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Original Article

Changes in the electrical activity of prefrontal neurons following methamphetamine-induced conditioned place preference in the rat

Zahra Taslimi[1], Abdolrahman Sarihi[2], Sara Karimi[1], Abbas Haghparast[1*]

1. Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Introduction: Methamphetamine (METH) addiction is an epidemic-growing problem globally. Studies confirmed a solid linkage between the prefrontal cortex (PFC) and drug-seeking. The present study aimed to investigate PFC neural activity changes after injection of METH following METH-induced conditioned place preference (CPP) in the rats.

Methods: After the development of CPP (0.5mg/kg METH for three days, SC), *in vivo* single-unit recordings were carried out the day after the post-test (post-conditioning day). On recording day, after stabilization and baseline recording (a 10-min period), the injection of METH (0.5mg/kg, SC) was performed and then, PFC neural activity was recorded for a 30-min period.

Results: The results revealed that the injection of METH on the post-conditioning test significantly increases PFC neurons' firing rate in animals that received METH during the CPP paradigm.

Conclusion: It seems that maybe, PFC neurons appear to be implicated in the associated METH reward pathway and repeated exposure to METH affected the sensitivity of neurons in this area.

Keywords:
Reward system
Prefrontal cortex
Methamphetamine
Neuronal activity
Conditioned place preference

Introduction

Methamphetamine (METH) is a neurotoxic psychostimulant drug and repeated exposure to this substance can lead to addiction (Panenka et al., 2013; Etaee et al., 2017). According to the 2017 National Survey on Drug Use and Health, approximately 1.6 million people (0.6 percent of the population) reported using METH. The average age of new METH users in 2016 was 23.3 years old. An estimated 964,000 people aged 12 or older (about 0.4 percent of the population) had a METH use disorder in 2017. They reported clinically significant impairment, including health problems, disability and failure to meet responsibilities at work, school or home as a result of their drug use. This number is significantly higher than the 684,000 people who reported having METH (national institute and drug abuse report).

* Corresponding author: Abbas Haghparast, Haghparast@sbmu.ac.ir
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Addiction to METH and the associated symptoms of disorientation and increased aggressiveness has become the most critical social problems (Rusyniak, 2013; Hori et al., 2015). In addition to being addicted to METH, people who use METH long term may exhibit symptoms that can include significant anxiety, confusion, insomnia, mood disturbances and violent behavior. They may also display many psychotic features, including paranoia, visual and auditory hallucinations and delusions (Rusyniak, 2013). Studies in chronic METH users have also revealed severe structural and functional changes in areas of the brain associated with emotion and memory, which may account for many of the emotional and cognitive problems observed in these individuals (Thompson et al., 2004; Chang et al., 2007; London et al., 2004). Unfortunately, there is no effective treatment for METH dependency and there are currently no medications for reducing the abstinence symptom (Gonzales et al., 2010; Ling et al., 2006).

Several investigations have extensively explained the harmful effects of METH on the central nervous system (Goncalves et al., 2014; Baptista et al., 2014). Prefrontal cortex (PFC) area, as a part of the mesocortical dopaminergic pathway, is activated when drug users are exposed to either the drug or drug-cues (Grant and Dawson, 1996; Volkow et al., 1999; Garavan et al., 2000; Sell et al., 2000; Daglish and Nutt, 2003; Tapert et al., 2003; Wilson et al., 2004; Volkow et al., 2002). Within the PFC, METH causes harmful neuroplastic changes in animals and humans associated with cognitive impairment and addictive behaviors (Bernheim et al., 2016).

METH affects PFC function, attention, impulse control and memory processes by making changes in neurotransmitters systems balance (Cadet and Bisagno, 2013). METH-use disorder may be relevant to the PFC's neurological changes, along with its glutamatergic projections to the nucleus accumbens (NAc) (Lominac et al., 2016). METH users are associated with a neurocognitive phenotype, which can influence a person's behavior and insight. In the METH-dependent participants, overall cognitive functions are affected precisely when memory and executive function are affected (Jones et al., 2016).

Addiction could alter electrophysiological activity (Krasnova and Cadet 2009; Baptista et al., 2014; Miguel-Hidalgo, 2009) in the brain regions that mediate cognitive and motivational functions. Parsegian et al. (2011) have shown that extended-access self-administration of METH could alter PFC neuronal activity. Another research also showed that the injection of METH could alter the medial PFC unit activity (Jang et al., 2007). Besides, the previous study confirmed that METH changed PFC neural activity during reinstatement in non-stressed rats.

Despite PFC's potential role in METH abuse, there are a few studies about the effect of METH on neural activity in this region. Thus, in this study, the electrical activity of the PFC neurons was recorded after METH-induced conditioned place preference (CPP). The CPP paradigm is a commonly used test for investigating the rewarding effects of abuse drugs in rodents (for review, see Tzschentke, 1998) and involves training animals to associate the drug-induced state with one side of the conditioning chamber. Although previous studies have revealed that METH can induce CPP in rodents (Berry et al., 2012; Cunningham and Noble 1992; Takahashi et al., 2020), there is not enough data regarding the effects of METH-induced CPP on brain electrical activity. The current study used a combination of behavioral and electrophysiological assessments in rats with a history of METH-induced CPP.

Materials and methods

Animals

In this set of experiments, male adult Wistar rats weighing 250-300g (Pasteur Institute, Tehran, Iran) were used. Animals were habituated to the vivarium (a climate-controlled environment on a 12h dark/light cycle) at least one week before the beginning of the experiments with free access to chow and tap water (Parvishan et al., 2011; Yazdi-Ravandi et al., 2014). The Research and Ethics Committee has approved all experiments at Hamadan University of Medical Sciences (No. 940208496), Hamadan, Iran. Each animal was used only once. Besides, every attempt has been made to reduce animals' suffering and only use the number of animals required to generate accurate scientific results.

Behavioral test

Conditioning apparatus and paradigm

Based on our previous study, the METH's rewarding properties were studied using a CPP paradigm (Taslimi et al., 2018a). Place conditioning boxes consisted of two-sided Plexiglas (30×30×40cm) that varied in tex-

ture and shading. Compartment A was vertical black and white with 2cm wide black stripes on its walls and a net-like floor. Compartment B was horizontal with white stripes, with a smooth floor, 2cm wide. The third compartment, C, was a red tunnel connecting the two preference compartments (30×15×40cm). Rats show no consistent preference in this apparatus for either large compartments (A and B), which supports our neutral CPP apparatus. This paradigm occurred for five consecutive days, which consisted of three distinct phases, pre-conditioning, conditioning and post-conditioning.

Pre-conditioning phase

Each animal was positioned in the box on the first day with free access to all compartments for a 10-min period. The animal's movement and time spent in each compartment were recorded (pretest day). Then, animals were randomly distributed for position conditioning to one of the two compartments.

Conditioning phase

This phase includes a 3-day schedule of conditioning sessions. The conditioning training was performed twice a day for a 30-min time with a saline and METH interval of 6h (0.5mg/kg, purity>98%, a gift from the Iran drug control headquarters) pairing alternated morning and afternoon design. In this phase, by closing the detachable gate, animals received METH or saline while being restricted to one compartment for a 30-min period.

Post-conditioning phase

This phase was done on day 5 (the test day), one day after the last conditioning session. Each animal was tested only once in a drug-free state. The removable gate was picked up for testing. The rat could access all compartments for a 10-min period. A camera (Panasonic) recorded the time spent for each rat and data were analyzed by the Maze router software, a video monitoring system for automating behavioral experiments (Science Beam Company, Tehran, Iran). As the index of preference, the conditioning score was calculated as the time spent in the drug-paired compartment minus the time spent in the saline-paired compartment. Besides, the total distance traveled was separately reported in experimental and control groups for each animal. On post-conditioning day (test day), no injection was given (Attarzadeh-Yazdi et al., 2013; Taslimi et al., 2018b).

Animal stereotactic surgery

Animals were deeply anesthetized with urethane (1.5g/kg, IP, if required with additional doses; Sigma-Aldrich, Germany). Then, after removing the cranial surface's scalp and appearance, the rat was mounted on a stereotaxic frame (RWD Life Science, China), and the bregma was identified and used as the stereotaxic reference point. For electrode insertion, a small burr hole was drilled in the skull above the PFC (+3.2 to +3.4 mm AP, ±0.7 mm ML) (Paxinos and Watson 2006; Taslimi et al., 2019). The body temperature was conserved for the whole experiment by using a heating pad.

Extracellular single-unit recording

A parylene-coated tungsten microelectrode (1MΩ impedance tip; USA) was stereotaxically advanced into the PFC of the right/left side of the brain, 2.8-4.4 mm below the skull surface. A manual microdriver was then used to direct the electrode to the PFC until maximum spike amplitude and signal to noise ratio were observed. Signals from the electrode were pre-amplified for impedance matching with a unity gain preamplifier, amplified 10,000 times using a differential amplifier (DAM-80; WPI, Sarasota, FL), bandpass filtered at 0.3–10 kHz and digitalized at 50kHz sampling rate

and 12-bit voltage resolution using a data acquisition system (D3109; WSI, Tehran, Iran). All-or-none spike events were detected using a window discriminator (W3205; WSI, Tehran, Iran) based on the spike amplitude. The spike frequencies were counted and indicated online in time bins of 1000ms over the entire recording time through online-sorter software (Spike; Science Beam, Tehran, Iran). Only one single cell per rat with a stable spike amplitude and waveform during the experimental procedure was recorded.

Experimental procedure

In the present study, *in vivo* single-unit recording was established to detect the PFC neural activity in the anesthetized rat that has already passed the METH-induced CPP. On the day after the post-test (post-conditioning day), the baseline activity of neurons in the PFC region was extracellularly recorded for a 10-min period. METH (0.5mg/kg) was then subcutaneously injected and the recording was continued for another thirty minutes. In a separated group, animals received saline instead of METH after baseline recording, and the sin-

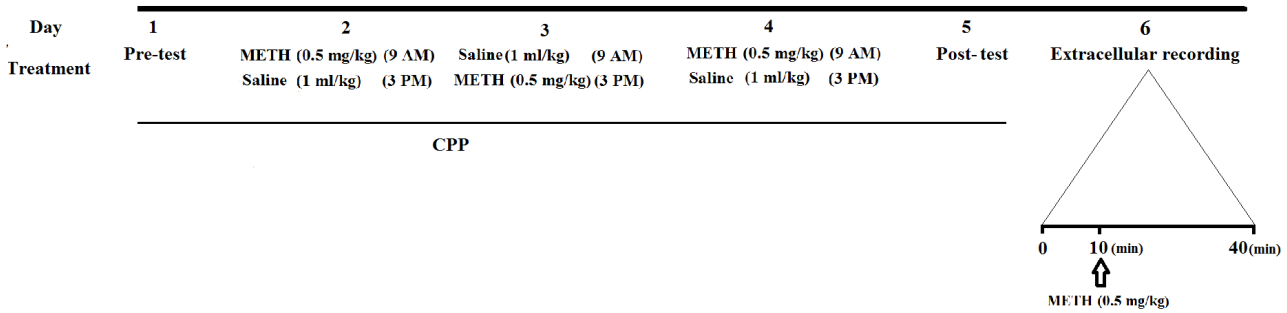

FIGURE 1. Experimental schedule of the conditioned place preference (CPP) paradigm and extracellular single-unit recording procedure.

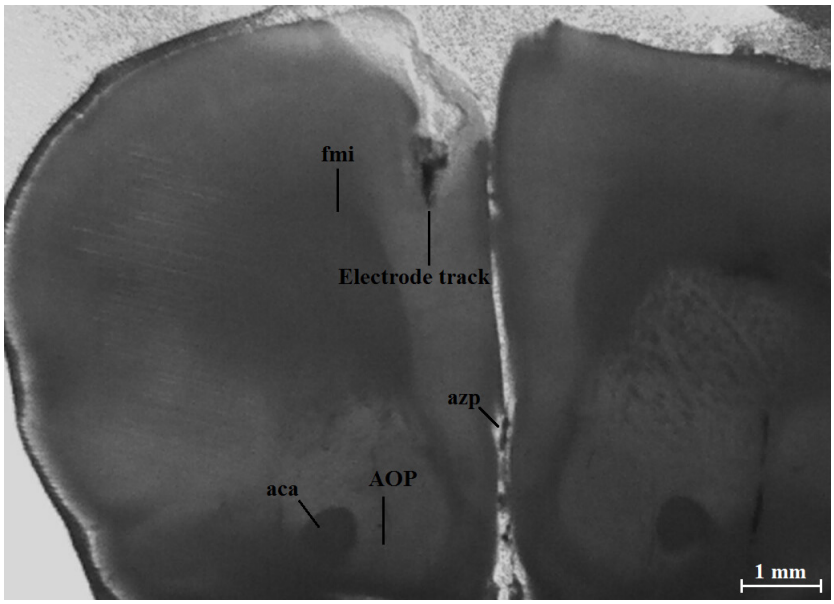

FIGURE 2. Representative photomicrograph showing the electrophysiological recording site located in the PrL-PFC. aca, anterior commissure, anterior part; AOP, anterior olfactory nucleus, posterior part; azp, azygous pericallosal artery; fmi, forceps minor of the corpus callosum. Scale is 1 mm (Adapted from Taslimi et al., 2018; Elsevier license agreement # 4894751112800).

gle-unit recording was continued with the same protocol mentioned above as a saline-control group. All animals had passed the CPP protocol before single-unit recording (Figure 1). Changes in the firing rate of neurons in this area following the METH or saline application were considered and reported as the effects of the drug/saline on the electrical properties of PFC neurons.

Histological verification

At the end of the experiments, the animals were overdosed with urethane and perfused with 10 percent formalin solution and 0.9 percent saline. The brains were removed and cut coronally in the 50-µm sections. The neuroanatomical location of the tip of the microelectrode was confirmed using rat brain atlas (Paxinos and Watson, 2006) in all control (saline-treated) and experimental (METH-treated) animals (Figure 2; Adapted from Taslimi et al., 2018a; Elsevier license agreement number 4894751112800).

Statistical analysis

Spike sorting and clustering were carried out via the T-Distribution Expectation Maximization method (Spike; Science-Beam, Tehran, Iran). Data were processed by commercially available software SPSS 24. Two-way repeated-measures ANOVA was applied to compare the effects of METH and saline on the neural firing rate. An independent sample Student *t*-test was used to compare similar effects elicited by the drug and saline before and after their applications. Data were presented as mean±SEM and statistical significance was set at $P<0.05$.

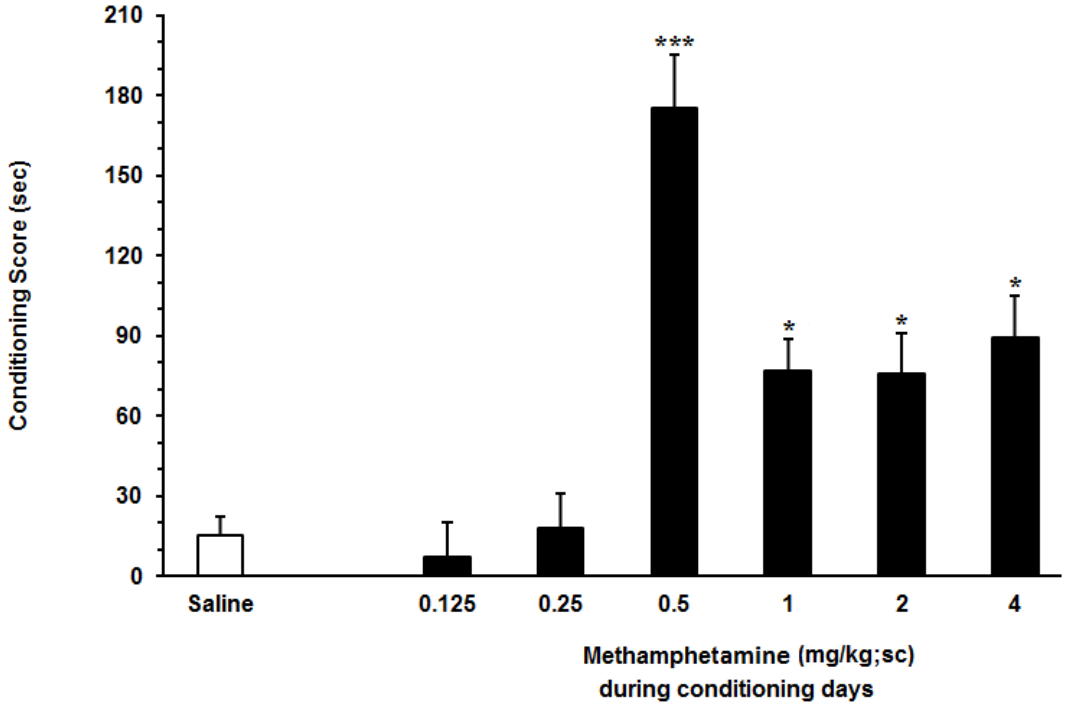

FIGURE 3. Effect of different doses of METH on place preference in rats. Each point shows the mean±SEM for 7-10 rats in each group (Adapted from Taslimi et al., 2018; BCN Journal license agreement #BCN-2020-L291). $^{*}P<0.05$ and $^{***}P<0.001$ compared with saline-control group.

Results

In the first set of experiments, the dose-response effects of different doses of METH (0.125, 0.25, 0.5, 1, 2 and 4mg/kg; SC) on the CPP paradigm (n=8) were examined. One-way ANOVA followed by Dunnett multiple comparison test ($F(6, 55)=17.25$, $P<0.0001$) revealed significant differences in conditioning scores among the vehicle (saline) and experimental groups (Figure 3 adapted from Taslimi et al., 2018, BCN Journal license agreement number BCN-2020-L291). Our findings showed that the most effective dose of METH is 0.5mg/kg ($P<0.001$).

Investigating the effects of METH or saline injection on PFC neural activity following METH-induced CPP

The extracellular single-unit recording was conducted for a 40-min period (10min baseline and 30min after METH/saline injection) after the stabilization period on the day after the post-test (post-conditioning day). Two-way repeated-measures ANOVA followed by Bonferroni post-*hoc* test showed that there were significant differences in the firing rate of the PFC neurons before and after injection of METH or saline in the rats ($F(1, 23)=16.82$, $P<0.0001$; Figure 4).

Comparison of the PFC activity changes of excited neurons between saline- and METH-treated animals following METH-induced CPP

In this set of experiments, the effect of METH injection (0.5 mg/kg) on the firing rate of excited neurons in the PFC was investigated in more detail. METH or saline was injected after baseline recording (10min) and recording was continued for a 30-min period (Figures 5A and B). Neural activity in six neurons was recorded from 4 individual rats that received saline showed that there were three excited (50%) and three unaffected (50%) neurons (Figure 5G). Animals (4 rats) received METH (0.5mg/kg) in the same protocol (after baseline recording [10min] and recording was continued for a 30-min period). From 6 neurons recorded in this group, this dose elicited excitatory responses in 3 (50%) (Figures 5E, F and G) and inhibitory responses in the rest neurons (Figures 5B, C and G). However, analysis of the data from neurons showing an excitatory response in both groups revealed a significant difference in the neurons' firing rate after injection of METH and saline. The percentage of changes in the firing rate of the PFC neurons after METH injection increased as compared to saline-treated animals ($t=3.558$ $df=4$, $P<0.01$; Figure 5H). When considering the length of the excitation in the subset of neurons, the mean effect of METH was signifi-

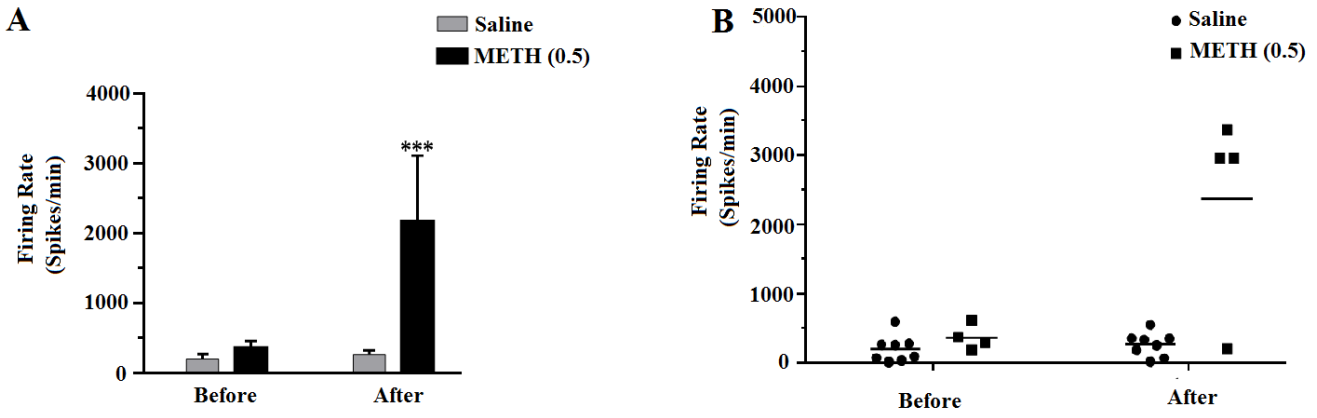

FIGURE 4. Effect of METH and/or saline injections on PrL-PFC neural activity in METH-induced CPP in the rats. Two-way repeated-measures ANOVA followed by Bonferroni post-*hoc* test showed significant differences in the firing rate of the PrL-PFC neurons before and after injection of METH or saline in the rats. A, showing the mean of data. B, the value of individual data of each group. $^{***}P<0.001$

cantly higher than that of saline (t=4.886 df=3, $P< 0.01$; Figure 5I) on the firing rate of the PFC neurons.

Discussion

In the present study, electrophysiological recordings of the PFC were performed to investigate neural activity in animals that have already passed the METH-induced CPP after applying METH/saline on the day after post-test (post-conditioning day). The main finding of this study was that: (1) METH (0.5mg/kg) significantly changed the firing rate of neurons in the PFC; (2) After METH injection, a shift in the number of exciting neurons and percentage of changes in firing rate in the PFC neurons were significantly more than those in saline-treated animals. In parallel with the previous study, 0.5mg/kg of METH as an effective dose of METH could induce CPP in the rat (Taslimi et al., 2018a).

Brain areas distinct from the medial cortex have been associated with drug-seeking (Fuchs et al., 2005; Lasseter et al., 2010). Several studies have also implicated that the PrL-ACC (McFarland and Kalivas, 2001) and PFC (Capriles et al., 2003; McLaughlin and See, 2003; See, 2005) area is a critical component in the circuitry for drug-seeking behaviors including cocaine and heroin (LaLumiere and Kalivas, 2008) in the rats. The present findings indicate the critical role of the PFC area in the METH-induced CPP and -seeking behavior. It has been shown that PFC is involved in modulating various memories and spatial learning processes (Maviel et al., 2004; Cao et al., 2013). Investigations have shown that the PFC area receives information from the emotion-related brain structures that have a crucial role in reward-associated learning and memory (Palombo et al., 2017). Furthermore, this area receives a wide range of sensory and limbic inputs from the hippocampus, amygdala, ventral tegmental region (VTA) and orbitofrontal cortex which can be activated by contextual indications (Miller and Cohen, 2001; Mulder et al., 2000; Van den Oever et al., 2010). Generally, the mesocorticolimbic dopaminergic projections from the VTA to the NAc and PFC are established as the reward system, and the activation of these projections is the central part in the development of psychological dependence (Russo and Nestler 2013). These projections are the dominant feature of drugs of abuse associated with euphoria (Broom and Yamamoto, 2005; Huang et al., 2018). Furthermore, it has been shown that chronic METH users have memory, learning and cognitive deficits among psychiatric symptoms (Garske et al., 2013), and extended-access self-administration of METH changes the baseline firing rate and burst properties of PFC neurons continuously (Parsegian et al., 2011, Janetsian et al., 2015). Poor cortical impulse control specifies addictive behavior and abused psychostimulants such as METH induce neuro-adaptations within the PFC (Cadet and Bisagno, 2013; González et al., 2019).

The obtained data in the present study indicated that the METH administration could excite the PFC neurons following induced CPP. Prior research showed the activation of the VTA dopaminergic inputs in the NAc and PFC after the acute administration of METH (Fallon and Moore, 1978; Haber and Knutson, 2010). Following METH self-administration, a significant decrease in the AMPA/NMDA (α-amino-3-hydroxy-5-methyl-4-

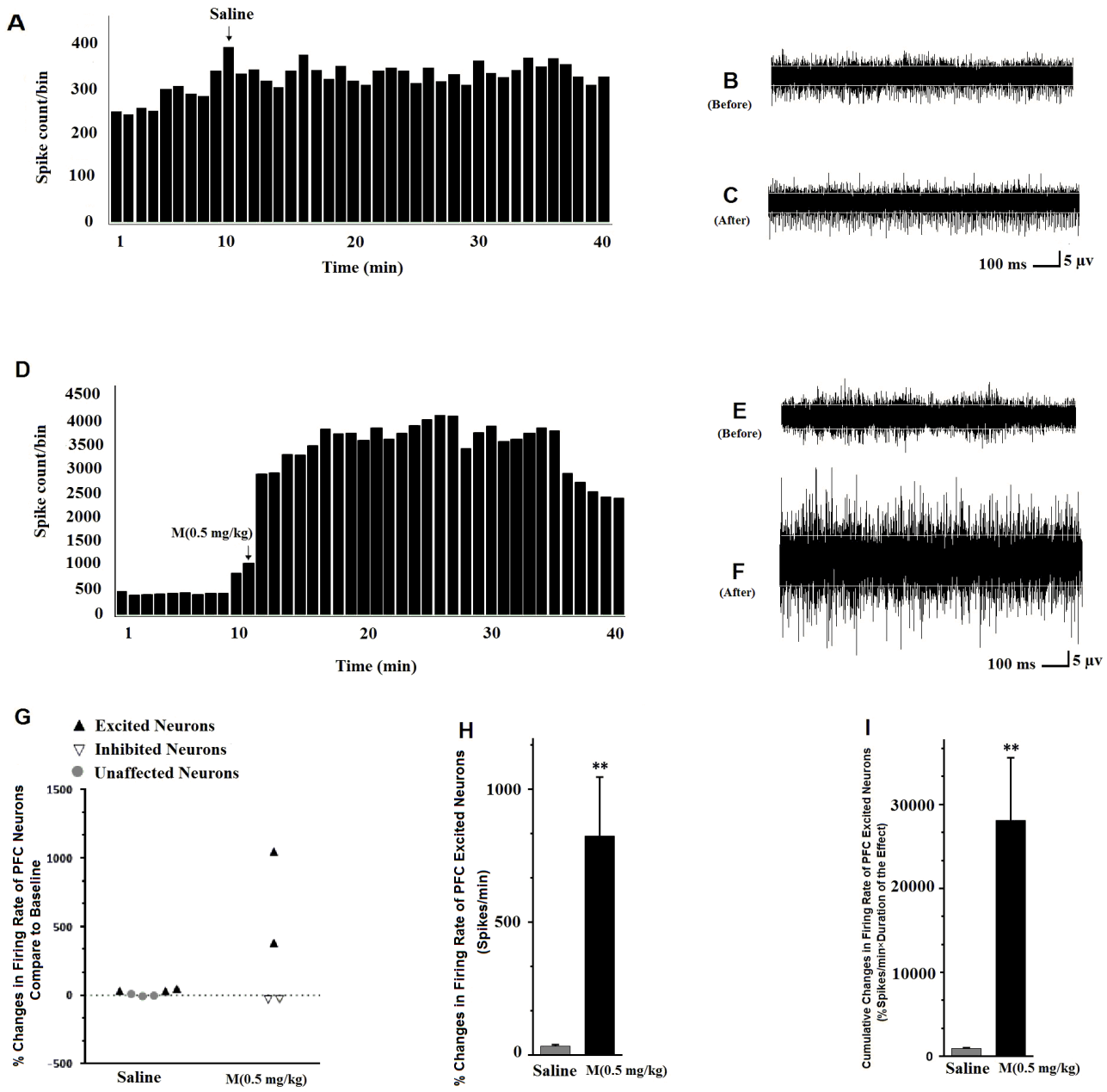

FIGURE 5. Comparison of the activity of PrL-PFC excited neurons between METH- and saline-treated animals after METH-induced CPP. A, histogram representing spike count per time bins of 1min over the entire recording during SC injection of saline. B, are the presentative pattern of baseline spontaneous firing recorded from a PrL-PFC neuron. C, firing pattern of the same neuron recorded after SC injection of saline. D, histogram representing spike count per time bins of 1min over the entire recording. METH increased the firing frequency of the recorded neuron. E, a representative pattern of baseline spontaneous firing recorded from a PrL-PFC neuron. F, firing pattern of the same neuron recorded after s.c. injection of a threshold dose of METH. G, scatterplot illustrating the PrL-PFC neurons with different responses to SC injection of saline (n=5) or METH (n=6). H, in the subclass of exited neurons with different response to saline injection (mean±SEM: 925.9±76.95, N=2) and METH injection (mean±SEM: 28100±7461, N=3), the percentage of firing rate changes was significantly different between saline- and METH-treated groups. I, Excitation in the METH-treated group was dramatically greater than that in the saline-treated group. $^{**}P<0.01$

isoxazole propionic acid /N-methyl-D-aspartate) ratio in mPFC, driven by an increase in NMDA currents (Mishra et al., 2017). METH alters postsynaptic mechanisms at a cortical level. METH also effectively increase synaptic concentrations of dopamine in the nigrostriatal pathway (Bustamante et al., 2002; Fowler et al., 2008; Haber and Knutson, 2010) by reversing both vesicular monoamine transporter 2 and the dopamine transporter (Sulzer et al., 1995; Sora et al., 2009). Besides, METH augments glutamate levels in the PFC (Stephans and Yamamoto, 1995). This increase in glutamate at the cortex activates the glutamatergic corticostriatal neurons via postsynap-

tic connections (Gerfen, 1989; Bellomo et al., 1998) and increases glutamate release in the striatum (Stephans and Yamamoto, 1995).

Furthermore, previous studies showed that intravenous self-administration of the METH increases burst firing within the PFC glutamate neurons in the rats (Parsegian et al., 2011) and elicits a persistent change in extracellular glutamate in the PFC and ventral striatum (Lominac et al., 2012; Parsegian and See, 2014). It has been shown that the expression of motivated behaviors associated with abused drugs is due to glutamate transmission in the corticostriatal pathway, and the glutamate projection from the dorsomedial PFC to the NAc has an important role in the reinstatement of drug-seeking behaviors for several drugs of abuse (McFarland et al., 2003), such as METH (Rocha and Kalivas, 2010).

Conclusion

In conclusion, the present findings it seems that the PFC area, perhaps is implicated in the METH-induced CPP and its reward-associated learning. Repeated exposure to METH leads to significant scale alterations in physiological processes that may drive cortical networks. However, future investigations with molecular and electrophysiological approaches are needed to clarify how to change information processing and drug-associated behaviors in addicted individuals.

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Conflicts of interest

The authors declare no conflicts of interest.

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