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# Possible involvement of medial prefrontal cortex in amphetamine-induced sensitization of mesolimbic dopamine function

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**Abstract**

We examined the role of the dopamine projection to the medial prefrontal cortex in amphetamine-induced sensitization of meso-nucleus accumbens dopamine function. In the first experiment, male rats received bilateral microinfusions either of 6-hydroxydopamine or of vehicle (sham) into prefrontal cortex. Six weeks later animals from both groups were injected once daily for 5 consecutive days with either amphetamine or saline. Two days after the last daily injection, all the animals were each implanted with a voltammetric electrode into nucleus accumbens. Increases in dopamine-dependent electrochemical signals elicited by amphetamine were monitored 3–4 days later using chronoamperometry. The results showed that amphetamine stimulates dopamine efflux to a greater extent in the nucleus accumbens of lesioned than of sham-lesioned animals. Furthermore, of the animals with prefrontal cortical lesions, amphetamine-induced dopamine efflux was greater in animals previously treated with the drug than in animals with no prior drug experience. In a second experiment, sensitization to the acute locomotor-stimulant effect of amphetamine was examined in prefrontal cortex-lesioned and sham-lesioned animals. The locomotor response of all animals to a test dose of amphetamine was first monitored and then on each of the subsequent 5 days, lesioned and sham-lesioned animals received an injection either of amphetamine or of saline. Five and then 13 days later, the locomotor response of all animals to the test dose of amphetamine was again measured. The results of this study showed that prefrontal cortex-lesioned animals were *less* responsive to the first amphetamine injection than sham-lesioned animals. However, after repeated daily administration, the acute locomotor response of lesioned animals to amphetamine was significantly greater than that of sham-lesioned animals with the same drug history. These findings are generally consistent with evidence from other sources suggesting that the dopamine input to medial prefrontal cortex exerts an indirect, inhibitory influence on mesolimbic dopamine transmission. They also suggest that long-term changes to a dopamine-sensitive mechanism in prefrontal cortex may contribute to the development of stimulant-induced sensitization of mesolimbic dopamine function.

*Keywords:* Dopamine, mesocortical; Locomotor activity; Nucleus accumbens; Voltammetry; 6-Hydroxydopamine lesion

## 1. Introduction

It is now well known that the acute locomotor-stimulant effect of *d*-amphetamine and of several other drugs that facilitate dopamine transmission increases with repeated administration. One of the more consistently observed central correlates of behavioral sensitization to amphetamine is increased metabolism and synaptic release of dopamine in nucleus accumbens. The mechanism by which repeated amphetamine administration later augments the drug's stimulant action on dopamine transmission has yet to be identified. However, there is evidence suggesting that the ventral tegmental area, where the dopamine projection to nucleus accumbens originates, is an important site for the development of sensitized dopamine function (see review by Kalivas and Stewart, 1991).

The ventral tegmental area also contains dopamine neurons that innervate cortical regions including medial prefrontal cortex. Several different lines of evidence suggest that dopamine transmission in subcortical structures such as nucleus accumbens is indirectly modulated by the dopamine projection to prefrontal cortex. Frontal cortex ablations have long been known to increase spontaneous and stimulated locomotor activity (Iversen, 1971). More recently, microinjections of

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dopamine receptor agonists and antagonists into prefrontal cortex have been reported to decrease and increase, respectively, dopamine transmission in nucleus accumbens (Louilot et al., 1989) as well as locomotor activity elicited by intra-nucleus accumbens injections of amphetamine (Vezina et al., 1991). In addition, 6-hydroxydopamine lesions of prefrontal cortex dopamine terminals have been found to potentiate stress-elicited increases in nucleus accumbens dopamine utilization (Deutch et al., 1990). Taken together, these findings suggest that one consequence of increased dopamine transmission in prefrontal cortex is an attenuation of dopamine transmission in nucleus accumbens. Since amphetamine is known to elevate extracellular dopamine levels in both nucleus accumbens and prefrontal cortex (Maisonneuve et al., 1990), the drug's ability to stimulate locomotor activity and dopamine efflux in nucleus accumbens would be expected to be enhanced when dopamine transmission in prefrontal cortex is interrupted.

The effects of dopamine-depleting lesions in prefrontal cortex have been examined in several studies but these have yielded inconsistent results. Whereas prefrontal cortex lesions have been reported by some to potentiate spontaneous (Bubser and Schmidt, 1990; Carter and Pycock, 1980; Pycock et al., 1980) and amphetamine-induced locomotion (Carter and Pycock, 1980; Pycock et al., 1980) others have failed to observe such changes following similar lesions (Clarke et al., 1988; Joyce et al., 1983; Oades et al., 1986). Furthermore, while prefrontal cortex dopamine depletion has been found by some to not affect measures of basal dopamine synthesis in nucleus accumbens (Bubser and Schmidt, 1990; Clarke et al., 1988; Deutch et al., 1990; Joyce et al., 1983; Rosin et al., 1992), others have reported evidence of higher basal dopamine synthesis (Leccese and Lyness, 1987; Martin-Iverson et al., 1986; Pycock et al., 1980).

We previously have reported in vivo electrochemical evidence indicating that dopamine efflux elicited in nucleus accumbens by a sexual stimulus increases with repeated daily testing (Mitchell and Gratton, 1991) and that the development of sensitized dopamine transmission resulting from such repeated stimulation is potentiated in animals with partial dopamine depletions in prefrontal cortex (Mitchell and Gratton, 1992). The effect of prefrontal cortex dopamine depletion was not apparent upon first exposure to the stimulus; the sexual stimulus initially elicited similar increases in dopamine levels in lesioned and sham-lesioned animals. Rather, the facilitatory effect of prefrontal cortex dopamine depletion emerged gradually with each daily exposure to the sexual stimulus. This finding indicates that the increased responsiveness of the meso-nucleus accumbens dopamine pathway following prefrontal cortex dopamine depletion is experience dependent. It also raises the possibility that a dopamine-sensitive mechanism in prefrontal cortex mediates the development of sensitized meso-nucleus accumbens dopamine transmission resulting from repeated injection of psychostimulants.

In the present study, we examined the involvement of meso-prefrontal cortex dopamine neurons in the development of sensitized mesolimbic dopamine function produced by repeated amphetamine administration. Sensitization to the acute stimulant effects of amphetamine administration on locomotion and extracellular levels of dopamine in nucleus accumbens was studied in animals with partial depletion of prefrontal cortex dopamine. High-speed chronoamperometry and monoamine-selective electrochemical electrodes were used to monitor changes in dopamine-dependent electrochemical signals in nucleus accumbens of freely behaving rats.

## 2. Materials and methods

### 2.1. Animals

Male Long-Evans rats (Charles River, St Constant, PQ, Canada) weighing 300–400 g at the time of surgery were used. The animals were housed singly on a 12 h light-dark cycle (lights off at 09:00 h) with food and water available ad libitum.

### 2.2. Surgery

*6-Hydroxydopamine lesions*

The animals were injected with atropine sulphate (0.1 mg/kg i.p.), anesthetized with sodium pentobarbital (60 mg/kg i.p.) and placed in a stereotaxic apparatus. Thirty to 45 min prior to infusing 6-hydroxydopamine (Sigma, St. Louis, MO, USA), desmethylimipramine (25 mg/kg i.p.) was injected to inhibit uptake of the toxin by norepinephrine terminals. Bilateral 6-hydroxydopamine infusions were performed at 3 successively deeper sites within prefrontal cortex (flat skull coordinates: 3.5 mm anterior to bregma, 0.6 mm lateral to the midline, and 2.0, 3.0 and 4.0 mm ventral to dura. Each site was infused with 4 $\mu$g of 6-hydroxydopamine in 0.5 $\mu$l of 0.2% ascorbic acid-saline solution over a 2 min period. The injector was left in position for an additional 2 min following each injection to allow diffusion of the drug solution. Sham-lesioned animals were prepared in the same manner but were injected with the vehicle only. Behavioral tests and implantation of electrochemical probes were performed 4–6 weeks after lesioning.

*Electrochemical probe implantation*

Lesioned and sham-lesioned animals were prepared for stereotaxic surgery as described above and were

then each implanted with an electrochemical probe into nucleus accumbens (flat skull coordinates: 1.6 mm anterior to bregma, 1.6 mm lateral to the midline, and 7.4 mm ventral to the surface of cortex). An Ag/AgCl reference electrode and a stainless steel ground wire were implanted in parietal cortex. Miniature pin connectors soldered to the electrochemical electrode and reference and ground wires were inserted into a plastic strip connector that was then secured with dental acrylic cement to 5 stainless steel screws threaded into the cranium. Electrochemical recordings began 2–3 days after surgery.

### 2.3. In vivo electrochemistry

The electrochemical probe consisted of 3 carbon fibers (fiber diameter = 30 $\mu$m; Avco Specialty Materials, Lowell, MA, USA) extending 50–70 $\mu$m beyond the tip of a pulled glass capillary. The exposed fibers were repeatedly dipped in a 5% solution of Nafion (Aldrich, Milwaukee, WI, USA), a procedure that reduces the contribution to the electrochemical signal of anionic species such as dihydroxyphenylacetic acid (DOPAC) and ascorbic acid (Gerhardt et al., 1984). Immediately before implantation, each electrode was calibrated for its sensitivity to dopamine and for its selectivity for dopamine versus ascorbic acid. All calibrations were performed in 0.1 M phosphate-buffered saline (pH 7.4) containing 250 $\mu$M ascorbic acid to mimic brain extracellular conditions. Only probes displaying a highly linear response ($r > 0.997$) to increasing concentrations of dopamine were used. The electrodes used in the present study had selectivity ratios of 1500:1 to 2000:1 for dopamine against ascorbic acid and detection thresholds for dopamine of 20–30 nM.

Electrochemical recordings were performed using a microcomputer-controlled high-speed chronoamperometric apparatus (Medical Systems Corp., Greenvale, NY, USA). An oxidative potential of +0.55 V was applied to the electrochemical probe, relative to the Ag/AgCl reference electrode, for 100 ms at a rate of 5 Hz. The resulting oxidation current was digitally integrated over the final 80 ms of each 100 ms pulse. The sums of every 5 oxidative cycles were first converted, on-line, to values of nM changes in dopamine concentration using the in vitro calibration factor and then graphically displayed on a video monitor at a rate of 0.5 Hz. The reduction current generated when the potential was returned to resting level (0.0 V for 100 ms) was digitally integrated and summed in the same manner and served as an index to identify the main electroactive species undergoing oxidation. With Nafion-coated electrodes and a sampling rate of 5 Hz, the magnitude of the reduction (red) current flow elicited by increases in dopamine concentration is typically 60–80% of the corresponding increase in oxidation (ox) current (red:ox = 0.6 to 0.8; Doherty and Gratton, 1992; Gerhardt et al., 1989; Gratton et al., 1989; Mitchell and Gratton, 1991,1992). Previous work also indicates that the oxidation of ascorbic acid is virtually irreversible (red:ox = 0), whereas that of DOPAC is almost entirely reversible (red:ox = 0.9 to 1.0); the red:ox ratios for norepinephrine and serotonin are 0.4 to 0.5 and 0.1 to 0.3 respectively. Thus the simultaneous monitoring of both the oxidation and reduction currents associated with the electrochemical reaction provides an on-line method of assessing the neurochemical identity of the predominant electroactive species contributing to the signal.

Electrochemical recordings were conducted in a sound-attenuating chamber with glass doors. Lesioned ($n = 11$) and sham-lesioned animals ($n = 12$) were randomly assigned to one of two treatment conditions: repeated amphetamine or repeated saline administration. All the animals were first allowed to habituate to the chamber once daily for 2–3 days. The day following the last habituation session, all animals were injected with amphetamine (2.0 mg/kg i.p.) and placed in the chamber for 120–150 min. On each of the subsequent 5 days, lesioned and sham-lesioned animals were injected with either amphetamine (4.0 mg/kg i.p.) or an equivalent volume of saline and placed in the chamber for 120–150 min. Two days following the last daily injection, the animals were each implanted with an electrochemical probe into nucleus accumbens. Three to four days after surgery (5–6 days after the last daily amphetamine injection), the animals were connected to the chronoamperometric instrument via a shielded cable and a low-impedance multi-channel commutator (Airflyte, Bayonne, NJ, USA). The primary signal amplifier (gain = $1 \times 10^8$) was connected directly into the animal's strip connector to minimize electrical interference. Following 60–90 min of stable electrochemical recordings, all the animals received a challenge injection of amphetamine (2.0 mg/kg i.p.).

The effects of pretreatment (amphetamine vs. saline) and of lesion (sham-lesion vs. lesion) on the peak amplitude, the rate of rise and the duration of electrochemical signal increases elicited by the challenge injection of amphetamine were analyzed using a 2-way analysis of variance (ANOVA). Peak increase was defined as the maximum amplitude of the electrochemical signal increase relative to the basal signal whereas the duration of increase was defined as the time the signal remained above the basal signal. The rate of rise of amphetamine-elicited signal increases was determined by measuring the magnitude of the increase at one-third the time to peak (TP 1/3) and expressing the data as a percentage of the peak increase. This procedure provides a measure of the electrochemical response to amphetamine relative to its peak response

and to the time at which it occurred after injection. Measures were performed at TP 1/3 because those at earlier time points were often confounded by the transient increases in the electrochemical signal associated with handling and the injection. The analysis of amphetamine-induced signal increases took into account the slow downward drift in the basal electrochemical signal (see Fig. 2). The red : ox ratio of each record was obtained by dividing the digitized reduction current value at the peak of the increase by that of the oxidation current.

At the end of the experiment, all rats were deeply anesthetized with sodium pentobarbital (75 mg/kg i.p.) and transcardially perfused with saline followed by 10% formalin. The brains were removed and stored in 10% formalin until they were sliced in 20 $\mu$m sections for histological verification of electrode placements.

### 2.4. Locomotor activity

The effect of prefrontal cortex dopamine depletion on the behavioral response to repeated amphetamine administration was studied in a separate group of animals. Locomotor activity was monitored in chambers each equipped with 2 photoelectric switches; interruptions of the light beams were recorded by a microcomputer. Lesioned ($n = 16$) and sham-lesioned rats ($n = 20$) were randomly assigned to one of two treatment conditions: repeated amphetamine (lesioned-amphetamine, $n = 7$; sham-amphetamine, $n = 10$) or repeated saline administration (lesioned-saline, $n = 9$; sham-saline, $n = 10$). All animals were first acclimatized to the activity chambers during 3 daily 150 min sessions and each animal was tested in the same activity chamber throughout the experiment. On the day following the last habituation session, the locomotor activity elicited by amphetamine (0.5 mg/kg i.p.) was monitored in all animals for 150 min (pretest). On each of the subsequent 5 days, lesioned and sham-lesioned animals were injected with either amphetamine (1.0 mg/kg i.p.) or saline (1 ml/kg i.p.) and were then placed in their respective activity chambers. Five (1st challenge) and then 13 (2nd challenge) days following the last daily injection, the activity elicited by amphetamine (0.5 mg/kg i.p.) was again monitored in all animals; the animals remained in their home cages on intervening days. This dose of amphetamine was chosen to minimize the chances of confounding measures of locomotor activity with stereotypic behaviors that often emerge with repeated injection of the drug (Segal and Kuczenski, 1987).

The effects of the pretreatment (amphetamine vs. saline) and of the type of lesion (sham vs. 6-hydroxydopamine) on the total activity counts during the pretest session and each of the 2 challenge sessions were analyzed using a 2-way ANOVA.

### 2.5. Post-mortem measurements of monoamine levels

At the end of the experiment the animals were decapitated and their brains were rapidly removed, frozen in crushed dry ice then stored at −80°C. The brains were sliced in 300 $\mu$m sections and nucleus accumbens and prefrontal cortex were dissected. Tissue pellets were expelled into an ice-cold medium of 0.15 M sodium acetate (pH 5.0) that also contained 0.1 mM edetic acid and 10 ng/ml of 3,4-dihydroxybenzylamine as an internal standard. The tissue was disrupted by freeze-thawing, centrifuged at $10\,000 \times g$ for 5 min and the supernatant was measured for monoamine content using high-performance liquid chromatography coupled to electrochemical detection. The mobile phase consisted of 0.15 M sodium acetate, 80 mg/l edetic acid, 100 mg/l octyl sodium sulfate and 4% acetonitrile (pH 3.8) and was pumped at 1.3 ml/min (2000 psi back pressure) using a pulseless pump. The electrode potential was maintained at +0.74 V relative to an Ag/AgCl reference electrode. Sample concentrations of dopamine, DOPAC, serotonin and norepinephrine were estimated from peak heights as compared to those obtained from injections of known amounts of pure analytical grade compounds. The remaining pellet was resuspended in 0.1 N sodium hydroxide for protein assay. Monoamine and metabolite levels were expressed as pg/$\mu$g protein.

## 3. Results

### 3.1. In vivo electrochemistry

Electrochemical data were obtained from 23 animals with histologically confirmed electrode placements in the nucleus accumbens (lesioned-amphetamine, $n = 5$; sham-amphetamine $n = 6$; lesioned-saline, $n = 6$; sham-saline, $n = 6$). As can be seen in Fig. 1, the magnitude of amphetamine-elicited signal increases recorded in nucleus accumbens depended on whether the animals had received 6-hydroxydopamine or sham lesions to prefrontal cortex and to some extent also on whether or not the animals had previously received amphetamine. The statistical analysis confirmed these observations, revealing significant effects of the lesion ($F(1,19) = 6.113$, $P = 0.025$) and of the drug treatment ($F(1,19) = 5.565$, $P = 0.03$) on the peak increase in electrochemical signal elicited by amphetamine; there was no significant lesion by treatment interaction. Subsequent analysis of simple effects revealed that, of those animals repeatedly pretreated with amphetamine (lesion-amphetamine vs. sham-amphetamine), drug-induced signal increases peaked at higher levels in animals with 6-hydroxydopamine lesions to prefrontal cortex ($F(1,19) = 8.576$, $P = 0.009$). Furthermore, of the

two groups of 6-hydroxydopamine-lesioned animals (lesion-amphetamine vs. lesion-saline), animals that had been repeatedly injected with amphetamine showed the highest amplitude signal increases in response to amphetamine ($F(1,19) = 8.123$, $P = 0.010$).

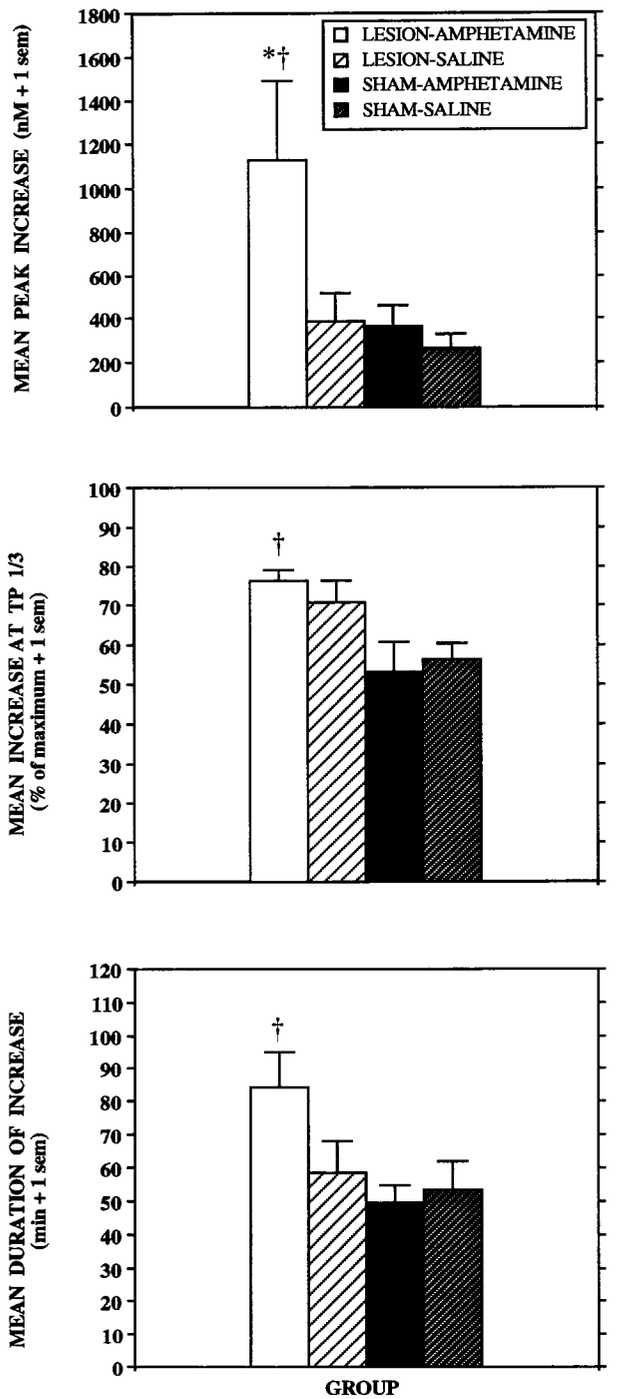


Fig. 1. Mean (+1 S.E.M.) peak amplitude (top), rate of rise (middle) and duration (bottom) of amphetamine-elicited (2.0 mg/kg i.p.) electrochemical signal increases recorded in nucleus accumbens of prefrontal cortex lesioned and sham-lesioned animals 1 week after 5 once-daily injections of amphetamine (4.0 mg/kg i.p.) or saline. * Significant main effect of repeated amphetamine pretreatment ($P \leq 0.05$). † Significant main effect of 6-hydroxydopamine lesion to prefrontal cortex ($P \leq 0.05$).

A significant effect of lesion was also found on the duration of amphetamine-elicited increases in signal ($F(1,19) = 5.648$, $P = 0.03$). On this measure, however, there was no significant effect of drug treatment nor was there any significant lesion by treatment interaction. Simple effects analysis indicated that, of the animals that had previously received amphetamine (lesion-amphetamine vs. sham-amphetamine), increases in signal elicited by amphetamine were longer-lasting in prefrontal cortex lesioned than in sham-lesioned animals ($F(1,19) = 8.017$, $P = 0.011$). Although the trend was not statistically signifcant, amphetamine-induced signal increases recorded in lesioned animals (lesion-amphetamine vs. lesion-saline) were generally longer-lasting in animals that had been repeatedly treated with the drug.

Similarly, there was a significant effect only of lesion on the magnitude of amphetamine-elicited signal increases at TP 1/3 ($F(1,19) = 11.753$, $P = 0.003$), that is, amphetamine-elicited signal increases rose at a faster rate in lesioned than in sham-lesioned animals. An analysis of simple main effects revealed that, in animals previously treated with amphetamine (lesion-amphetamine vs. sham-amphetamine), the electrochemical signal increased more rapidly in response to the drug when prefrontal cortex had been lesioned ($F(1,19) = 8.61$, $P = 0.008$).

Examples of amphetamine-elicited signal increases recorded in nucleus accumbens of a lesioned and a sham-lesioned animal are presented in Fig. 2. Both animals had received 5 once-daily injections of amphetamine 7 days prior to testing. The upper and lower traces of each record represent changes in oxidation and reduction currents, respectively. The mean red : ox ratio ($\pm 1$ standard deviation) for all 23 animals tested was $0.810 \pm 0.094$; red : ox ratios of this magnitude are characteristic of an increase in dopamine (or DOPAC) concentration at the electrode surface.

### 3.2. Locomotor activity

There was no significant difference between lesioned and sham-lesioned animals in the level of spontaneous locomotor activity (Student-$t = 1.581$, $df = 34$, $P = 0.100$); the mean total activity counts ($\pm 1$ S.E.M.) recorded during the last habituation session was 1015.3 ($\pm 85.2$) and 1192.2 ($\pm 73.3$) for lesioned and sham-lesioned animals respectively.

The statistical analyses of the total locomotor activity counts recorded following the pretest and the two challenge injections of amphetamine are summarized in Fig. 3. These revealed a significant effect of lesion ($F(1,32) = 18.393$, $P = 0.0002$) and of session ($F(2,64)$

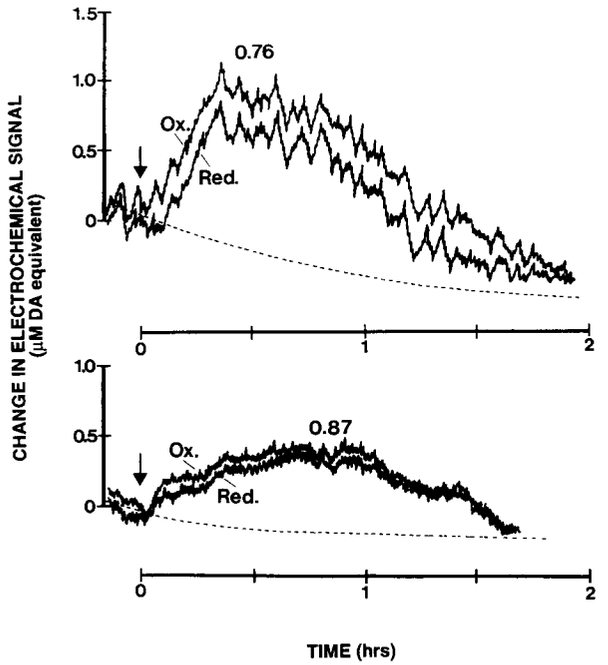


Fig. 2. Examples of amphetamine-induced (2.0 mg/kg i.p.) electrochemical signal increases recorded in nucleus accumbens of prefrontal cortex-lesioned (top) and sham-lesioned (bottom) animals 1 week after 5 once-daily injections of amphetamine (4.0 mg/kg i.p.). Arrows indicate time of injection and dashed lines represent the basal electrochemical signal. In both records, upper and lower traces are changes in oxidation (Ox.) and reduction (Red.) currents respectively. The red:ox ratios (0.76 and 0.87) are indicative of a predominant contribution of dopamine to the electrochemical signal increase.

$= 6.988$, $P = 0.002$), as well as a significant interaction between the effects of lesion, treatment and session ($F(2,64) = 4.374$, $P = 0.02$). Post-hoc analysis (Newman-Keuls) indicated that lesioned animals repeatedly injected with amphetamine were significantly more active in response to both the first and second challenge injections of amphetamine than were lesioned, saline-pretreated animals and sham-lesioned animals whether repeatedly treated with amphetamine or saline. In contrast, the increase in locomotion produced by the pretest injection of amphetamine was significantly greater in sham-lesioned animals than in lesioned animals ($F(1,32) = 5.820$, $P = 0.025$). In other words, prefrontal cortex-lesioned animals were significantly less responsive than sham-lesioned animals to the locomotor-stimulant effect of the first amphetamine injection. Within-session changes in locomotor activity produced by the pretest and challenge injections of amphetamine are presented in Fig. 4.

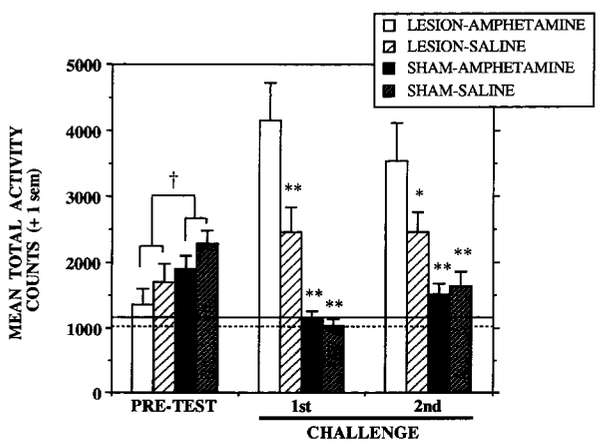


Fig. 3. Mean (+1 S.E.M.) total activity counts recorded following the pretest and the 2 challenge injections of amphetamine (0.5 mg/kg i.p.). Asterisks indicate significant differences ($^{*}P < 0.05$; $^{**}P < 0.01$) in comparison to lesioned animals repeatedly pretreated with amphetamine (1.0 mg/kg i.p.). $^{\dagger}$ Significant difference ($P < 0.05$) between lesioned and sham-lesioned animals. Horizontal lines indicate mean total activity counts of lesioned (dashed line) and sham-lesioned (solid line) recorded during the last habituation session.

### 3.3. Post-mortem measurements of monoamine levels

Tissue levels of dopamine, DOPAC, norepinephrine, and serotonin in prefrontal cortex and nucleus accumbens of lesioned and sham-lesioned animals used in the locomotor activity tests are presented in Table 1. Prefrontal cortex levels of dopamine and DOPAC were significantly ($P < 0.05$) lower in lesioned animals when compared to those of sham-lesioned animals. While prefrontal cortex levels of serotonin were similar in lesioned and sham-lesioned animals, there was a noticeable, albeit statistically unreliable, reduction in norepinephrine levels in lesioned animals (66.58% of sham-lesioned animals). Levels of monoamines in nucleus accumbens of lesioned and sham-lesioned animals did not differ significantly nor was there any effect of repeated amphetamine administration on monoamine content in prefrontal cortex and nucleus accumbens of lesioned and sham-lesioned animals.

## 4. Discussion

The results of the present study indicate that the acute stimulant effect of amphetamine on locomotor activity is potentiated by partial dopamine-depleting lesions to prefrontal cortex but only when animals have had prior experience with the drug. In fact, the present results show that lesioned animals were significantly *less* responsive to the first (pretest) amphetamine injection than were their sham-lesioned counterparts. This finding is in apparent disagreement with previous reports that dopamine depletion in prefrontal cortex enhances the acute locomotor-stimulant effect of amphetamine (Carter and Pycock, 1980; Pycock et al., 1980). The reasons for this discrepency are not clear. However, one obvious explanation that can be ruled out is that the dose of the first amphetamine injection (0.5 mg/kg) was too low. Similar prefrontal cortex

lesions have been reported previously to not affect locomotion stimulated by a dose of amphetamine 3 times higher (1.5 mg/kg) than that used in the present study (Joyce et al., 1983). Furthermore, the fact that the locomotor activity of sham-lesioned increased in response to the pretest amphetamine injection makes it clear that, alone, the low dose of amphetamine used in the present study cannot account for the apparent subsensitivity of lesioned animals.

A potentially important factor in the response of prefrontal cortex-lesioned animals to the first injection of amphetamine may be the selectivity of the lesion. Prefrontal cortex is also innervated by norepinephrine-containing neurons in locus coeruleus and like dopamine, norepinephrine generally inhibits the activity of prefrontal cortex neurons (Bunney and Aghajanian, 1976). In the present study, norepinephrine levels in prefrontal cortex of lesioned animals were reduced by approximately 30% when compared to sham-lesioned animals. Although not statistically significant, such reductions in prefrontal cortex norepinephrine would presumably have behavioral effects. However, we can only speculate as to how they contributed to the present results. Data from several studies suggest that the extent of sparing of the norepinephrine innervation of prefrontal cortex has important consequences for the behavioral effects of dopamine depletion in this region. Bilateral electrolytic lesions of the ventral tegmental area that spare the norepinephrine projection to prefrontal cortex have been reported to cause increased locomotor activity, the intensity of which is related to the extent of dopamine depletion (Tassin et al., 1978). Such lesions were reported to also result in compensatory increases in dopamine $D_1$ receptors in prefrontal cortex (Tassin et al., 1982). However, when both the dopamine and norepinephrine inputs to prefrontal cortex are destroyed no such increases in locomotor activity and dopamine $D_1$ receptor binding are observed (Taghzouti et al., 1988; Tassin et al., 1986). While there are numerous methodological differences with the present study, the results of these earlier studies indicate that the modulatory influence of prefrontal cortex on meso-nucleus accumbens dopamine function may depend on the complex interplay between the dopamine and norepinephrine neurons that innervate this cortical region.

The novelty of the testing environment and other sources of stress may underlie some of the discrepancies between the present results and those of previous studies. Stress is known to stimulate locomotor activity as well as dopamine efflux in prefrontal cortex and nucleus accumbens (Abercrombie et al., 1989; Doherty and Gratton, 1992) and partial dopamine depletion in prefrontal cortex has been shown to potentiate stress-induced increases in dopamine nucleus accumbens levels (Deutch et al., 1990). Furthermore, exposure to stresses such as footshock or even an intraperitoneal saline injection is sufficient to later sensitize animals to the acute stimulant effect of amphetamine (Antelman et al., 1980). Thus, it is conceivable that in earlier studies, exposure to a seemingly innocuous stress contributed to potentiate and perhaps even sensitize prefrontal cortex animals to the acute locomotor stimulant effect of the first amphetamine injection. Since the animals in the present study had been extensively acclimatized to the testing environment prior to receiving the first amphetamine injection, such an interaction between stress and amphetamine would have been minimized. The fact that spontaneous locomotor activity in lesioned and sham-lesioned animals (during the last habituation session) did not differ in the present study, makes it clear that the two groups of animals reacted similarly to the testing environment; it is also consistent with the results of several reports indicating no change in spontaneous locomotor activity (Clarke et al., 1988; Joyce et al., 1983; Oades et al., 1986) or in basal levels of subcortical dopamine (Deutch et al., 1990; Joyce et al., 1983; Rosin et al., 1992) following dopamine-depleting lesions of prefrontal cortex.

In the present study, repeated amphetamine administration sensitized lesioned but not sham-lesioned animals to the acute locomotor stimulant effect of the drug. Apart from the possibility that the 'sensitizing' dose of amphetamine used in the present study (1.0 mg/kg) was too low or that the number of injections was insufficient, we can offer no explanation for the

Table 1
Levels (mean pg/μg of protein ±1 S.E.M.) of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), norepinephrine (NE) and serotonin (5-HT) in prefrontal cortex and nucleus accumbens of 6-hydroxydopamine-lesioned and sham-lesioned animals. Levels in lesioned animals are also expressed as percent of levels in sham-lesioned animals

| | Prefrontal cortex | | | Nucleus accumbens | | |
|---|---|---|---|---|---|---|
| | Sham | Lesioned | % | Sham | Lesioned | % |
| DA | 24.06 ± 1.67 | 9.18 ± 0.65 [a] | 38.15 | 53.29 ± 9.08 | 54.22 ± 3.42 | 100.09 |
| DOPAC | 13.94 ± 2.99 | 5.86 ± 0.91 [a] | 42.04 | 48.02 ± 10.69 | 47.45 ± 5.48 | 104.31 |
| NE | 4.04 ± 0.76 | 2.69 ± 0.30 | 66.58 | 3.67 ± 0.33 | 3.19 ± 0.50 | 87.19 |
| 5-HT | 3.48 ± 0.42 | 2.97 ± 0.31 | 85.34 | 8.44 ± 2.24 | 6.02 ± 0.65 | 91.94 |

[a] Significant at $P < 0.05$ (Student's $t$-test) when compared to sham-lesioned animals.

apparent lack of behavioral sensitization in sham-lesioned animals. A decrease in locomotion concomitant to an increase in stereotypy would be one obvious explanation for these results; stereotypic behaviors (e.g. grooming, focused sniffing) that are incompatible with locomotion and that normally occur at high doses of amphetamine can also be observed in sensitized animals in response to lower doses of the drug. However, the within-session pattern of increases in locomotion elicited by the challenge injections of amphetamine is inconsistent with that of animals engaged in stereotypic behaviors (see Fig. 4). Had amphetamine induced stereotypic behaviors, activity scores would have been low during the first 30–60 min of the session, when brain levels of amphetamine are presumably highest, but would have been expected to increase above pretest levels during the latter part of the session (Segal and Kuczenski, 1987). Our data indicate instead that changes in locomotor activity paralleled the rise and fall in brain concentrations of amphetamine.

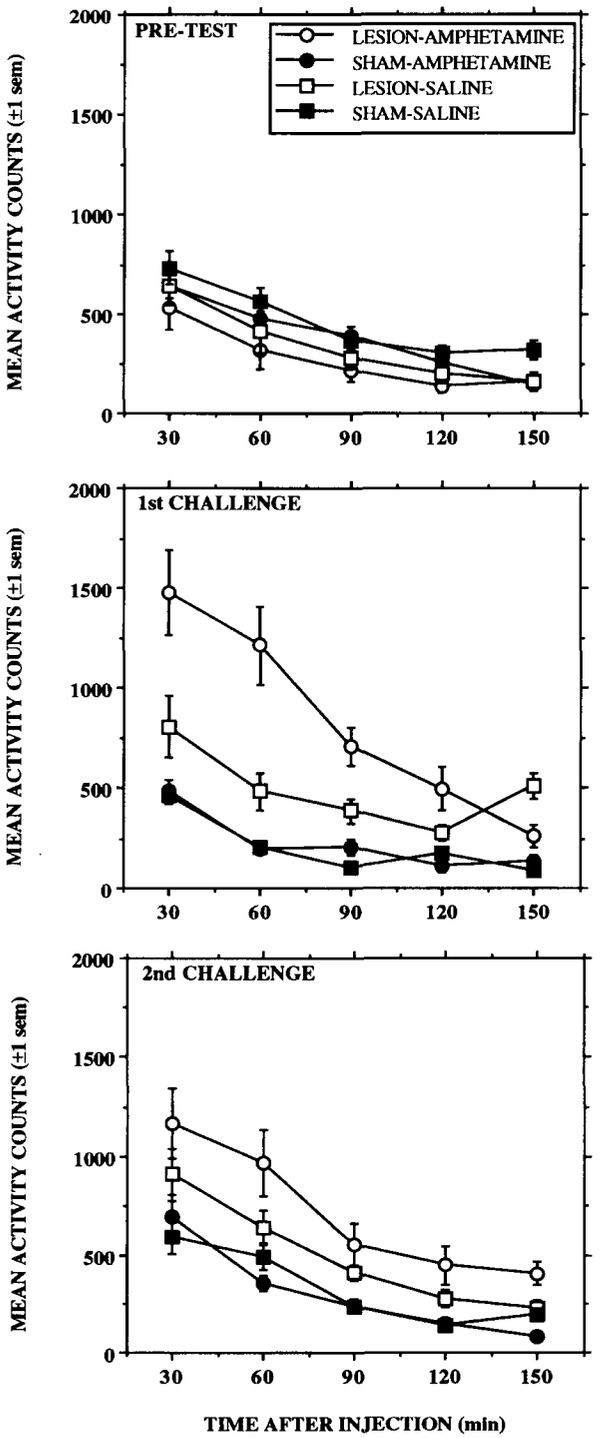


Fig. 4. Mean (±1 S.E.M.) activity counts recorded at 30 min intervals following the pretest injection (top) and the 1st (middle) and 2nd (bottom) challenge injections of amphetamine (0.5 mg/kg i.p.).

Voltammetry was used in the present study to monitor amphetamine-induced increases in extracellular dopamine levels. The main weakness of this technique is that it does not provide sufficient information to positively identify the electroactive species responsible for increases in oxidation current. The most problematic species are ascorbic acid and DOPAC since their extracellular concentrations can be 2–3 orders of magnitude higher than that of dopamine (Zetterström et al., 1988). However, several procedures have been developed to help differentiate the contribution of these and other oxidizable compounds to the electrochemical signal. First, the tips of the carbon-fiber electrodes used in the present study were coated with Nafion, a perfluoro ionomer that promotes the exchange of cations such as dopamine and impedes the exchange of anionic species such as ascorbic acid and DOPAC (Gerhardt et al., 1984). The electrodes used in the present all had dopamine to ascorbic acid selectivity ratios greater than 1500:1 (range = 1500:1 to 2000:1); thus substantially reducing the chances that ascorbic acid contributed significantly to the increases in signal elicited by amphetamine. The dopamine to DOPAC selectivity ratio of these electrodes, however, is lower (500–800:1); thus, a possible contribution of DOPAC to the signal increases cannot be ruled out on the basis of electrode selectivity alone. Still, the possibility that increases in extracellular DOPAC are responsible for the amphetamine-induced increases in electrochemical signal reported here can be ruled out for other reasons. While amphetamine potently increases extracellular levels of dopamine, it is well known to produce a pronounced and long-lasting *decrease* in extracellular DOPAC levels, presumably as a result of depriving intracellular monoamine oxidase of its substrate. Thus, instead of the signal increases that were observed, amphetamine administration should have been followed by significant *decreases* in signal had DOPAC, rather than dopamine, been the predominant electroactive species detected by the electrode.

Inasmuch as dopamine is primarily responsible for the signal increases reported here, the present results

indicate that the effect of prefrontal cortex dopamine depletion on amphetamine-stimulated locomotion reflects, at least in part, greater dopamine efflux in nucleus accumbens. Furthermore, as was the case in the behavioral experiment and similar to the results of a previous study (Mitchell and Gratton, 1992), the present electrochemical data suggest that partial dopamine-depleting lesions of prefrontal cortex enhanced amphetamine-induced dopamine efflux to greater extent in animals that had been repeatedly injected with the drug than in animals that had received the drug only once prior to testing. Surprisingly, the results also suggest that the two groups of sham-lesioned animals responded to amphetamine with comparable increases in dopamine efflux. Thus, intact animals that had received repeated daily amphetamine prior to testing apparently did not sensitize to the acute stimulant effect of the drug on meso-nucleus accumbens dopamine transmission. Although congruent with the failure to observe a sensitized locomotor response to amphetamine in sham-lesioned animals, these results are no less difficult to explain. Unlike the behavioral experiment, the dose and number of injections of amphetamine ($1 \times 2.0$ mg/kg/day and $5 \times 4.0$ mg/kg/day) should have been sufficient to produce sensitization of dopamine efflux. For lack of any other explanation, it may be that sensitization of dopamine transmission in sham-lesioned, saline-treated animals occurred as a result of the first, pretest injection of amphetamine. While sensitization following a single drug administration has been reported previously (Browne and Segal, 1977), it is also the case that repeated drug administration leads to a considerably more robust and long-lasting effect (Robinson, 1988). Thus it remains unclear why amphetamine apparently stimulated dopamine efflux to the same extent in both groups of sham-lesioned animals.

What is clear from the present behavioral and electrochemical data, is that the facilitatory effect of dopamine-depleting lesions to prefrontal cortex on meso-nucleus accumbens dopamine function is experience dependent. One implication of this finding is that sensitization of meso-nucleus accumbens dopamine function may reflect, at least in part, long-term changes of meso-prefrontal cortex dopamine transmission. The nature of these changes is, at present, still a matter of speculation but is likely to reflect the unique properties of meso-prefrontal cortex dopamine neurons. These neurons exhibit higher spontaneous firing rates than do meso-nucleus accumbens dopamine neurons and have few if any impulse-regulating autoreceptors (Bannon et al., 1987; Chiodo et al., 1984); although amphetamine elevates dopamine levels in prefrontal cortex (Maisonneuve et al., 1990) it does not reduce the spontaneous firing activity of meso-prefrontal cortex dopamine neurons (Eihorn et al., 1988). Thus, the activity of meso-prefrontal cortex dopamine neurons is not subjected to the tight negative feedback that controls meso-nucleus accumbens dopamine cell firing. Furthermore, although dopamine release from both meso-prefrontal cortex and meso-nucleus accumbens dopamine neurons is subjected to similar negative feedback control (by terminal release-modulating autoreceptors; Wolf and Roth, 1987), autoregulation of dopamine synthesis in these two systems differs. Unlike dopamine synthesis in meso-nucleus accumbens neurons, which is tightly coupled to autoreceptors, meso-prefrontal cortex neurons do not seem capable of direct control over dopamine synthesis (Bannon et al., 1980, 1987; Chiodo et al., 1984; Galloway et al., 1986). Nonetheless, synthesis in meso-prefrontal cortex dopamine neurons does appear to be sensitive to intracellular levels of dopamine such that any changes in dopamine levels would presumably lead to changes in rate of synthesis. However, because of the relatively smaller dopamine pool and the faster turnover rate of meso-prefrontal cortex dopamine neurons (Bannon et al., 1987), any alteration in dopamine synthesis would presumably have a more profound effect on the availability and the release of dopamine in these neurons compared to their meso-nucleus accumbens counterparts (Galloway, 1990).

Although the 6-hydroxydopamine model is not directly comparable, the present results may suggest that repeated amphetamine administration eventually decreases the drug's acute stimulant effect on dopamine release in prefrontal cortex. Evidence in support of this suggestion comes from a number sources including a recent study showing that the acute stimulant effect of stress on prefrontal cortex dopamine efflux is abolished in animals that had received a sensitizing regimen of cocaine injections (Sorg and Kalivas, 1993). Similarly, whereas dopamine transmission in nucleus accumbens sensitizes to the acute stimulant effect of opiates with repeated administration, recent evidence suggests that it may tolerate in prefrontal cortex (Vezina et al., 1992). Results inconsistent with these studies have been reported, however. Contrary to what Sorg and Kalivas (1993) observed in cocaine-pretreated animals, repeated amphetamine administration was reported to later enhance stress-induced dopamine release in prefrontal cortex (Hamamura and Fibiger, 1993). In addition, repeated amphetamine injection into prefrontal cortex has been reported to not alter the locomotor response to systemic amphetamine, cocaine and caffeine administration (Hooks et al., 1992). Thus, there is evidence both for and against the idea that decreased responsiveness of the meso-prefrontal cortex dopamine system contributes to stimulant-induced sensitization of meso-nucleus accumbens function.

There are at least two pathways by which meso-prefrontal cortex dopamine neurons can influence

dopamine transmission in nucleus accumbens: via corticofugal neurons to nucleus accumbens and to the ventral tegmental area. The ventral tegmental area would appear to be the more interesting site of interaction because of evidence implicating this area in the initiation of behavioral sensitization to psychostimulants and opiates (Kalivas and Stewart, 1991; Kalivas and Weber, 1988; Vezina and Stewart, 1990). Furthermore, we have recently shown that intra-ventral tegmental area injections of $\mu$-opiates stimulate dopamine efflux in prefrontal cortex as potently as in nucleus accumbens (Noel and Gratton, 1995). Taken together with the present data, the results of these studies raise the intriguing possibility that dopamine neurons that project to prefrontal cortex or a prefrontal cortex input to the ventral tegmental area or both mediate the initiation of behavioral sensitization induced by repeated intra-ventral tegmental area as well as systemic drug administration.

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