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Effect of the environmental enrichment on the severity of psychological dependence and voluntary methamphetamine consumption in methamphetamine withdrawn rats

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HIGHLIGHTS

- Symptoms of METH withdrawal include depression, anxiety and drug craving.
- The environmental enrichment alleviates behavioral deficits induced by METH withdrawal.
- The environmental enrichment reduces voluntary consumption of METH in withdrawn rats.

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ABSTRACT

Previously results have been shown that chronic methamphetamine causes dependence, withdrawal syndrome and drug craving. Also, environmental enrichment (EE) has been shown protective effects in several animal models of addiction. This study evaluated effect of the EE on the anxiety-depression profile and voluntary METH consumption in METH-dependent rats after abstinence. The rats were chronically treated with bi-daily doses (2 mg/kg, at 12 h intervals) of METH over a period of 14 days. METH dependent rats reared in standard environment (SE) or EE during spontaneous METH withdrawal which lasted 30 days. Then, the rats were tested for anxiety (the elevated plus maze-EPM) and depression (forced swim test-FST) and also voluntary consumption of METH using a two-bottle choice paradigm (TBC). The results showed that the EE rats exhibited an increase in EPM open arm time and entries ($P < 0.05$), lower levels of immobility ($P < 0.001$) as compared with the SE groups. Preference ratio of METH was less in the METH/EE rats than the SE group during 2 periods of the intake of drug ($P < 0.05$). Environmental enrichment seems to be one of the strategies in reduction of behavioral deficits and the risk of relapse induced by METH withdrawal.

1. Introduction

Methamphetamine (METH) is an addictive psychostimulant that dramatically affects the central nervous system (CNS) [7]. Recent findings have shown that chronic METH use alters synaptic plasticity in the brain, which may contribute to its adverse effects [35], include dependence, withdrawal syndrome and drug craving [9,17,34]. The METH use causes neurotoxicity in multiple neurotransmitter systems [13,18,41]. METH-induced alterations in dopamine levels in mesolimbic, nigrostriatal systems and prefrontal cortex involve in craving and rewarding effects of drug [16,28]. Two common withdrawal symptoms of METH include depression and anxiety [20] that could contribute to drug dependence and craving [25,38]. Thus, reversal or prevention of the synaptic modifications induced by METH use could be a useful method for the treatment of relapse to METH seeking. It seems that the environmental enrichment (EE) models could impact on brain's reward system and vulnerability to drug abuse [37]. In Environmental Enrichment (EE) models, laboratory animals take place in large cages with physical stimuli include small toys and running wheel, which is much richer than the standard housing, and allow

Abbreviations: METH, methamphetamine; EE, environmental enrichment; SE, standard environments.

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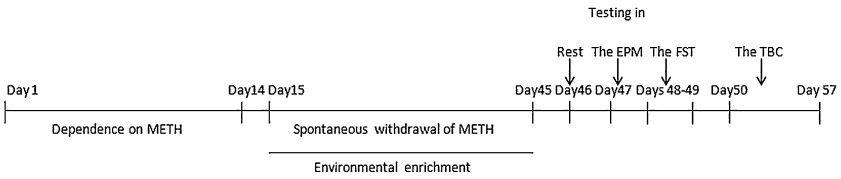

Fig. 1. Timeline of experiments (see Section 2 for details).

animals to explore, play and exercise; in this condition the animal could have more control over the environment [32,33]. It is recognized that EE models in rodents produce a range of plastic responses in the brain including neurogenesis [22], ameliorate some of the neurodegenerative and psychiatric disorders [26], reduce anxiety, depressive-like behaviors and endocrine-behavioral reactivity to stress [32], and enhance brain-derived neurotrophic factor (BDNF) levels [15].

There are controversial reports about the effects of EE on the behavioral responses to cocaine and amphetamines. Some evidence indicates that EE reduces amphetamine and cocaine self-administration and seeking behaviors [11,12], and MDMA (Ecstasy)-induced conditioned place preference (CPP) [1], or enhances amphetamine-induced CPP [3].

Thus, a more important question would be whether EE could blunt the deleterious effects of chronic methamphetamine exposure after abstinence. Therefore, in present study, we assessed effect of EE on the anxiety and depressive like-behaviors and also, voluntary consumption of METH in animal models of METH intake in METH-dependent rats during a 30-day withdrawal period.

2. Materials and method

Male Wistar rats (200 ± 10 g) were housed at a 12-h light/dark cycle at 22–24 °C temperature, 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 (were approved by University Ethics Committee). All efforts were made to minimize the number of animals and their suffering. The 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 [24,36] with slight modifications. Normal saline solution was similarly injected into control rats. All rats were placed in standard cages over injection period.

Standard environments (SE) consisted standard plastic cages (42 cm × 34 cm × 15 cm), while enriched environment (EE) consisted larger cages (96 cm × 49 cm × 38 cm) containing plastic tunnels, rope, swing, balls, ramp, ladder, shelters, step, cube and a running wheel, which were cleaned and changed every 2–3 days to maintain its novelty, with food and water ad libitum [5]. The rats were housed 8 per cages in both of EE and SE housing, and handled during cage cleaning every 2–3 days.

The 32 rats were divided randomly into four groups ($n = 8$ rats per group): saline-standard environment (Sal/SE), saline-enriched environment (Sal/EE), METH-standard environment (METH/SE) and METH-enriched environment (METH/EE). In each of the four groups, saline or METH injection was performed for 14 days. On day 15, rats were placed in their home cages (SE or EE) with no injection, for 30 days (drug abstinence). From day 46, all rats were rested in standard cages. On days 47–49, all animals were tested in the elevated plus maze (EPM) and followed by the forced swim test (FST). On day 50, METH-withdrawn rats were housed individually in standard cages with two bottles for 8 days to evaluate the voluntary consumption of METH (on days 50–57), with food and water access (see Fig. 1).

In the test of anxiety, the rats were individually placed in the center of the EPM with two open (50 cm × 10 cm) and closed (50 cm × 10 cm × 40 cm) arms, and a central platform (10 cm × 10 cm), and allowed to explore the apparatus for 5 min, as described previously [21]. Time spent in, and entries into open and closed arms were measured during each 5 min test. The apparatus was cleaned after each trial with water.

The FST was used to assess the depressive-like activity. The test was carried out in a Plexiglas cylinder of 45 cm height and 20 cm diameter filled with 25 °C water up to a height of 30 cm. The rats were forced to swim in two trials. The first trial lasts 15 min, and followed 24 h later by a 5 min test. The following parameters were measured: swimming time, escaping time (toward the cylinder wall), immobility time (floating in the water, do only necessary movements to keep its head above water) [27]. On the test day, swimming sessions were videotaped from a lateral angle using a Nikon Camcorder, and above parameters were accomplished by experimenters blind. The water was exchanged for each rat. After each session, the rats were immediately removed from water, dried with a towel and were kept in a heated room until completely dry before being returned to their home cages.

Voluntary METH consumption and preference were quantified using a two-bottle choice paradigm over an 8-day period, as a model of METH intake [30], slightly modified in the rats after 4 weeks of withdrawal. One day before the test, all METH-withdrawn rats were kept in individual cages. The concentration of METH was 20 mg/l on days 1–4 and 40 mg/l on days 5–8 in one bottle, water was in control bottle. The rats had access to both bottles for 18 h to prevent from anorexia associated with METH consumption. To minimize effects related to learning, the position of the bottles was changed at the time of daily bottle weighing. The contents of both bottles were measured between 8:00 and 9:00 am daily. Body weights of the rats were measured every day. The daily consumption of METH measured based on mg/kg/18 h. Preference ratios (ml METH solution consumed/total ml consumed from both bottles) and also, the average of water consumption were evaluated during a 4-day period. The oral METH at relatively low doses causes arousing and rewarding effects in the rats and humans [8,31].

The data expressed as the mean ± standard error of the mean (S.E.M.). These data were analyzed by using two-way analyses of variance (ANOVA) with the fixed factors treatment (saline and METH) and groups (SE and EE), and with repeated measures as required. Post hoc analyses included Tukey's test. Preference ratios and water consumption during a 4-day period were analyzed by Student's t-test. The statistical differences were considered significant at $P < 0.05$.

3. Results

The results of the elevated plus maze (EPM) are illustrated in Fig. 2. Two-way ANOVA revealed a significant effect of group ($F_{1,28} = 29.7$, $P < 0.0001$), ($F_{1,28} = 48.7$, $P < 0.0001$) and treatment ($F_{1,28} = 13.2$, $P < 0.0001$), ($F_{1,28} = 14.7$, $P < 0.001$) for open arm time and entries, respectively. Also, two-way ANOVA revealed