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Effects of Acute and Chronic Restraint Stress on Reinstatement of Extinguished Methamphetamine-Induced Conditioned Place Preference in Rats

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Abstract

Introduction: Methamphetamine (METH) is a neurotoxic psychostimulant with highly addictive potential and leads to compulsive drug use and vulnerability to relapse. Environmental cues, such as drug exposure, peer influence and social stress, are the powerful triggers of drug relapse. In this study, we tried to find out the effect of acute and chronic restraint stress on reinstatement of extinguished METH-induced conditioned place preference (CPP) in rats.

Methods: Subcutaneous (s.c.) administration of METH (0.125, 0.25, 0.5, 1, 2 and 4 mg/kg) could induce CPP which dose of 0.5 mg/kg was more potent than other doses. In extinction phase, rats were put in the CPP box for 30 min per day for 8 consecutive days. After extinction, animals were exposed to restraint stress (3-h period, as an acute stress) 60 min before subcutaneous administration of ineffective dose of METH (0.125 mg/kg) in order to reinstate the extinguished METH-induced CPP. For induction the chronic stress during extinction phase animal exposed the restraint stress for a 1-h period/day.

Results: The results showed that the effective dose of METH to induce CPP was 0.5 mg/kg. Also result revealed that physical stress (restraint stress) acute and chronic can significantly induce reinstatement of METH-induced CPP (P<0.001) in extinguished animals.

Conclusion: Additionally, the chronic restraint stress could reduce duration of extinction (maintenance) of METH-induced CPP. It is supposed that exposure the stress induce the relapse in abstinent amphetamine, but acute and chronic situation have a different reaction.

Keywords: Reward; Stress; METH; Reinstatement; Conditioned place preference.

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1. Introduction

METH is a psychostimulant that reinforces behavioral answering and brings about compulsive medicine use and vulnerably to relapse (NIDA report, 2010.). Though the precise neurobiological mechanisms underlying METH addicting behavior remain unknown, while rewarding effect of the drug plays a critical role. As well, relapse to drug intake is the most difficult challenge in the treatment of addiction, and the neurobiological mechanisms that underlie the persistence of such behavior remain poorly comprehended (Sulzer, Sonders, Poulsen, & Galli, 2005). Discussion between stress and drugs has been successfully patterned in rodents; thus, coverage to various acute and chronic stressors triggers drug-seeking for many drugs (Conrad et al., 2010; Faravelli et al., 2012). Furthermore, it has been proven that preference for the drug-paired environment can be reinstated by drug priming injections or stressors (Conrad et al., 2010; Sinha, 2008). Specialized medical researchers have indicated that stress is not only a risk factor in the development of habit but also an urge trigger to drug maltreatment. However, the mechanisms of stress-induced drug relapse have been still discussed for many years (De Giovanni, Guzman, Virgolini, & Cancela, 2016). In fact stressful activities modify the experience of brain areas active in the rewarding effects of psychostimulants (Belujon & Grace, 2011). Also, it has been suggested environmental stressors produce long-term changes in the function of brain reward pathways in the same way as drugs of abuse do (Quadros & Miczek, 2009). Exposure to stress increases drug seeking behavior and the risk of addictive drug use in human and animal models of drug addiction by the mechanisms that are not completely understood yet (Karimi et al., 2014). Immobilization stress is a kind of psychological stress that produces two major disruptions described in the literary works, a decrease in food intake (Marti, Marti, & Armario, 1994) and anxiety (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002; Sotomayor-Zarate et al., 2015). Restraint

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stress has been used to stimulate reinstatement of extinguished choice in CPP trained animals for different drugs: METH (Han et al., 2014), nicotine (Leao, Cruz, & Planeta, 2009) and cocaine (Briand & Blendy, 2013). Acute stress is sudden and short-term. This really is stress resulting from specific events or situations that involve novelty, unpredictability, a threat to the spirit, and leave with a poor sense of control. While chronic stress is the long-term stuff and unabated stress, this is resulting from repeated direct exposure to situations that lead to the discharge of stress hormones (Koob, 2008). Stress increases drug seeking behavior and the risk of addictive drug and the mechanisms that are not clearly understood yet. Consequently, in this study, we attempted to examine the effects of acute and chronic restraint stress on the reinstatement of extinguished METH conditioned place preference in rats.

2. Materials & methods

2.1. Animals

Animals were housed in categories of four per cage in a 12/12 h light/dark cycle (light on between 7: 00 a.m. and 7: 00 p.m.) with free access to food and water ad libitum. Adult male albino Wistar rats (Pasteur Company, Tehran, Iran) weighing 200-280 g were used in these experiments. The animals were randomly assigned to different control and treatment plan groups. Each animal applied only once. Rats were familiar with their new environment and handled for you week prior to experimental process was started. All tests were executed in obedience with the guide for the care and use of laboratory animals (National Institutes of Health Newsletter No. 80-23, revised 1996) and were approved by your research and Ethics Panel of Hamadan University of Medical Sciences, Hamadan, Iran.

2.2. Drugs

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In the present study the following drug was used: METH (Purity > 98%, gift from the Iran drug control headquarters) that was dissolved in sterile saline.

2.3. Apparatus

2.3.1. Conditioning place preference paradigm

A three-compartment CPP apparatus (30 cm × 30 cm × 40 cm) was used in these experiments (Haghparast et al., 2011). Place conditioning was conducted using an un-biased procedure. The apparatus was made of Plexiglas which was divided into three sized, two equal size with different textured compartments and one smaller size as a null compartment by means of a removable wall, but distinguishable by texture. To provide the tactile difference between the compartments, one of the compartments had a smooth floor while the other compartment had a net-like floor. Two preference compartments were differently striped black and white on their walls. The null compartment was a red tunnel (30 cm × 15 cm × 40 cm) connecting the two preference compartments. In this apparatus, rats showed no consistent preference for none of the large compartments, which supports our unbiased CPP paradigm. This paradigm took place in five consecutive days, which consisted of three distinct phases: pre-conditioning, conditioning and post-conditioning. In all phases, animals were tested during the same time period each day.

Pre-conditioning phase. On day 1 (pre-exposure), each rat with free access to all compartments was placed distinctly into the apparatus for 10 min . Animal displacement was recorded and analyzed on this day (pre-test day). In the experimental setup used in this study, the animals did not show an unconditioned preference for any compartments. Animals were then randomly assigned to one of the groups for place conditioning and 6–8 animals were used in each following experiment.

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Conditioning phase. This phase consisted of a 3-day plan of conditioning sessions. In this phase, animals received two trials in which they experienced the effects of the drugs while enclosed to one compartment for 30 min and other trials in which they experienced the effects of saline while enclosed to the other compartment by closing the not fixed wall. Access to the compartments was blocked on these days.

Post-conditioning phase. On the 5th day (test day) the not fixed wall was removed, and the rats could access the entire apparatus. The mean time spent in compartments during a 10-min period was recorded for each rat. In order to calculate the conditioning score, the difference in time spent for the drug-paired place and saline-paired place (two equal size compartments) was measured as the preference criteria. Time spent in each compartment and animal displacement were recorded by using a camera (Panasonic) placed 2 m above the CPP boxes and locomotion tracking was measured by Maze router software (Science Beam company, Iran). A video tracking system for automation of behavioral experiments was used (Ebrahimian et al., 2016).

2.4. Induction of METH extinction

Following the preference test day, the animals during the conditioning phase were exposed to extinction training with access to all compartments in the CPP apparatus without any drug injection for 30 min each day. This procedure was repeated for each animal in the control and experimental groups until the calculated CPP scores in two consecutive days in extinction period became similar to those on the pre-conditioning day. Conditioning score (CPP score) represents the time spent in the drug-paired place minus the time spent in saline-paired place which were recorded by Maze router software. Thus, the criterion for extinction or maintenance of the METH rewarding properties in all groups was a lack of significant differences in preference scores between two

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consecutive days in the extinction period and the preference score on the pre-conditioning day (Haghparast et al., 2013).

2.5. Restraint Stress test

To induce acute stress induction animals immobilized for 3 h once a day just before the reinstatement phase, for chronic stress, rats were exposed to immobilization stress for 1 h daily during extinction period in rodent immobilization bags (Santibanez, Gysling, & Forray, 2006; Vyas, Bernal, & Chattarji, 2003). Briefly, each rat was placed in an acrylic mesh restrainer device (length 20 cm, width 7 cm, height 6 cm) while control rats were kept in their home cages; immediately after, all animals were tested for reinstatement of METH-CPP (Quadros & Miczek, 2009).

2.6. Experimental design

2.6.1. METH dose-response effect on conditioned place preference paradigm

In these experiments, a dose–response relationship for METH on CPP paradigm was established. Different doses of METH (0.125, 0.25, 0.5, 1, 2 and 4 mg/kg) injected subcutaneously, to CPP induction during three days of conditioning phase (acquisition). In control group, animals received saline instead METH.

2.6.2. Reinstatement of extinguished METH-induced condition place preference in rats

In this set of experiments, animals during three days exposed to one distinct chamber in the presence of METH (0.5 mg/kg; s.c.) and alternative chamber in the presence of vehicle (Saline). The day after test day, animals were given free access to

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both chambers for 8 days (extinction phase) . To assess the METH-induced reinstatement, two groups of animals treated with ineffective dose of METH (0.125 and 0.25 mg/kg; s.c.), and another group received saline as a vehicle group. Conditioning score and distance traveled were recorded during reinstatement phase during a 10-min period (Fig. 1 A, B).

2.6.3. Effect of exposure to acute restraint stress on reinstatement of METH-induced CPP in rats

To examine the possible role of acute application of restraint stress on reinstatement of extinguished METH-induced CPP, animals passed conditioning and extinction phase, The day after extinction rats exposed the restraint stress for 3-h period, and after 60 min, animals placed in CPP apparatus and received ineffective dose of METH (0.125 mg/kg) to induce reinstatement phase. Conditioning score and distance traveled were recorded during 10-min period (Fig. 1 C).

2.6.4. Effect of exposure to chronic restraint stress on reinstatement of METH-induced CPP in rats

In order to examine the possible effect of chronic restraint stress in reinstatement of extinguished METH-induced CPP, after conditioning phase animal daily received restraint stress for 1 h, after 60 min animals placed in entire apparatus (free access) to induce extinction phase. The day after extinction phase animals received ineffective dose of METH (0.125 mg/kg) to induce reinstatement of METH (Fig. 1 D).

2.7. Statistics

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Conditioning score represents the difference between the times spent in the drug- and saline-paired compartments, and is expressed as mean ± SEM (standard error of mean). Data were processed by commercially available software Graph Pad Prism® 5.0. In order to compare the conditioning scores and distance traveled obtained in all groups (vehicle and experimental groups), one-way analysis of variance (ANOVA) and repeated measures or randomized block model followed by post hoc analysis (Dunnett's or Newman-Keuls's test) were used, as appropriated. *P*-values less than 0.05 ($P<0.05$) were considered to be statistically significant.

3. Results

In the first set of experiment, we examined the dose response effects of different doses of METH (0.125, 0.25, 0.5, 1, 2 and 4 mg/kg) injected subcutaneously, on CPP paradigm (n= 8). One-way ANOVA followed by Dunnett's test [$F(6, 55) = 17.25$, $P<0.0001$] revealed that there were significant differences in conditioning scores among the vehicle (saline) and experimental groups (Fig. 2). Our findings showed that the most effective dose of METH is 0.5 mg/kg ($P<0.001$).

3.1. Reinstatement of extinguished METH induced CPP in rats

Subcutaneous injection of METH (0.5 mg/kg) during 3 conditioning days induced significant preference ($P<0.001$) for the METH-paired chamber in comparison with saline-paired chamber. During the extinction period, without any injection, the CPP score was calculated every day. The CPP induction by METH gradually moderated over days and the time spent in METH-paired chamber did not differ from the saline one by 7th and 8th extinction days. After the last extinction day, the animals were tested for reinstatement.

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Subcutaneous injection of METH priming dose (0.25 mg/kg) could induce reinstatement, $F(3, 23) = 8.031$, $P<0.0001$] and CPP score on reinstatement day significantly increased compared to pre-test phase ($P<0.001$; Fig. 3) (n= 8).

3.2. Effect of exposure to acute restraint stress on reinstatement of METH-induced CPP in rats

In this set of experiments, the possible effect of acute restraint stress on reinstatement of extinguished METH-induced CPP was examined. Animals passed conditioning and extinction phase as described before but the day after extinction (reinstatement phase), animals exposed to restraint stress for 3-h period, $F(8, 62) = 6.644$, $P<0.0001$; Fig. 4]. Animals received ineffective dose of METH for reinstatement (0.125 mg/kg), after exposure to acute restraint stress. Conditioning score and distance traveled were recorded during 10-min period, $F(2, 20) = 12.27$, $P=0.0004$] (n= 8). As results shown, ineffective dose of METH for reinstatement induction, together with acute restraint stress could reinstatement of METH.

3.3. Effect of exposure to chronic restraint stress during extinction phase on reinstatement of METH-induced CPP in rats

To assess the chronic stress effects on reinstatement of METH. Each day during extinction phase, before putting the animals in CPP apparatuses, they exposed to the restraint stress for 1 hour. The CPP score was calculated every day (Fig. 1). In this experiment group chronic stress could diminish extinction phase for one day [$F(7, 63) = 7.998$, $P<0.0001$; Fig. 5] (n= 8). The day after extinction phase animals in chronic stress groups received ineffective dose of METH for reinstatement (0.125 mg/kg). Comparing the conditioning score between

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reinstatement day and pretest using student t test showed significant difference [t_p (7) = 6.271, P<0.001; Fig. 5].Which indicated that METH ineffective dose for reinstatement induction, together with chronic restraint stress, could reinstatement of METH.

3. Discussion

Stressful activities modify activity in areas of the brain involved in the rewarding effects of psychostimulants. Although all factors responsible for relapse to drug seeking are not completely known, addicting drugs and stress are considered to bring about medication craving and reinstatement of extinguished drug-seeking in retrieving drug abusers (Sadeghzadeh, Babapour, & Haghparast, 2016). The major finding of our study was that the acute and chronic restraint stress potentiates the effect of low-dose of METH and could reinstate METH conditioning place preference in the rat. Nevertheless, for the first time, our data provided evidence that chronic immobilization stress could reduce duration of extinction of METH induced conditioning place preference. Thus the results of the current research further add to the growing literature in engagement of stress in urge and reward pathway. Drug-associated stimuli, stress, and drugs of abuse are hypothesized to trigger reinstatement to drug reward-related behaviors (Lu, Shepard, Hall, & Shaham, 2003). Previous studies have shown that stressors, such as restraint (Pacchioni, Gioino, Assis, & Cancela, 2002), footshock (Wang, Luo, Ge, Fu, & Han, 2002), butt pinching (Katz & Roth, 1979), and defeat (Covington & Miczek, 2001), cause drug reward and reinstatement efficiently. Interestingly, this current analyze also provides the proof about the duration of restraint stress for causing reinstatement of extinguished METH-CPP. This despite the fact that as mentioned that the acute and chronic stressors have a different and separate efficiency.

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It has already been shown that acute restraint stress activates orexin neurons in the lateral hypothalamus, which send projections to the VTA, releasing orexins that activate dopaminergic neurons and reward pathway (Tung et al., 2016). Several lines of evidence also have suggested that the reinstatement of drug seeking behaviors is mediated by dopamine receptors (Dai, Kang, Wang, & Ma, 2006; Gilbert et al., 2005). As well, Mazid et al., in 2016 suggest that desperate stress could affect opioid-related learning (Mazid et al., 2016). As well, it confirmed that desperate food deprivation facilitate reinstatement of morphine CPP in rats (Sadeghzadeh et al., 2016). Furthermore acute social defeat stress involve on the reinstatement of the CPP caused by cocaine (Montagud-Romero et al., 2015). Conrad et al revealed that cold swim stress can have long-term results on cocaine seeking habit (Conrad et al., 2010). On other hands experiment show that experience of chronic stress significantly decreases cocaine induced activation of reward pathway (Glynn et al., 2016). Also, it has been reported that exposure to chronic stress protocol significantly reduces dopamine extracellular levels induced by cocaine (Sotomayor-Zarate et al., 2015). Past studies have shown that repeated restraint stress direct exposure enhances excitatory drive to the basolateral amygdala (BLA) an area critical for behavioral responses to be anxious (Padival, Quinette, & Rosenkranz, 2013). As we mentioned chronic stress in our study decrease duration of METH extinction, and animal exposure to reinstatement phase, sooner than those received acute stress or control group. It seems that chronic stress affected to reward pathway and extinction process since chronic stress may have an aversive impact on daily living, individuals may have a tendency to cope using drugs. Chronic stress has a worst effects than desperate stress. Exposure to stress filled life events and hypothalamic-pituitary-adrenal (HPA) axis dysfunction have been implicated in the development of several psychological disorders that are comorbid with craving (Faravelli et al., 2012). Mahoney el al in 2015 mentioned that stimulant users endorse greater impulsivity, life stress and sensation seeking is clearly evident and methamphetamine users endorsed

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significantly higher number of life stressors and increased life stressors may account for their methamphetamine usage patterns (Mahoney et al., 2015). Presented the value of environment in drug addiction, our data support the idea that the restraint stress evoked the reinstatement of METH-CPP responses. Together, these studies raise the intriguing opportunity that the behavioral impact of stress exposure on incubation of reinstatement noticed here could also be due to alterations in activity within the brain area which involved in stress process.

Conclusions

It conclude that acute and chronic restraint stress could reinstate METH conditioning place preference by ineffective dose of METH for reinstatement induction. These studies will finally lead us closer to developing effective ways to cut down craving and prevent urge in abstinent amphetamine abusers. However, further behavioral, electrophysiological and molecular investigations are needed to elucidate brain areas involvement pathway in psychological stress and medication relapse.

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Finding

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Figure Legends

Fig. 1. A) Experimental protocols for METH-induced reinstatement of conditioned place preference (CPP) in the rats. **B)** In the set of experiments, 24h following the last day of the extinction period, animals were placed into the CPP box and tested for place preference (CPP test) by only injection of the priming dose of METH (0. 25 mg /kg; sc). **C)** In the set of experiments (ineffective METH dose + Acute restraint stress-induced reinstatement), upon extinction was established, rats were given a 3-h restraint stress period and after 60 min, animals were placed into the CPP box and tested for reinstatement by only injection of the ineffective dose of METH (0.125 mg /kg; sc). **D)** In the set of experiments, after the CPP acquisition, 60 min before animal placing into the CPP box, animal received 1h restraint stress as a chronic stress period during daily the extinction period, 24h following the last day of the extinction period animal tested for reinstatement by only injection of the ineffective dose of METH (0.125 mg /kg; sc).

Fig. 2. Effect of different doses of METH on place preference in rats. Each point shows the mean ± SEM for 7-10 rats in each group.

* $P<0.05$ and *** $P<0.001$ compared with saline-control group

Fig 3. Dose–response effects of METH on the reinstating of extinguished METH -induced conditioned place preference. In right panel, animals received METH (0.5 mg/kg; sc) during conditioning phase, t_p (5) = 8.598, ($P<0.001$). The day after post-conditioning day, animals were given free accesses to both chambers for 8 days. To assess the METH -induced

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reinstatement, animals received ineffective doses of METH 0.125 and 0. 25 mg/kg and saline as a control group. Each column represents the mean ± SEM of 6 rats.

*** $P<0.001$ compared with pre-test day

† $P<0.01$, †† $P<0.001$ and ††† $P<0.0001$ different from post-test day

++ $P<0.01$ compared with last day of extinction period

Fig 4. Effect of exposure to acute restraint stress on reinstatement of METH-induced CPP in rats. The day after extinction, animals were faced to acute restraint stress (3-h period). Animal received ineffective dose of METH for reinstatement (0.125 mg/kg). In reinstatement phase, conditioning score and were recorded during 10-min period. Each column represents the mean ± SEM of 7 rats.

** $P<0.01$ and *** $P<0.001$ compared with pre-test day

† $P<0.01$ and ††† $P<0.0001$ different from CPP test in post-conditioning phase

++ $P<0.01$ compared with last day of extinction period

Fig 5. Effect of exposure to chronic restraint stress on reinstatement of METH-induced CPP in rats. Animal was exposed to restraint stress every day during extinction phase 1-h per/day. After relapse animals received ineffective dose of METH for reinstatement (0.125 mg/kg). Each column represents the mean ± SEM of 8 rats.

*** $P<0.001$ compared with pre-test day

† $P<0.01$, †† $P<0.001$ and ††† $P<0.0001$ different from post-test day

+++ $P<0.001$ compared with last day of extinction period

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