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Research report

Psychostimulant treatment for ADHD is modulated by prefrontal cortex manipulation

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ABSTRACT

The psychostimulant amphetamine (Amph) is widely used treatments for attention-deficit hyperactivity disorder (ADHD). Chronic intermittent exposure to psychostimulants induces behavioral sensitization. The objective of this study was to investigate the role of prefrontal cortex (PFC) in the acute and chronic effect of Amph using the open-field assay. Male Sprague–Dawley rats were assigned randomly to three groups, (1) an intact control group (2) a PFC sham-operated group, and (3) a PFC lesion group. All the three groups showed increases in locomotor activity after acute amphetamine injection ($P < 0.05$), and activity levels were especially augmented in PFC lesion group. Following chronic amphetamine, the control group and sham-operated group exhibited behavioral sensitization ($P < 0.05$). However, the PFC lesion group failed to exhibit behavioral sensitization and the pattern of locomotion was altered, which indicated that the nature of behavioral sensitization was changed. The results suggest that PFC lesion enhance the acute effects of amphetamine on locomotor activity and is required for development of behavior sensitization.

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1. Introduction

The psychostimulants amphetamine (Amph) and methylphenidate (MPD) are widely used treatments for attention-deficit hyperactivity disorder (ADHD) [14]. Chronic intermittent exposure to psychostimulants such as amphetamine, methylphenidate, and cocaine can induce behavior sensitization [9,13,23,29,31,35,41,44]. Behavioral sensitization is the progressive augmentation of behavioral responses to psychostimulant after recurring psychostimulant administration, and is considered to be an experimental model for processes leading to substance abuse, drug-induced psychosis, and other consequences of repeated exposure to psychostimulants or environmental stressors [1,42].

The motive circuit, which is responsible for translating motivationally relevant stimuli into adaptive motor responses including drug-induced behavioral sensitization, is a target for psychostimulant administration [19,20]. The induction of behavioral sensitization is believed to occur in the ventral tegmental area (VTA) which projects to the Nucleus accumbens (NAc), the prefrontal cortex (PFC), and other central nervous system (CNS) areas. Additionally, reciprocal communication exists between these CNS sites [20,25,41].

Amphetamine initially acts to release dopamine (DA) from vesicular monoamine transporters (VMATs) into the synaptic cleft, thereby increasing intra-neuronal concentrations of this transmitter. In addition, amphetamine binds to the dopamine transporters (DATs) and releases dopamine from presynaptic neurons into the synaptic cleft, increasing synaptic DA [16,34]. Over time, alterations of dopamine transmission system by psychostimulants in the motive circuit elicit some adverse effects such as tolerance, withdrawal or behavioral sensitization [19]. Behavioral sensitization to amphetamine may implicate not only the mesoaccumbens dopaminergic neurons, but also other structures of the mesocorticolimbic system, such as the medial prefrontal cortex and more specifically its glutamatergic component [3,4]. Repeated administration of psychostimulants reduced dopamine transmission in the PFC, thus increasing the potential behavioral responses to psychostimulants [19,32]. PFC may therefore have an important role in behavioral sensitization to amphetamine. It was reported that electrolytic lesion of the prefrontal cortex prevented the induction of behavioral sensitization to repetitive injections of the stimulant methylphenidate [23].

The present study's objective was to investigate the role of the PFC in the acute and chronic effect of amphetamine with three groups of rats; control intact group, sham PFC operated group, and electrolytic PFC lesion group using the open field assay [8,9,11–13,23,42–44].

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Table 1
Schedule of amphetamine administration.

Group	Experimental day						
	Day 1*	Day 2	Days 3–7	Day 8*	Days 9*–14*	Days 15*–17	Day 18*
Control	Saline			Saline	0.6 mg/kg amphetamine i.p. injection	Washout	0.6 mg/kg amphetamine i.p. injection
Sham	Saline	Surgery	Recovery	Saline	0.6 mg/kg amphetamine i.p. injection	Washout	0.6 mg/kg amphetamine i.p. injection
Lesion	Saline	Surgery	Recovery	Saline	0.6 mg/kg amphetamine i.p. injection	Washout	0.6 mg/kg amphetamine i.p. injection

Table 1 displays the experimental protocol for the three rat groups, and when and what was the treatment and the recording day.
All injections were i.p. = intra peritoneal, in the same volume (0.8 ml) given at about 09:00 AM.
* Indicate the recording day.

2. Materials and methods

2.1. Animals

Twenty adult male Sprague–Dawley rats which weighed 180–200 g (Harlan, Indianapolis, IN, USA) were randomly divided into three groups, (1) an intact control group ($N = 6$), (2) a sham-operated group ($N = 6$), and (3) a PFC lesion group ($N = 8$). Animals were housed in cages 3–5 days before the experiment for adaptation. Animals had free access to food and water and kept at ambient temperature of 21 ± 2 °C and relative humidity of 37–42% and maintained on a 12:12 light/dark cycle (light on at 06:00). All recordings started at 09:00 AM and lasted for 120 min. All efforts were made to minimize the number of animals used and to minimize animal suffering. The study was conducted according to the declaration of Helsinki and approved by the local Animal Welfare Committee.

2.2. Drugs

Amphetamine was dissolved in 0.9% saline solution to make 0.6 mg/kg amphetamine. This amphetamine dose was adapted from previous dose response experiment since it elicited significant ($p < 0.01$) behavioral sensitization in our previous work [8,10–12]. Each animal was weighed before injection, and all injections were equalized to the volume of 0.8 ml. Injections were administered intra-peritoneally (i.p.) and the recordings started immediately after injection.

2.3. Surgeries

For the sham-operated and electrolytic lesion surgeries, rats were anesthetized with 50 mg/kg sodium pentobarbital, i.p., and placed in a stereotaxic apparatus. An incision was made in the scalp and cranial muscles were removed, and a small hole (1.0 mm) was made bilaterally above the PFC according to the atlas of Paxinos and Watson [27], at 3.2 mm anterior to bregma and 0.6 mm lateral to each side of midline. The electrode was made up of two insulated (except at the tip) twisted stainless steel wires, 80 μm in diameter. Bilateral electrolytic lesion was created by running 3 mA current through the electrode for a minute in three steps, first at 4.4 mm below the skull, next at 3.4 mm below the skull, and the last at 2.4 mm below the skull. After the surgery, the skin of the head was closed using wound closing staples. For the sham group, the electrodes were placed in identical locations for the same amount of time but without any current.

2.4. Procedure

Animals were kept on the vivarium and on each experimental day (Table 1) they were placed in the experimental open field boxes, and allowed 20–30 min adaptation period, i.e., all recordings in all the experimental day were done after adaptation period in the testing cages. On experiment day 1, after the adaptation period, all of the animals were injected with saline and their locomotor activity was recorded for two hours post saline injection. On experiment day 2, the lesion group received bilateral electrolytic lesions of PFC while sham group received the same procedure without current. After 5 days of recovery, animals were placed in the testing cages and allowed 20–30 min adaptation period, then the three groups were injected with saline and recording were resumed (i.e., experiment day 8, Table 1). On experiment day 9–14, the three groups were daily injected with single dose of 0.6 mg/kg amphetamine at about 09:00 AM in the testing cages (Table 1). On experiment days 15–17 no injection was given but recording were resumed at the same time as on previous days. The re-challenge injection of 0.6 mg/kg amphetamine in saline was given on day 18 and recording was resumed for additional two hours as before.

2.5. Recordings

The locomotor recording was done using a computerized animal activity monitoring (CAAM; AccuScan Instruments, Inc., Columbus, OH) system. The activity chambers consisted of clear acrylic open field cages (40.5 cm × 40.5 cm × 31.5 cm), which contain two levels of 16 infrared beams and their motion sensors 6 and 12.5 cm above the floor of the cage. The activity monitoring system checked for interruptions of each infrared beam at a frequency of 100 Hz. Interruption of any beam was recorded as an activity score and was counted by the AccuScan Analyzer. Cumulative counts were complied and downloaded every 10 min to a PC, using the OASIS program, which organized these counts into specific locomotor indices. Three different motor indices were recorded for 2 h postinjection: horizontal activity (HA), which is the measure of the total number of beam interruptions that occur in the horizontal sensor (lowest tier) during a given period (2 h); total distance (TD), which is the measure of the TD traveled in centimeters in a given period; the number of stereotypic movements (NOS), which is the measure of the number of repetitive episodes with at least a 1-s interval intermission. Recording started immediately after injection and lasted for 120 min.

2.6. Histology

After completion of the experiment, the animals were overdosed with sodium barbital and perfused intracardially with 10% formaldehyde containing about 3% potassium ferrocyanide. Brains were removed and placed in 10% formaldehyde for at least 48 h. Then, the brains were sectioned in the coronal plane at 120 μm thickness. The atlas of Paxinos and Watson [27] was used to determine the size and placement of the lesions.

2.7. Data analysis

The 10 min bins of locomotor activity counts were used to produce two types of analysis.

(1) Each bin was plotted sequentially to produce 2 h of temporal recording after the injection. Standard error (S.E.) for each bin was calculated and the significance of changes between the experimental days was assessed using ANOVA, and where ANOVA was significant, Post hoc analysis was done. Significant changes in at least two consecutive bins were considered as a significant drug effect.
(2) The sums of 2-h activity (12 bins) were used to get the average activity level during the initial 2 h after injection for each group (control, sham, and lesion). Comparisons between different groups were made with repeated measures ANOVA, and Post hoc analysis was performed when ANOVA was significant. Significant difference was set at two-tailed $P < 0.05$. Five planned comparisons were made. (1) Experimental day 1 was compared to experimental day 8 to determine whether the sham or lesion operations altered the baseline activity. (2) Experimental day 8 was compared to experimental day 9 to obtain the acute amphetamine effect (Table 1). (3) The locomotor activity levels on experimental day 9 were compared among the three groups to determine whether there was difference in the intensity of acute amphetamine effect. (4) Experimental day 9 was compared to experimental day 14, when the last amphetamine maintenance injection was given to determine whether sensitization to amphetamine was induced. (5) Experimental day 9 (the initial amphetamine treatment to intact animals) was compared to experimental day 18 (the last day of amphetamine re-challenge administration) to see whether the sensitization to chronic treatment was expressed after 3 days of washout (Table 1).

3. Results

3.1. Effect of saline on baseline activity

Previous studies have shown that, in untreated and saline-treated rats, motor activity was stable except for minor and statistically insignificant fluctuations, for 16–42 days [8–13,42–44]. Therefore, in the intact control group, the activity of experimental day 1 after saline injection was used as baseline control [8–13,42–44] (Table 1).

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