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Cannabidiol inhibits priming-induced reinstatement of methamphetamine in REM sleep deprived rats

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ABSTRACT

Methamphetamine (METH) is a widely abused and a severely addictive psychostimulant. Relapse is the main cause of concern when treating addiction. It could manifest after a long period of abstinence. Previous studies showed that there is a strong connection between sleep impairment and relapse. Also, it has been reported that cannabidiol might be a potential treatment for drug craving and relapse. In this study, we used conditioned place preference (CPP) to investigate whether Cannabidiol (CBD), a phytocannabinoid, can prevent METH-induced reinstatement in Rapid Eye Movement Sleep Deprived (RSD) rats. In order to induce CPP, the animals were given METH (1 mg/kg; sc) for five days. The effective priming dose of METH (0.5 mg/kg, sc) reinstated the extinguished METH-induced CPP. In order to investigate the effect of RSD on METH-induced reinstatement, we used the inverted flowerpot technique to deprive the rats of REM sleep. We found that 24 h-RSD could facilitate priming-induced reinstatement of METH. In addition to this, the ICV administration of CBD 10 μg/5 μl could suppress the METH-induced reinstatement even in RSD rats. In conclusion, the administration of CBD 10 μg/5 μl effectively prevents METH-induced CPP, even in a condition of stress. CBD can be considered an agent that reduces the risk of the relapse; however, this requires more investigation.

1. Introduction

Methamphetamine (METH) is a widely abused, highly potent and severely addictive psychostimulant (Courtney and Ray, 2014). One of the major problems in the treatment of addiction is the high rate of relapse even after a prolonged period of drug abstinence (O'Brien, 2005). It has been found that three types of stimuli could induce drug reinstatement in the animal models, namely: 1) stress 2) drug-associated cues and 3) drug priming (De Wit, 1996; Mantsch et al., 2016; Shaham et al., 2003). Despite the high numbers of METH users, as of now, there is no FDA-approved pharmacotherapy available for METH addiction (Gonzales et al., 2010).

Sleep includes two phases, namely Rapid Eye Movement (REM) and non-rapid eye movement. Sleep disturbance is common in patients during the recovery from drug abuse (Angarita et al., 2014) and may have a negative impact on the patients' mood which might be a possible factor leading to relapse (Knapp et al., 2007). Also, several findings suggest that sleep plays a critical role in reward memory reconsolidation (Shi et al., 2011). Moreover, sleep disorders have been presumed to have intensified the craving of drugs and thus promote relapse (Chen et al., 2015; Teplin et al., 2006). Clinical studies have suggested that sleep problems could sometimes be severe enough to induce drug reinstatement (Smith et al., 2014). REM sleep deprivation (RSD) elicited a long-term sensitized response to the acute administration of amphetamine and potentiated behavioral sensitization induced by the priming administration of the drug (Kameda et al., 2014). Besides, it has been shown that RSD activates the hypothalamic-pituitary-adrenal axis. Hence, it is considered a strong stress (Galvao Mde et al., 2009; Hipolide et al., 2006). Since it is known that stress induces reinstatement, it was expected that RSD could cause such an effect. The role of REM sleep in the reward processing can be indirectly proved by the studies of RSD in drug-induced conditioned place preference.

Cannabidiol (CBD) is a non-psychotomimetic compound of the herb *Cannabis sativa* (Izzo et al., 2009). In the central nervous system (CNS), CBD has neuroprotective (Santos et al., 2015), anti-oxidative and anti-inflammatory properties (Costa et al., 2004; Fernandez-Ruiz et al., 2013). Also, several findings indicate that this compound shows therapeutic characteristics in the neuropsychiatric disorders, including anxiety, schizophrenia, addiction and epilepsy (Campos et al., 2012; Devinsky et al., 2014). Moreover, Parker et al. showed that CBD failed to induce conditioned place preference (Parker et al., 2004). It was revealed that the administration of CBD reduced the reinforcing properties, motivation, and relapse for ethanol (Viudez-Martinez et al., 2017). Also, CBD can be used as an effective and a novel treatment for

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weakening the memories associated with drugs leading to abuse, thereby decreasing the risk of drug relapse (De Carvalho and Takahashi, 2016).

To the best of our knowledge, no study has been conducted on the effects of CBD on METH-induced reinstatement in RSD rats. The aim of this study was to investigate whether CBD could disrupt the METH-induced reinstatement in RSD rats. Hence, we used CPP, to assess the motivational properties, including the rewarding effects of psychostimulants in animals.

2. Materials and methods

2.1. Animals

In this study, adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 220–280 g at the beginning of the experiments were used. The animals were kept under standard laboratory conditions in a 12:12-h light/dark cycle (lights on at 07:00 h) with free access to laboratory chow and tap water. The animals were randomly assigned to different experimental groups. The rats were habituated to their new environment and handled for one week before the experimental procedure was started. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals essential to produce reliable scientific data. The experiments were conducted between 9:00 a.m. till 3:00 p.m. All experiments were performed in accordance with the guide for the care and use of laboratory animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.SM. REC.1394.153).

2.2. Drugs

Methamphetamine Hydrochloride (synthesized and analyzed by Laboratory of Medicinal Chemistry, School of Pharmacy, Baghiyatallah University of Medical Sciences, Tehran, Iran) that was freshly diluted in normal saline and was given subcutaneously (sc). Cannabidiol (Tocris Bioscience, Missouri, USA) was dissolved in dimethyl sulfoxide 10% and phosphate buffer solution 90% and injected with a 5-μl volume into the lateral cerebral ventricle.

2.3. Surgery and microinjection procedures

All rats were anesthetized with ketamine-xylazine (100 mg/kg ketamine-10 mg/kg xylazine). The stereotaxic coordinates for the intracerebroventricular (ICV) injection were as follows: a guide cannula was implanted in the left ventricle of rats using stereotaxic surgery (1.6 mm lateral and 0.5 mm posterior to bregma, 4.2 mm deep from dura). The cannula was secured by dental cement and anchored to stainless steel screws that were fixed to the skull. In order to inhibit clogging, the stainless steel obturator was inserted into the guide cannula. Animals were allowed to recover for 5–7 days from surgery before experiments.

Microinjections were done by the injector canal was connected to a 5 μl Hamilton syringe by polyethylene tubing (PE-20), and then drugs were infused into the lateral ventricle over a 2-min period. The injection needle was kept in place for 60s to allow the drug to completely diffuse from the tips and prohibited drug backflow, after that the obturator was reinserted into the guide cannula.

2.4. Conditioned place preference paradigm

The conditioned place preference (CPP) is a prevalent method to evaluate motivational properties such as rewarding or aversive effects of drugs in animals.

2.5. Apparatus

A three-compartment CPP apparatus (30 cm × 30 cm × 40 cm) was used in these experiments. Place conditioning was conducted using an unbiased procedure (Attarzadeh-Yazdi et al., 2014; Sadeghzadeh et al., 2015). The Plexiglas apparatus was divided into two equal-sized compartments with the third section being the null section which connected the two equal size sections (30 cm × 15 cm × 40 cm). Both compartments had white backgrounds with black stripes in dissimilar orientations (Vertical vs. Horizontal). To provide the tactile difference between the compartments, one of them was floored by a smooth panel while the other had a net floor. In this apparatus, rats showed no consistent preference for either compartment, an observation that supports our unbiased conditioned place preference paradigm. All compartments were placed in a quiet and isolated room under a constant light and sound situation. The room was equipped with a light centered above the compartment, turned on every session (Arezoomandan et al., 2016; Ebrahimian et al., 2016; Karimi et al., 2014).

2.6. Conditioned place preference protocol

CPP paradigm, took place on seven consecutive days in three distinct phases, including pre-conditioning, conditioning, and post-conditioning. For all of these phases, the animals were tested during the same time period each day.

Preconditioning phase: The rats were transported from the animal housing room to the test room at least 30 min prior to the start of the experiment, for habituation. To determine the baseline chamber preference – during the pre-conditioning phase – on the first day, each animal was placed separately in the start box with the removable door removed and rats were permitted to move freely in all three chambers for 10 min. The distance traveled and the time spent in each compartment was recorded. Each animal which spent ≥ 80% of the total test time in a compartment was considered to have initial bias and was excluded from the study. The animals that did not show any preference for either of the compartments were then randomly chosen to one of the two compartments for place conditioning and seven to eight animals were used for each group.

Conditioning phase: The conditioning phase started one day after the pre-conditioning session and consist of ten 45-min sessions (five with saline and five with drug pairing) in a five-day schedule. These sessions were conducted twice each day (from day 2 to day 6) within 6-h intervals. For conditioning trials, the animals received METH (1 mg/kg s.c.) and were immediately confined to the conditioning compartment for 45 min; about 6 h later, the rats were injected with saline and immediately put in the saline-paired compartment for 45 min.

Post-conditioning phase: This phase was carried out on day 7, following the last conditioning day. In order to determine a conditioning score (CS), as a preference index, the guillotine door was removed so that rats could access freely the entire apparatus for 10 min. The time spent for each rat in both compartments during a 10-min period was recorded by a 3CCD camera (Panasonic Inc., Japan) and analyzed using the Ethovision software (Version 7), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands). Each animal's CS was calculated in all groups. Also, total distance traveled for each animal was also recorded in the control and experimental groups.

2.7. Locomotion tracking apparatus

The locomotor activity of each animal was recorded using the locomotion tracking apparatus by a video tracking system (Ethovision software). In these experiments, the total distance traveled (in centimeters) for each animal was measured in pre- and post-tests for the control and experimental groups.

2.8. Extinction

Following the acquisition of the CPP, the rats were placed in the CPP box daily without injection of METH, and the time spent in each compartment was recorded by the Ethovision software each day. This procedure was done for all groups until the calculated CS in two subsequent days in the extinction period were similar to those on the pre-conditioning day. Thus, the criterion for the extinction of the METH-rewarding properties in all groups was a lack of significant difference in the CPP scores between two subsequent days of the extinction period and the CPP score on the pre-conditioning day (Sadeghzadeh et al., 2015; Arezoomandan et al., 2016).

2.9. Reinstatement

In reinstatement studies, return to drug seeking, occurs when animals are exposed to priming injection of drugs, drug cues or stressors following extinction. In our study, once an extinction criterion was reached, as mentioned above, the rats are tested for reinstatement of drug seeking by an injection priming doses of METH (0.25 or 0.5 mg/kg), that failed to induce METH conditioning. Following the injection, rats were placed into the CPP chamber for 10 min during the reinstatement test while permitted to explore the entire apparatus on the reinstatement day (24 h following the last extinction day). The conditioning score and distance traveled are recorded during the 10-min period (Attarzadeh-Yazdi et al., 2014; Arezoomandan et al., 2016).

2.10. REM sleep deprivation protocol

The inverted flowerpot technique is the most widely used method for REM sleep deprivation studies. This method is applicable to deprive REM sleep and permit other sleep stages (Machado et al., 2004). In this model, several rats are deprived together in order to inhibit isolation stress (Gurel et al., 2014; Soto-Rodriguez et al., 2016). We placed 7 rats into one cage containing 15 small platforms (6 cm in diameter) surrounded by water (water up to 1 cm below the surface of the platform). One platform was kept empty to decrease immobilization stress. Therefore, the animals were able to freely move and interact with each other. REM sleep is associated with muscle atonia, so when REM sleep starts animals fall from the platform into the water. Thus, the animal wakes up and climbs onto the platform again.

3. Experimental design

3.1. Experiment 1: dose–response effects of METH on the reinstatement of extinguished METH-induced CPP in rats

In this set of experiments, three groups of animals during five days were exposed to one distinct chamber in the presence of METH (1 mg/kg; sc) and alternative chamber in the presence of saline. The day after the post-conditioning phase (test day), all groups were allowed free access to both chambers for ten days. This procedure was repeated for each rat until the CPP scores in two consecutive days in the extinction period became similar to those on the pre-conditioning day (Arezoomandan et al., 2016; Attarzadeh-Yazdi et al., 2014). One day after the last extinction trial, the animals came into the reinstatement phase and received different priming doses of METH (0.25 and 0.5 mg/kg; sc) or saline immediately prior to being placed into the CPP chamber for 10 min.

3.2. Experiment 2: The effects of 6 and 24 h REM sleep deprivation on the reinstatement of extinguished METH-induced CPP in rats

The aim of this experiment was to assess whether the RSD could facilitate the reinstatement of extinguished METH conditioned place preference. To achieve this purpose, animals that passed the conditioning and extinction phases as described before, divided two groups: one group of animals was exposed to 6 h-RSD ($n = 7$) and another group was exposed to 24 h-RSD ($n = 7$). All the groups in this experiment were treated with an ineffective priming dose of METH (0.25 mg/kg; sc) just before the reinstatement test to facilitate RSD-induced reinstatement of seeking behaviors, the conditioning score and distance traveled were recorded during a 10-min period.

In order to show whether RSD by itself would only induce reinstatement without any priming dose of METH, animals that passed the conditioning and extinction phases as described, underwent 6 or 24 h-RSD ($n = 5$ in each group). Finally, all animals spent reinstatement test without METH injection.

3.3. Experiment 3: The effect of ICV administration of CBD on the reinstatement of METH-induced conditioned place preference

To find out the effect of CBD on METH-induced reinstatement. After extinction was established, on reinstatement day, 60 min after the CBD 10 μg/5 μl administration ($n = 6$) (Murillo-Rodriguez et al., 2006) or CBD solvent ($n = 4$), the effective priming dose of METH (0.5 mg/kg; sc) was injected and immediately the rats were placed in CPP box and the time spent and distance traveled were recorded for 10 min.

3.4. Experiment 4: The effect of ICV administration of CBD, on the RSD-induced reinstatement of extinguished METH CPP

Three groups were assigned to investigate the impact of CBD on the reinstatement of METH in RSD rats. After extinction was established, on reinstatement day, one group as a control only was deprived of 24 h-REM sleep ($n = 6$). Two other groups received dose 1 ($n = 5$) or 10 μg/5 μl (n = 6) CBD before they endured REM sleep deprivation for 24 h. All the groups in this experiment were treated with an ineffective priming dose of METH (0.25 mg/kg; sc) just before the reinstatement test, the conditioning score and distance traveled were recorded during a 10-min period.

3.5. Histology

After completion of behavioral testing, the animals with the ICV cannulation were intensely anesthetized with Ketamine and Xylazine. Then, they were transcardially perfused with 0.9% saline and 10% formalin solution. The brains were removed, blocked and cut coronally into 50-μ sections through the cannulae placements. The histological results were plotted on the representative sections taken from the rat brain atlas of Paxinos and Watson (Paxinos, 2005). Only the results from animals with correct cannulae placements were included in the data analysis.

3.6. Statistics

The CPP score represented the differences between the times spent in the drug- and saline-paired compartments, and was expressed as mean ± SEM (standard error of mean). The data were processed by the commercially available software GraphPad Prism® 5.0. To compare the CPP scores and distance traveled which was obtained from two or more controls and experimental groups, independent samples/paired *t*-test, or repeated measures/block randomized one-way analysis of variance (ANOVA) followed by post hoc analysis (Dunnett's or Newman–Keuls's test) were used as appropriated, respectively. P-values < 0.05 ($P < 0.05$) were considered to be statistically significant.

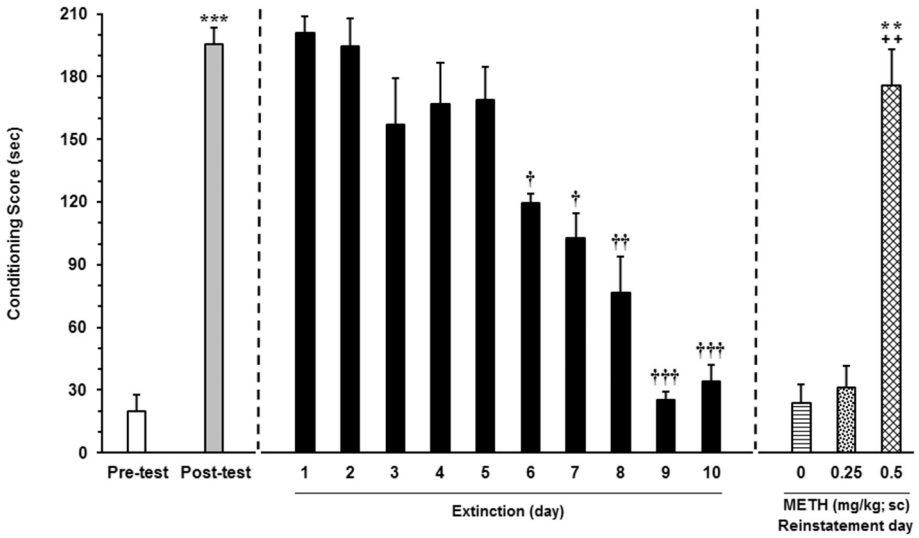

Fig. 1. Dose-response effects of METH on the reinstating of extinguished METH-induced conditioned place preference. (A) The conditioning scores were measured in pre- and post-conditioning days. Animals received METH (1 mg/kg; sc) during the conditioning phase. (B) The day after post-conditioning day, animals were allowed free access to both chambers for ten days as extinction period. The conditioning scores were measured during the extinction period every day. (C) To assess the METH-induced reinstatement, animals received priming doses of subcutaneous METH (0.25 and 0.5 mg/kg) and saline (1 ml/kg) following 24 h after the last extinction day (reinstatement day). Conditioning score and distance traveled were recorded during these phases. Each bar shows the mean ± SEM for 5 rats.
**P < 0.01 and ***P < 0.001 different from the pre-test day.
†P < 0.05, ††P < 0.01 and †††P < 0.001 different from the post-test day.
++P < 0.01 different from extinction day.

4. Results

4.1. Dose-response effects of METH on the reinstatement of extinguished METH conditioned place preference

As shown in the right panel of Fig. 1, a paired sample t-test indicated that there was a significant difference between the pre- and post-test conditioning scores [t_p (5) = 8.598, P < 0.001]. It indicated that injection of METH during the conditioning phase had induced place preference. Furthermore, one-way repeated measures ANOVA followed by Dunnett's multiple comparison test [$F_{(6, 54)}$ = 5.922, P < 0.0001; Fig. 1, mid panel] confirmed that the animals in these groups had extinguished their preference for the METH-paired compartment on the tenth day extinction day (i.e. no significant difference between CPP score on pre-conditioning, the ninth and tenth extinction days). On the other hand, after the extinction period, the animals received the different priming doses of METH (0.25 and 0.5 mg/kg; sc) or saline, for reinstating the extinguished METH preference in rats. One-way ANOVA followed by Dunnett post hoc analysis showed that there were significant differences between the conditioning scores obtained on the last extinction day and reinstatement days at a dose of 0.5 mg/kg METH (effective priming dose) [$F_{(3, 19)}$ = 10.11, P = 0.0006; Fig. 1, left panel]. Additionally, the Dunnett's multiple comparison test indicated that there were significant differences between the conditioning scores in the reinstatement days at the dose of 0.5 mg/kg METH (effective priming dose) and saline-treated animals [$F_{(3, 19)}$ = 10.74, P = 0.0004].

4.2. Effect of REM sleep deprivation on the reinstatement of METH-induced conditioned place preference

The statistical analysis of obtaining data in left panel of Fig. 2, from the paired samples *t*-test, indicated that daily injection of METH during the conditioning phase (1 mg/kg; sc) had induced place preference [t_p (6) = 6.054, P = 0 < 0.001], because there was a significant difference between pre- and post-test in conditioning scores. Also, as shown in the mid panel of Fig. 2, there was a significant difference between post-test and last day of extinction in conditioning scores [t_p (6) = 9.321, P = 0 < 0.001] indicated that the animals in these groups had extinguished their preference for the METH-paired compartment on the tenth extinction day (i.e. no significant difference in the time spent in the compartment paired previously with METH or saline, on the ninth and tenth extinction days). On the other hand, after the extinction period, the animals were divided into two groups 6 h-RSD and 24 h-RSD animals – then they were tested for evaluating the reinstatement of METH-induced CPP following the RSD condition in the rats. One-way ANOVA followed by Dunnett post hoc analysis showed that there were significant differences between the conditioning scores obtained on the last extinction day and the reinstatement day in 24 h-RSD group [$F_{(3, 27)}$ = 6.85, P = 0.0043; Fig. 2, right panel]. Additionally, a one-way block randomized ANOVA followed by Dunnett's multiple comparison test indicated that there were significant differences among the conditioning scores on the reinstatement day in the 24 h-RSD group and pre-test [$F_{(3, 27)}$ = 6.859, P = 0.0017; Fig. 2, right panel]. Additionally, as depicted in Supplementary Fig. 1, our data showed 6 or 24 h-RSD was not enough to induce reinstatement of METH in the condition of absent of METH priming.

4.3. Effect of ICV administration of CBD, on the reinstatement of METH-induced conditioned place preference

As depicted in the left panel of Fig. 3, indicated that daily injection of METH during the conditioning phase (1 mg/kg; sc) had induced place preference [t_p (5) = 5.084, P < 0.001], because there was a significant difference between pre- and post-test in conditioning scores. There was a significant difference between post-test and last day of extinction in conditioning scores [t_p (4) = 6.32, P = 0 < 0.001; Fig. 3, mid panel] indicated that the animals in these groups had extinguished their preference for the METH-paired compartment on the tenth extinction day. There was a significant difference among last day of extinction, CBD (10 μg/5 μl) and CBD solvent groups in conditioning score [$F_{(2,14)}$ = 15.94, P < 0.0004; Fig. 3, right panel]. One-way ANOVA followed by Dunnett post hoc analysis showed there was a significant difference among pre-test, reinstatement day of CBD (10 μg/5 μl) and reinstatement day of CBD solvent in conditioning score [$F_{(2,15)}$ = 18.29, P < 0.0002; Fig. 3, right panel]. Also, there was a significant difference between conditioning scores in reinstatement day of groups that received 10 μg/5 μl doses of CBD and CBD solvent [$t_{(8)}$ = 4.188, P < 0.01; Fig. 3, right panel] to show that CBD solvent lacked effect on reinstatement.

4.4. Effect of ICV administration of CBD, on the reinstatement of METH in REM sleep deprived rats

As was shown in the left panel Fig. 4, from the paired samples *t*-test, indicated that daily injection of METH during the conditioning phase (1 mg/kg; sc) had induced place preference [t_p (5) = 10.53, P = 0 < 0.001]. There was a significant difference between post-test and last day of extinction in conditioning scores [t_p (5) = 6.456,

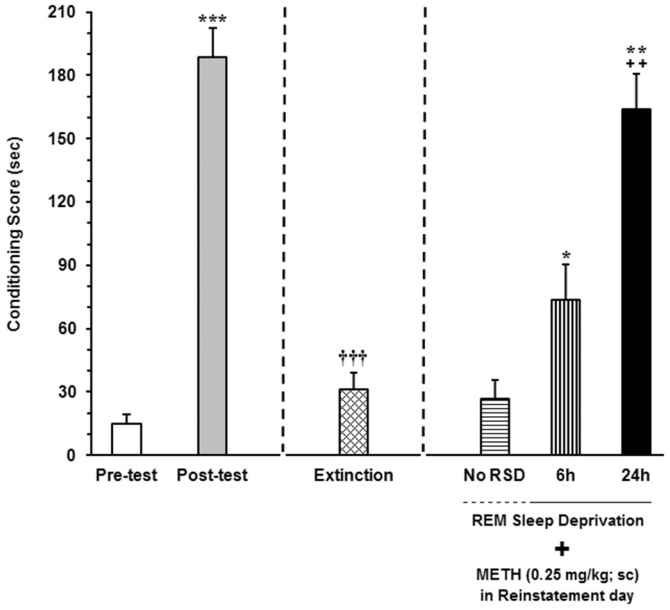

Fig. 2. The effect of RSD on the reinstatement of extinguished METH-induced conditioned place preference. (A) The conditioning scores were measured in pre- and post-conditioning days. Animals received METH (1 mg/kg; sc) during the conditioning phase. (B) The day after post-conditioning day, animals were allowed free access to both chambers for seven days as extinction period. The conditioning scores were measured during the extinction period every day. (C) To assess the RSD-induced reinstatement, the conditioning scores in three groups of animals (non-RSD, 6 and 24 h-RSD groups) were measured in the reinstatement day after injection of ineffective priming dose of subcutaneous METH (0.25 mg/kg). Each bar shows the mean ± SEM for 7 rats.
*P < 0.05, **P < 0.01 and ***P < 0.001 different from the pre-test day.
†††P < 0.001 different from the post-test day.
++P < 0.01 different from extinction day.

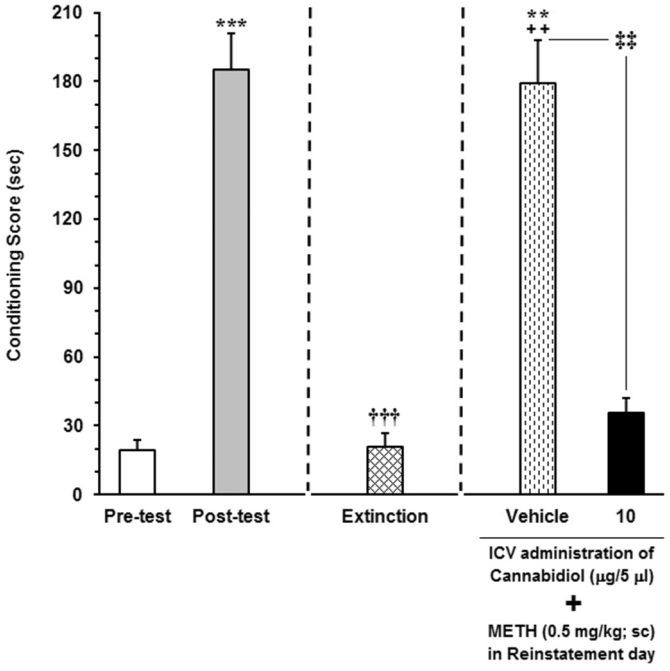

Fig. 3. Effects of microinjections of vehicle (Veh), and CBD 10 µg/5 µl, into the lateral cerebral ventricle on METH priming-induced reinstatement of extinguished METH-induced conditioned place preference. Each bar shows the mean ± SEM for 4–6 rats.
†††P < 0.001 different from the post-test day.
++P < 0.01 different from extinction day.
‡‡P < 0.01.

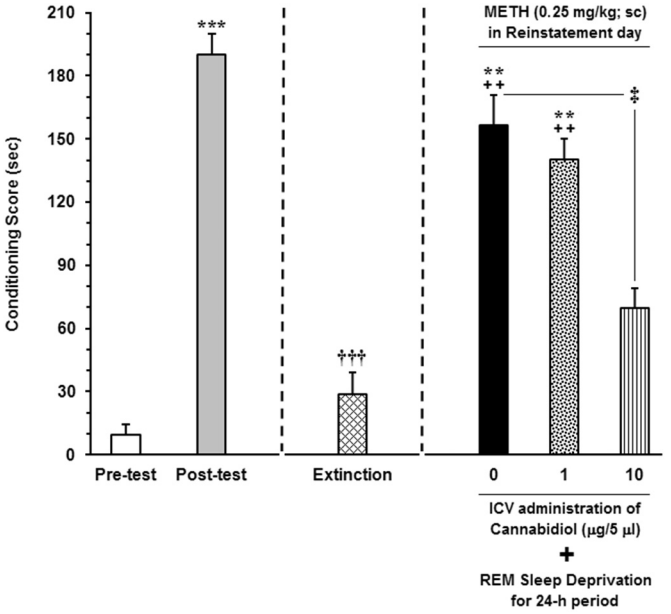

Fig. 4. Effects of microinjections of different doses of CBD, into the lateral cerebral ventricle on RSD-induced reinstatement of extinguished METH-induced conditioned place preference. Each bar shows the mean ± SEM for 5–6 rats.
**P < 0.01 and ***P < 0.001 different from the pre-test day.
†††P < 0.001 different from the post-test day.
++P < 0.01 different from extinction day.
‡P < 0.05.

P = 0 < 0.001; Fig. 4, mid panel] indicated that the animals in these groups had extinguished their preference for the METH-paired compartment on the tenth extinction day. One-way ANOVA followed by Dunnett post hoc analysis showed that there were significant differences between the conditioning scores obtained on the pretest and the reinstatement day in the groups RSD and CBD-RSD [F (3, 22) = 11.13, P < 0.0002; Fig. 4, right panel]. One-way ANOVA followed by Dunnett post hoc analysis showed that there were significant differences between the conditioning scores obtained on the last extinction and the reinstatement day in groups RSD and CBD-RSD [F (3, 22) = 7.209, P = 0.002; Fig. 4, right panel]. One-way ANOVA followed by Dunnett post hoc analysis showed that there were significant differences between the conditioning scores obtained on the pretest and the reinstatement day in groups RSD and CBD-RSD [F (3, 22) = 11.13, P < 0.0002; Fig. 4, right panel]. To examine the effect of the CBD on the 24 h-RSD induced reinstatement, the rats received ICV microinjection of two doses of CBD. The one-way block randomized ANOVA followed by Dunnett's Multiple Comparison Test [F (2, 16) = 4.115, P = 0.0393; Fig. 4, right panel] revealed a significant difference in the reinstatement CPP score between the vehicle-RSD group and the only animals that received the highest dose of CBD (10 µg/5 µl) (P < 0.05; Fig. 4, right panel).

5. Discussion

This study investigated the effects of CBD on the reinstatement of METH-induced CPP in rats using pharmacological approaches. The main findings from this study were the following: (i) Only a dosage of METH (0.5 mg/kg) could act as a effective priming dose to induce the reinstatement of METH, but a dosage of METH (0.25 mg/kg) act as an ineffective dose on METH-induced reinstatement, (ii) 24 h-RSD but not 6 h-RSD, facilitated priming-induced reinstatement of METH, (iii) Not only did ICV administration of CBD 10 µg/5 µl impair the METH-induced reinstatement, but also inhibited the reinstatement of METH in RSD rats.

The CPP procedure is often used in this field; nevertheless, this

practice has some disadvantages, compared to drug self-administration (e.g., low drug exposure, passive administration). The results of this study showed that 6 or 24 h-RSD failed to induce reinstatement without any priming dose of METH but 24 h-RSD could facilitate the reinstatement of METH. In line with our data, it was shown that the 6 h-RSD had no effect on the reconsolidation of the different models of the memory (Chen et al., 2014; Tian et al., 2009). It was reported that RSD induced a long-term sensitized response to the acute amphetamine administration and the potentiated behavioral sensitization induced by the priming administration of the drug (Kameda et al., 2014).

Previous studies have shown that different models of stress, such as, food deprivation (Sedki et al., 2015), forced swimming (Karimi et al., 2014), and foot-shock induced reinstatement of the drug (Nygard et al., 2016). Therefore, it can be considered that stress plays a particularly critical role in drug relapse (Mantsch et al., 2016; Nygard et al., 2016). The studies showed that RSD activates the stress axis (Galvao Mde et al., 2009; Hipolide et al., 2006). Our findings are consistent with the data from other studies, which showed that the different models of stress induced drug reinstatement. It was shown that RSD caused rats to seek a previously trained rewarding stimulation. Also, it was reported the acute sleep deprivation in rats increased goal-directed behaviors toward (Puhl et al., 2009).

The previous studies have shown that the different types of neurotransmitters, including serotonin (Ruedi-Bettschen et al., 2010), glutamate (Mahler et al., 2013; Miguens et al., 2013; Parsegian and See, 2014; Taepavarapruk et al., 2014) orexin (Mahler et al., 2013) and dopamine (Sadeghzadeh et al., 2015; Taepavarapruk et al., 2014; Parsegian and See, 2014) play an unquestionable role in the reinstatement of drugs. On the other hand, a lot of studies showed that some neurotransmitters, including dopamine (Lima et al., 2008), glutamate (Lopez et al., 2008; Xie et al., 2015), serotonin (Senthilvelan et al., 2006) and orexin (Arthaud et al., 2015), can be affected by RSD. For example, in the ventral tegmental area which is involved in the reward process, dopamine neurons express Fos during the recovery period after selective RSD (Maloney et al., 2002). Also, it was demonstrated that RSD reduced the rate of response to the acquisition and maintenance for food in rats, which might be because of a suppression of dopamine activity in the nucleus accumbens following 5 days RSD (Hanlon et al., 2005; Hanlon et al., 2010). This data conflicts with our results. This could be due to prolonged RSD and the use of food as reward.

Therefore, METH-induced reinstatement might have been facilitated by RSD while manipulating the different types of neurotransmitters. The other part of this study was performed in order to investigate whether CBD would be able to inhibit METH-induced reinstatement. Because the terminal half-life of the CBD is estimated at 18–32 h (Hawksworth and McArdle, 2004), we examined the effect of CBD on METH-induced reinstatement after 24 h. Also, Hosseinzadeh et al. reported the positive effect of ICV-administered CBD after 24 h on epilepsy (Hosseinzadeh et al., 2016). Our results showed that CBD 10 μg/5 μl could effectively prevent METH-induced reinstatement even in RSD rats, but CBD 1 μg/5 μl had no effect on the reinstatement of METH in RSD rats. These results are in agreement the other studies, which showed that CBD had a disruptive effect on the reconsolidation of contextual cocaine-related memories. (De Carvalho and Takahashi, 2016).

It was reported that cocaine-maintained behavior was prevented by the D2-like receptor partial agonist (Platt et al., 2003). Hence, CBD may inhibit reinstatement by acting as a partial agonist on dopamine D2 receptors (Seeman, 2016). Also, CBD attenuates dopaminergic sensitization induced by amphetamine within the mesolimbic pathway, which involves in reward pathway (Renard et al., 2016). Furthermore, CBD acts via the enhancement of serotonergic and glutamatergic transmission through the modulation of 5-HT1A receptors (Katsidoni et al., 2013; Linge et al., 2016). As mentioned above, these neurotransmitters play a critical role in drug reinstatement. Hence, it is expected that CBD can inhibit the reinstatement of METH by manipulating the different types of neurotransmitters. Norris et al. reported that the intra-accumbal administration of CBD dose-dependently inhibits the formation of associative fear memories and prevents the activity of dopaminergic neurons in the ventral tegmental area (Norris et al., 2016). While, Guimarães et al.showed that CBD can induce a strong Fos immunoreactivity in the nucleus accumbens, which is involved in the modulation of the reward system (Guimarães et al., 2004).

The last part of our study showed that CBD can inhibit reinstatement of METH in RSD rats. Because CBD modulates the glutamatergic, serotoninergic (Linge et al., 2016) and, dopaminergic (Seeman, 2016) systems, it is presumed that CBD can inhibit the effect of RSD on METH–induced reinstatement. Considered together, these results provide substantial evidence regarding the useful effect of CBD on the reinstatement of METH and highlight its therapeutic potential to reduce the risk of relapse. It will be helpful for future works to investigate the role of the inflammatory factors in METH-induced reinstatement using real-time, and determine the essential regions of the brain, such as the medial prefrontal cortex and the dorsal hippocampus, which play a role in METH-induced reinstatement by electrophysiological methods.

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Ethical statement

All experiments were done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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