–18 all animals were tested on the EPM and FST, respectively, 30 min after spontaneous behavioral testing during METH spontaneous withdrawal (see Fig. 1).

Spontaneous behavioral activity (stereotypy and locomotion) was recorded with a video imaging system as described previously [13]. Each rat was first placed in Plexiglas cylinder (45 × 30 cm) for a 10 min habituation period, and spontaneous behavioral activity was recorded over the next 20 min. The stereotypic movements scored during METH spontaneous withdrawal for 10 days using the following scales; 0 = sleeping, 1 = resting with open eyes but not moving, 2 = active (grooming and exploratory behaviors), 3 = stereotypy including oral (chewing, licking or biting), focused sniffing, and repetitive head and paw movements. The number of vertical movements (rearing) was also recorded in the locomotor activity test at the same time. After each test the floor of the box was cleaned. The body weight of each rat was monitored daily over 10 days, and a change in body weight was calculated days before and after.

To assess the level of anxiety, the rats were individually placed in the center of the elevated plus maze (EPM) with two open (50 × 10 cm, with a ledge of 5 mm) and closed (50 × 10 × 40 cm) arms, and a central platform (10 × 10 cm), and allowed to explore the apparatus for 5 min [21]. Time spent in, and entries into open and closed arms were measured during each 5 min test. In addition, the total number of arm entries was used as relative index of general activity. The apparatus was cleaned after each trial with water. Two days after METH cessation, on day 16, the rats were assessed by the EPM test (see Fig. 1).

The FST is a test of behavioral despair for rodents that used to assess the depressive-like activity. The test is carried out in a Plexiglas cylinder with a diameter of 20 cm, a height of 45, and the cylinder is filled with water 25 °C to a height of 30 cm. Animals are forced to swim in two trials, the first trial lasts 15 min, and followed 24 h later by a 5 min test. The following factors are evaluated: swimming time, escaping time (toward the cylinder wall), immobility time (floating in the water, do only necessary movements to keep its head above water) [11]. On the test day, swimming sessions were videotaped from a lateral angle using a Nikon Camcorder, and behavioral assessments were accomplished by observers blind for experimental groups. For each rat, water was exchanged. After each session, the rats were immediately removed from water, and dried with a towel in a heated room before being returned to their home cages. The FST conducted on days 17–18 during METH spontaneous withdrawal (see Fig. 1).

The data expressed as the mean ± standard error of the mean (S.E.M.). Data of spontaneous behavioral activity were analyzed with a 4 × 10 (group × day) two-way analysis of variance for repeated measures. Analysis of anxiety and depression was performed with the fixed factors treatment (saline and METH) and housing condition (SE and EE) by using two-way analyses of variance (ANOVA). Post-hoc analyses were included Tukey's test and using Bonferroni adjustments for multiple comparisons as required. Statistical differences were considered significant at $P < 0.05$.

3. Results

The results of stereotype behaviors are shown in Fig. 2A. Two-way ANOVA with repeated measures revealed a significant effect of day ($F_{9, 171} = 2.25$, $P = 0.021$), a significant effect of group ($F_{3, 19} = 313.43$, $P = 0.0001$) and a significant interaction between