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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enrichment on the severity of psychological dependence and voluntary methamphetamine consumption in methamphetamine withdrawn rats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- The environmental enrichment reduces voluntary consumption of METH in withdrawn rats.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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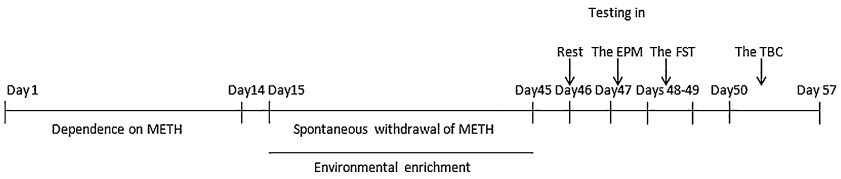

Fig. 1. Timeline of experiments (see Section 2 for details).

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

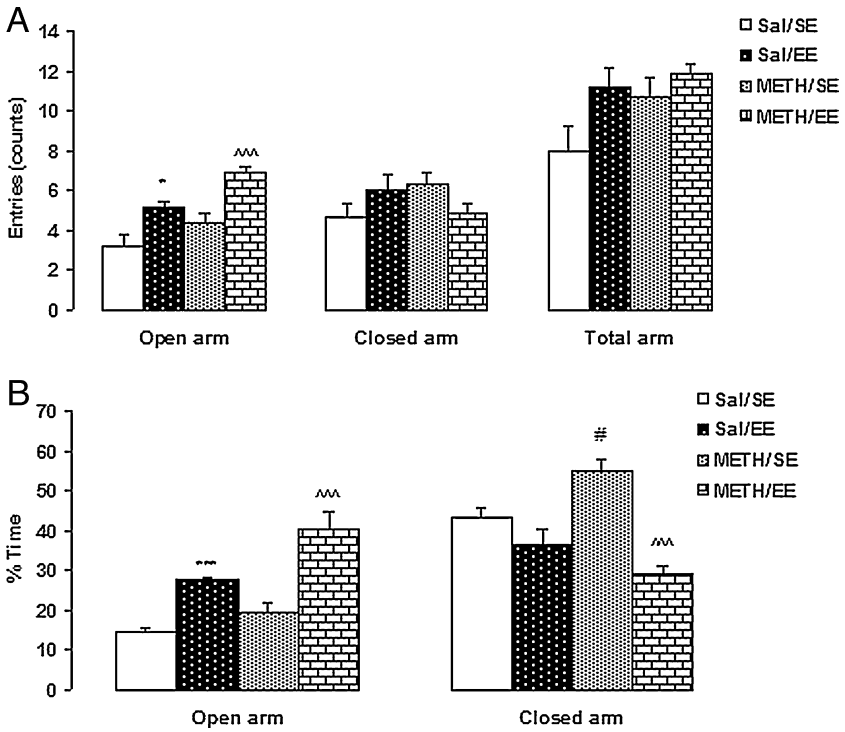

Fig. 2. Effect of environmental enrichment on the anxiety profile in METH withdrawn rats. (A) The number of entries and (B) time spent into open and closed arms. EE groups spent significantly more time in the open arms and made significantly more entries into the open arms than the SE groups. $^{*}P<0.017$, vs Sal/SE, $^{\wedge\wedge}P<0.0001$ vs METH/SE, $^{***}P<0.002$, vs Sal/SE, $^{\#}P<0.035$ vs Sal/SE group.

significant interactions between treatment and group on closed arm time ($F_{1,28}=11$, $P<0.003$) and entries ($F_{1,28}=5.63$, $P<0.025$). Between group comparisons showed that the number of open arm entries in EE groups was more than their controls ($P<0.017$, $P<0.0001$, respectively) (Fig. 2A). The Fig. 2B shows that the percentage of time spent in the open arms were significantly higher in the Sal/EE and METH/EE groups than the Sal/SE and METH/SE groups ($P<0.002$, $P<0.0001$, respectively). The percentage of time spent in closed arms in the METH/EE group was less than the METH/SE group ($P<0.0001$), also it was higher in the METH/SE group than the Sal/SE group ($P<0.035$).

The results of the FST using a two-way ANOVA revealed a significant effect of group ($F_{1,28}=37.33$, $P<0.0001$), and treatment ($F_{1,28}=12.2$, $P<0.002$), and a significant interaction between both factors ($F_{1,28}=4.42$, $P<0.045$) (Fig. 3). Between group comparisons showed less immobility time in the Sal/EE ($P<0.05$) and METH/EE ($P<0.0001$) and also displayed significantly more immobility time in METH/SE group ($P<0.001$) than their controls. There were no significant difference in swimming and escaping times between groups, ($P>0.05$) (data not shown).

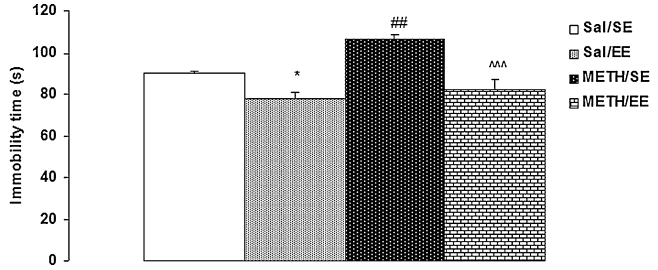

Fig. 3. Effect of environmental enrichment on the immobility time in the FST in METH withdrawn rats. The METH/SE group has shown higher immobility time than Sal/SE, while immobility time was less in METH/EE group than the METH/SE group. $^{*}P<0.05$ vs Sal/SE, $^{\#\#}P<0.001$ vs Sal/SE, $^{\wedge\wedge}P<0.0001$ vs METH/SE.

The results of the voluntary METH consumption during 4 days of intake (days 1, 4, 5 and 8) using a two-way ANOVA with repeated measures revealed a significant effect of days ($F_{3,42}=2.4$, $P<0.047$), groups ($F_{1,14}=9.56$, $P<0.022$) and a significant interaction between day × group ($F_{3,42}=4.7$, $P<0.044$) (Fig. 4). Between group comparisons showed that the intake of METH on fourth ($P<0.015$), fifth ($P<0.041$) and eighth ($P<0.002$) days is decreased significantly in METH/EE group than METH/SE group (Fig. 4A). In general, METH/SE rats exhibited a larger preference ratio compared to METH/EE group in the first and second periods ($T_{14}=2.49$, $P<0.026$; $T_{14}=2.03$, $P<0.05$, respectively) (Fig. 4B). There were no significant differences in voluntary water intake between groups in both periods ($P>0.05$), (Fig. 4C).

4. Discussion

This study provides novel evidence that enriched environments for 30 days during spontaneous METH withdrawal after chronic administration, reduces the voluntary consumption of METH and also anxiety and depressive-like behaviors in METH withdrawn rats, two main symptoms of METH withdrawal, as vulnerability factors to relapse. Our finding is consistent with previous results showing that the enriched environments decreased the response to amphetamine-induced stress-related behaviors such as anxiety [12,29], and depressive-like behaviors [4]. Presently, the neurobiological mechanisms underlying the reduced anxiety and depression following enriched environment are still not known. It may be due to direct and indirect involvement of a variety of neurotransmitter system including serotonin [4], norepinephrine [10], BDNF [15] and D2 receptor availability [23] in the various regions of brain following enriched environment. Therefore, the enriched environment was able to promote functional recovery in neurotransmitter systems involved in anxiety and depression. In present study, spontaneous METH withdrawal after chronic administration enhanced depressive and anxiety-related behaviors in novel and

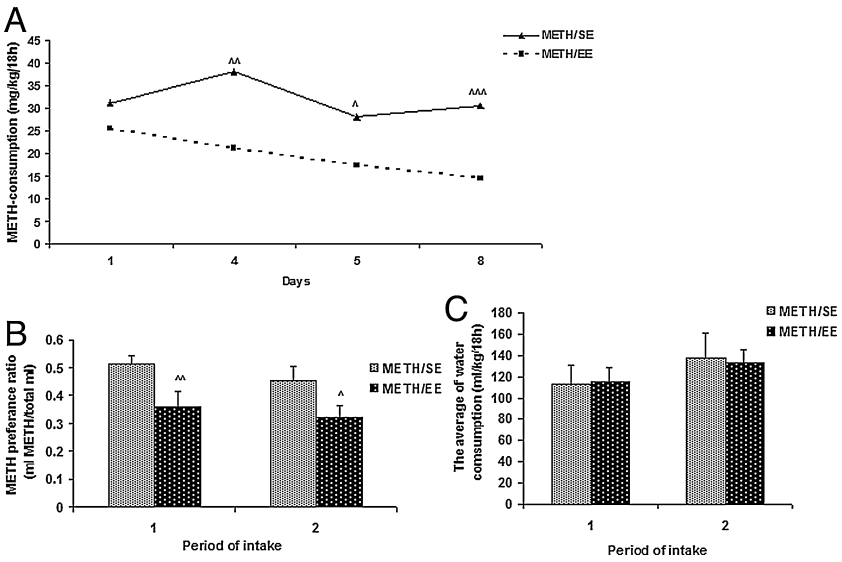

Fig. 4. Effect of environmental enrichment on the voluntary consumption of METH in withdrawn rats using a TBC paradigm. (A) The average of METH consumption during days 1, 4, 5 and 8 of intake. (B) Preference ratios and (C) the average of water intake in both periods. The METH/EE group showed a lower consumption of METH on days 4, 5 and 8 and also in both periods than METH/SE rats. In A; $^{\wedge\wedge}P<0.015$, $^{\wedge}P<0.041$, and $^{\wedge\wedge\wedge}P<0.002$ vs METH/SE. In B; $^{\wedge\wedge}P<0.026$, $^{\wedge}P<0.05$ vs METH/SE.

stressful conditions, while the enriched environment resulted in an improved coping with novel and stressful situations; which in turn lead to a reduced anxiety and depression levels in the Sal/EE and METH/EE groups in comparison with the Sal/SE and METH/SE groups.

Our findings have also shown that the enriched environment decreased the voluntary consumption of METH in withdrawn rats. No study has been conducted with the same nature thus far. Although, previous studies have shown that EE reduced self-administration and seeking behaviors of amphetamine and cocaine [11,12], MDMA (Ecstasy)-induced CPP [1].

Therefore, relatively low doses of oral METH in our study causes rewarding effects in the METH/SE rats, similar to human and animal studies [8,19]. In this study, the rats had free access to water and METH which preferred METH to water, reflecting an incentive demand for the drug in TBC model. Also, in present study, no significant difference between groups was observed in water intake using a two-bottle choice paradigm. Thus, we conclude that exposure to EE decreases the rewarding effects of METH which can reduce the risk of sensitivity and drug seeking after withdrawal [40]. The dopaminergic dysfunction [39], the low level of glutamate [2], and reduction of BDNF [6,14] may play a significant role in relapse of METH-seeking after protracted abstinence. In this regard, it has been shown that EE prevents methamphetamine-induced decrease of BDNF level after cessation of treatment with METH [6,14,15]. Also, it seems that antidepressant and antianxiety effects of enriched environment decreased voluntary METH consumption in withdrawn rats. Future studies need to examine the neurobiological mechanisms.

5. Conclusion

Our results have been shown that access to enriched environment during protracted abstinence from METH can decrease the anxiety and depressive-like behaviors and the voluntary consumption of drug in METH-withdrawn rats. Our findings may have a potential therapeutic application in the prevention of METH-induced behavioral sensitization and the risk of relapse in METH-dependent and withdrawn rats.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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