Repeated Daily Cocaine Alters Subsequent Cocaine-induced Increase of Extracellular Dopamine in the Medial Prefrontal Cortex

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ABSTRACT

Male Sprague-Dawley rats that were naive or that had been treated with five daily saline or cocaine injections (15 mg/kg i.p.) were subsequently challenged with an injection of cocaine, and extracellular dopamine content in the medial prefrontal cortex (mPFC) was measured using in vivo microdialysis. Cocaine challenge increased extracellular dopamine levels from base line in all three groups of rats, but the augmentation was significantly reduced in the cocaine-pretreated group, compared with the saline-pretreated group. In contrast, mPFC dopamine levels were not different among groups after challenge with systemic d-amphetamine. To test whether repeated cocaine treatment led to altered releasability of dopamine from mPFC terminals, challenge with KCl (10, 30 or 100 mM) or d-amphetamine (3, 30 or 300 μM) was made via infusion through the dialysis probe into the mPFC. No differences in dopamine levels were found between treatment groups for either drug at any dose. To determine whether the effects of cocaine were mediated by local actions within mPFC dopamine terminals, a cocaine challenge was administered through the microdialysis probe (1, 10 or 100 μM). In contrast to the systemic cocaine challenge, local infusion of cocaine elicited a significant increase in daily cocaine-pretreated rats, compared with saline-pretreated controls, at the lowest dose tested, with no differences at the higher two doses. In summary, daily cocaine-pretreated rats demonstrated a suppressed mPFC dopamine response to subsequent systemic, but not local, cocaine challenge. The results suggest that this apparent tolerance is not due to altered releasability of dopamine from mPFC terminals and may rely on altered afferent regulation of mesocortical dopamine neurons.

Repeated psychostimulant administration produces a progressive increase in the locomotor response in rodents, a process referred to as behavioral sensitization. The neuronal circuitry consistently implicated in mediating psychostimulant-induced locomotion and behavioral sensitization involves dopaminergic neurons projecting from the VTA to the nucleus accumbens (Kelley and Iversen, 1975; Robinson et al., 1988; Kalivas and Duffy, 1990; Pettit et al., 1990). In vivo microdialysis studies have revealed that cocaine-induced elevations of extracellular dopamine concentrations in the nucleus accumbens are augmented in rats behaviorally sensitized to cocaine (Kalivas and Duffy, 1990; Pettit et al., 1990).

Although the role of the mesoaccumbens dopamine pathway in cocaine-induced sensitization has been well studied, the role of the mPFC in sensitization is only beginning to be explored. Descending regulation by the mPFC on subcortical structures important for the development and expression of behavioral sensitization has been more extensively examined. Both spontaneous locomotor activity (Tassin et al., 1978) and acute amphetamine-induced locomotion are modulated by mPFC dopamine transmission (Thierry et al., 1979; Vezina et al., 1991). A negative correlation between locomotor activity and mPFC dopamine levels has been reported (Tassin et al., 1978). Dopamine plays an inhibitory role in mPFC neurons, because application of dopamine to PFC neurons inhibits the firing of these cells (Bunney and Aghajanian, 1976; Williams and Goldman-Rakic, 1995). The relationship between mPFC dopamine and locomotion is believed to occur directly via the inhibitory action of dopamine on EAA neurons in the mPFC and indirectly via dopamine-mediated increases in γ-aminobutyric acid release (Sesack and Bunney, 1989; Retaux et al., 1991). Therefore, dopamine release in the mPFC is postulated to influence locomotion via inhibition of EAA neurons projecting to subcortical sites (Carter and Pycock, 1980; Sesack et al., 1989; Berendse et al., 1992). Direct EAA projections have been identified from the mPFC.
to the nucleus accumbens, as well as to dopaminergic and nondopaminergic neurons in the VTA (Carter, 1980; Sesack and Pickel, 1992).

Dopamine levels in the nucleus accumbens and striatum are regulated by mPFC EAA efferents (Louilot et al., 1989; Taber et al., 1995; Karreman and Moghaddam, 1996). EAA efferents from the mPFC modulate mesolimbic dopamine release by inducing burst firing in these neurons (Garitano and Groves, 1988; Murase et al., 1993). The primary pathway for mPFC regulation of dopamine levels in the nucleus accumbens/striatum appears to be indirectly via EAA projections from the mPFC to the VTA. Taber et al. (1995) showed that direct electrical stimulation of the mPFC produces an increase in nucleus accumbens dopamine levels, which is blocked by glutamate antagonist infusion into the VTA. Karreman and Moghaddam (1996) have also provided strong evidence for indirect modulation of striatal dopamine levels by mPFC EAA output to the substantia nigra, rather than through a direct corticostral path.

Evidence is emerging that the mPFC may play an important role in behavioral sensitization and the reinforcing effects of psychostimulants. Rats have been shown to self-administer cocaine directly into the mPFC (Goeders and Smith, 1983), and destruction of mPFC dopamine terminals by 6-hydroxydopamine treatment results in the acquisition and maintenance of subthreshold doses of cocaine self-administration (Schenk et al., 1991). Behavioral sensitization to repeated amphetamine or repeated sex-related olfactory cues is augmented in rats with 6-hydroxydopamine lesions in the mPFC (Mitchell and Gratton, 1992; Banks and Gratton, 1995). Also, lesion of EAA neurons in the mPFC by ibotenic acid prevents amphetamine-induced sensitization (Wolf et al., 1995). These reports are consistent with an inhibitory role for mPFC dopamine on EAA efferents to subcortical sites modulating behavioral sensitization and reward processes.

A previous study in this laboratory examined the effects of cross-sensitization on mPFC dopamine levels (Sorg and Kalivas, 1993). Repeated exposure to footshock stress produced a decreased responsiveness of mPFC dopamine to a subsequent acute cocaine injection 1 week later. The converse of this cross-sensitization experiment showed that repeated cocaine administration produced complete blockade of the footshock-induced increase in mPFC dopamine levels. Thus, in contrast to dopamine transmission in the nucleus accumbens, tolerance rather than sensitization was observed in the mPFC. The goal of the present study was to examine whether repeated cocaine administration would produce the same effect on mPFC extracellular dopamine levels after a subsequent cocaine or amphetamine challenge and to further explore potential mechanisms mediating the tolerance phenomenon. The effect of systemic cocaine and amphetamine on extracellular dopamine content in the mPFC was assessed in daily cocaine- and saline-pretreated rats. A second series of experiments used intra-mPFC challenge of KCl, amphetamine or cocaine infusion through the microdialysis probe to determine whether the systemic effects of cocaine or amphetamine were mediated locally.

**Methods**

**Drugs.** Cocaine hydrochloride and d-amphetamine sulfate (gifts from the National Institute on Drug Abuse) were dissolved in isotonie saline for systemic injection and artificial CSF (see below) for intracranial infusion.

**Animal housing and surgery.** All procedures were conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Male Sprague-Dawley rats (Simonsen Laboratories, Gilroy, CA), weighing 250 to 320 g at the time of surgery, were given free access to food and water in a temperature- and humidity-controlled room with a 12-hr light cycle, with lights on at 7:00 A.M. For surgery, rats were anesthetized with Equithesin (3.0 ml/kg i.p.) and placed into a stereotaxic apparatus. Unilateral chronic guide cannulae (20 gauge) were placed into the right hemisphere at +3.2 mm from bregma, ±0.6 mm from midline and −1.5 mm from the skull (Paxinos and Watson, 1986). All rats were housed individually, in stainless steel hanging cages, for at least 5 days after surgery before the beginning of daily injections (at least 16 days before the dialysis day). All naive rats were left unhandled after surgery and housed for the same times as their daily saline- or cocaine-treated counterparts between surgery and the microdialysis day.

**Behavioral measures.** Behavioral activity was monitored in photocell chambers (Omnitech Electronics, Columbus, OH). Each monitor was housed in individual wooden boxes with individual lighting (10 W) and a fan to attenuate outside noise. Measures of horizontal photocell beam breaks were obtained at 20-min intervals, simultaneously with dialysis sample collection.

**Experimental paradigm.** A total of six experiments was performed. Three experiments were performed in which systemic injections were administered during microdialysis. Three additional experiments were carried out using local infusion of drugs through the microdialysis probe.

For all experiments involving systemic drug challenge, rats were administered either no pretreatment (naive), saline (1 ml/kg i.p.) or cocaine hydrochloride (15 mg/ml i.p.) once daily for 5 days. Six days later, the rats were placed into the photocell chambers, and dialysis probes were inserted through the chronic guide cannulae the evening before the experiment. Probe placement was performed the night before the experiment, to minimize damage-induced dopamine release during the experiment (Westenrik and Devries, 1988). The infusion pumps remained off during the night; the next morning, artificial CSF (5.0 mM glucose, 5 mM KCl, 120 mM NaCl, 1.4 mM CaCl₂, 1.2 mM MgCl₂, 0.15% phosphate-buffered saline, pH 7.4) was infused through the probe at a rate of 2.0 μl/min. After at least 2 hr of infusion, five 20-min base-line samples were collected, after which an acute challenge of saline (1 ml/kg i.p.), cocaine hydrochloride (15 mg/kg i.p.) or d-amphetamine sulfate (1.75 mg/kg i.p.) was administered. Sample collection continued at 20-min intervals for a minimum of 140 min. Average basal levels were calculated by averaging three of the five base-line values.

For experiments involving local drug infusion into the mPFC, rats were treated as described above, with the exception of the cocaine infusion study, in which naive rats were not used. Local infusion of KCl, d-amphetamine sulfate or cocaine dissolved in artificial CSF replaced systemic drug challenge. Three doses of each drug were given, as follows: KCl, 10, 30 and 100 mM (NaCl in artificial CSF adjusted to 115, 95 and 25 mM, respectively); d-amphetamine sulfate, 3, 30 and 300 μM; cocaine hydrochloride, 1, 10 and 100 μM. Five 20-min samples were collected after each switch of drug concentration was made.

**In vivo dialysis and dopamine measurement.** Dialysis probes (Robinson and Whishaw, 1988) with a membrane region 250 μm in diameter and 3 mm in length were inserted 3 mm below the guide cannulae. Dialysis samples were collected into 20 μl of mobile phase containing 2.0 pmol of dihydroxybenzylamine as an internal standard. The concentration of dopamine was measured using high performance liquid chromatography with coulometric electrochemical detection, as previously described (Sorg and Kalivas, 1991).

**Histology and data analysis.** At the completion of the experiments, the animals were given an overdose of sodium pentobarbital.
and perfused through the heart with phosphate-buffered saline followed by 10\% formalin/isotonic saline. Coronal slices (100 \mu m) were stained with cresyl violet, and probe placement was determined by light microscopy. Behavioral and neurochemical data were analyzed with a two-way ANOVA with one repeated measure over time (all time course data) or dose (figs. 3C, 4C and 5C). All P values reported from the two-way ANOVAs represent adjusted P values according to the Greenhouse-Geisser approach. In the case of a significant interaction, a least-squares difference analysis was performed. Basal levels of dopamine were analyzed with a one-way ANOVA. When data were transformed to percentage of base-line values, each animal’s response to drug infusion or injection was divided by its own average basal value.

**Results**

**Systemic challenge.** Figure 1, A to C, shows the response to an acute saline injection in naive, daily saline-pretreated and daily cocaine-pretreated rats. Although dopamine was increased after saline injection in all groups, no significant differences among treatment groups were found. Basal levels of dopamine were not significantly different among treatment groups (P = .68). Acute saline injection induced a slight increase in horizontal locomotor activity that was not different among the treatment groups (fig. 1C).

Figure 1, D to F, shows the response to an acute cocaine injection in naive, daily saline-pretreated and daily cocaine-pretreated rats. Before systemic cocaine challenge, basal levels of dopamine from naive, saline-pretreated or cocaine-pretreated rats were not different (P = .21). After a systemic cocaine challenge, all three groups demonstrated increases in dopamine concentration (fig. 1D). There were no significant differences among groups when absolute concentrations of dopamine were considered. However, figure 1E indicates that, when the data were analyzed as percent change from base-line values, saline-pretreated rats demonstrated a significant augmentation in dopamine levels, compared with naive or cocaine-pretreated rats. The enhanced levels were present after the first point collected (20 min) and subsided to concentrations similar to the other two groups by 40 min after cocaine challenge. The time course in figure 1F shows that the horizontal locomotor response tended toward a nonsignificant increase in cocaine-pretreated rats, compared with saline-pretreated controls. When total activity was accumulated over the 2-hr postinjection period, the behavioral response in daily cocaine-pretreated rats was significantly elevated above that of saline controls (fig. 1F, inset).

To determine whether an acute amphetamine challenge could elicit a dopamine response similar to that induced by cocaine, a systemic amphetamine injection was administered in naive, daily saline-pretreated and cocaine-pretreated rats. In some cases, amphetamine was administered to rats 3 hr after systemic saline treatment from the previous study (fig. 1, A–C), and the response was followed for a 1-hr period. In a subsequent study, rats were administered daily pretreatment as before and given only the amphetamine challenge. Because no differences in the responses to amphetamine challenge were noted between the two studies (P = .96), the data were combined, and only the data from the first 1 hr after injection are shown in figure 2. Basal dopamine levels among treatment groups were not significantly different (P = .092). Figure 2A indicates that absolute dopamine concentrations in naive animals were significantly elevated above saline- and cocaine-pretreated animals 20 min after amphetamine injection. However, when the data were analyzed as percentage of base-line values, naive animals responded similarly to saline-pretreated rats, and only a nonsignificant trend toward increased dopamine levels in the daily cocaine-
pretreated group was observed. Thus, the blunted responsiveness of dopamine levels observed after cocaine challenge in cocaine-pretreated rats was not apparent after systemic amphetamine challenge. Figure 2C indicates that the locomotor response to acute amphetamine injection was increased in all treatment groups but was not significantly different among the groups.

**Intra-mPFC challenge.** To test whether repeated cocaine treatment led to alterations in the releasability of dopamine in the mPFC, KCl was infused through the microdialysis probe placed in the mPFC. The results are shown in figure 3. Basal levels of dopamine were not different among groups (P = .35). No differences were detected among any of the three treatment groups at the three doses tested when data were examined as absolute values or as percentage of baseline levels.

The likelihood that cytoplasmic dopamine levels may have been altered was tested by infusing various doses of d-amphetamine through the microdialysis probe in the mPFC. Basal levels of dopamine were not different among treatment groups (P = .58). Figure 4 demonstrates that infusion of d-amphetamine through the probe did not produce differences among the treatment groups at any of the doses tested, although a tendency toward lower levels of dopamine was found in naive rats.

To determine whether the altered response of mPFC dopamine to a cocaine challenge may have resulted from cocaine-induced changes within the terminal region, cocaine was locally infused through the microdialysis probe as a challenge. In this experiment, only daily saline- and cocaine-pretreated rats were used, because the differences after systemic cocaine administration were observed between these
two groups. Basal dopamine concentrations were not significantly different between groups (P = .61). Figure 5, A and B, demonstrates that local infusion of cocaine into the mPFC produced a nonsignificant trend toward increased dopamine levels in cocaine-pretreated rats, compared with saline-pretreated controls, at the lower two doses tested (1 and 10 μM). Further analysis of the average percent change in dopamine levels accumulated during the last 1 hr of each dose revealed that levels in daily cocaine-pretreated rats were significantly increased, compared with saline-treated controls, after the lowest dose but not after the two higher doses of cocaine infusion (fig. 5C).

Discussion

The main findings from the present study can be summarized as follows. 1) Compared with saline-treated controls, mesoprefrontal dopamine neurons in cocaine-sensitized rats demonstrated apparent tolerance to the effects of subsequent systemic cocaine but not systemic amphetamine. 2) The tolerance was not due to decreased releasability of dopamine from vesicular or cytoplasmic pools in mPFC terminals, as determined by local mPFC infusion of KCl or amphetamine through the dialysis probe. 3) Local infusion of cocaine
through the dialysis probe into the mPFC did not mimic the effects of systemic cocaine but tended toward the opposite response, suggesting that tolerance of mPFC dopamine detected after systemic cocaine injection may be mediated by afferents to mesocortical dopamine neurons.

**Systemic cocaine and amphetamine.** The decline of cocaine-induced increases in mPFC dopamine levels in cocaine-sensitized rats is in contrast to consistent findings of an augmentation in extracellular dopamine levels occurring in mesoaccumbens projections after daily cocaine pretreatment (Robinson et al., 1988; Kalivas and Duffy, 1990; Pettit et al., 1990). However, previous findings from this laboratory have shown a similar phenomenon in the mPFC in a cocaine/stress cross-sensitization paradigm (Sorg and Kalivas, 1993). In those experiments, daily cocaine produced a complete blockade of the acute footshock-induced increase in mPFC dopamine; in the converse experiment, daily footshock stress induced a tolerance to systemic cocaine-induced increases in dopamine levels, compared with daily sham-treated (handled) controls. Both cocaine-induced release and stress-induced release of dopamine are impulse-dependent, whereas the effects of amphetamine are only partially dependent on impulse flow (Kuczenski, 1983; Mantz et al., 1989). Therefore, the differences in dopamine levels produced by daily saline and cocaine pretreatment after cocaine challenge may depend primarily on impulse-mediated dopamine release.

Tolerance of mPFC dopamine to a cocaine challenge was observed when percentage of base-line values, but not absolute dopamine concentrations, were expressed. It remains unknown whether it is the absolute dopamine levels or the percent change in concentration that is most relevant to functional changes in circuitry postsynaptic to mPFC dopamine terminals.

Recent studies examining extracellular dopamine levels in the mPFC have reported that, when amphetamine or methamphetamine is administered daily to rats, subsequent acute stress (Hamamura and Fibiger, 1993), local KCl infusion or systemic amphetamine administration (Stephans and Yamamoto, 1995) elicits an augmentation in dopamine levels. Thus, mesoprefrontal neurons are capable of sensitized responding if repeated amphetamine is used as the sensitizing stimulus. Differences between repeated amphetamine and cocaine may lie in their different mechanisms of action (Carboni et al., 1989; Cadoni et al., 1995). Relevant to the induction of sensitization is the demonstration that cocaine does not decrease firing of mesoprefrontal neurons, whereas amphetamine inhibits these neurons (Chiodo et al., 1984; White et al., 1987), and both drugs inhibit firing of mesoaccumbens neurons (White et al., 1987; Einhorn et al., 1988).

The lack of impulse-regulating autoreceptors on prefrontocortical neurons (Chiodo et al., 1984) or weak feedback via the reciprocal projection from the mPFC to the VTA may explain the absence of inhibition by cocaine, whereas the mechanism of the depressive effect of amphetamine on mesocortical neurons remains unknown. Thus, initiation of sensitization of dopaminergic pathways after repeated systemic psychostimulant administration may depend on the ability of a repeated intermittent stimulus to attenuate or arrest impulses in the vicinity of the VTA.

Although behavioral sensitization was present in cocaine-challenged animals, daily cocaine-pretreated rats given an amphetamine challenge failed to demonstrate sensitized behavorial responding. Previously, we demonstrated a nonsignificant trend toward cross-sensitization of locomotor activity in response to acute cocaine after daily footshock stress (Sorg and Kalivas, 1993). In that study, as well as the present work, it was noted that, when rats are implanted with a microdialysis probe in the mPFC, locomotor activity is diminished, compared with those implanted in the nucleus accumbens (Kalivas and Duffy, 1990, 1993). Thus, placement of a dialysis probe into the mPFC may impose a reduced upper limit on locomotor output. The increased response in locomotor activity after amphetamine, compared with that after cocaine challenge, in the present study may indicate an approach to this upper limit; that is, when animals are implanted in the mPFC, the dose of amphetamine used (1.75 mg/kg i.p.) may be high enough to cause maximal increases in all pretreatment groups. Alternatively, this dose of amphetamine may produce some stereotypic behavior in daily cocaine-pretreated rats to a greater extent than in saline-pretreated controls. Some stereotypic movements would not necessarily have been detected by the automated photocell system and would compete with locomotor activity, potentially diminishing any differences between treatment groups.

**Local mPFC infusion of KCl, amphetamine and cocaine.** The absence of differences among treatment groups receiving intra-mPFC infusion of KCl suggests that no difference in the ability of mPFC dopamine terminals to release dopamine from vesicular stores was present. Similarly, local infusion of d-amphetamine into the mPFC did not produce differences in extracellular dopamine concentrations among treatment groups. Amphetamine is believed to promote dopamine release from nonvesicular stores at lower concentrations via reversal of the dopamine transporter (Fischer and Cho, 1979; Liang and Rutledge, 1982). At higher concentrations, amphetamine also depletes vesicular dopamine storage by destroying the proton gradient and thus releasing dopamine into the cytoplasm, whereby it can be released via the dopamine transporter (Sulzer and Raappaport, 1990; Cadoni et al., 1995). Unlike KCl-induced release, amphetamine-induced increases in extracellular dopamine are independent of Ca++ influx (Carboni et al., 1989; Westerink et al., 1989). The finding that no differences existed among groups at any of the doses of amphetamine tested suggests that the ability to release dopamine from the cytoplasmic pool is unaltered in daily cocaine-pretreated rats, compared with controls. Of significance is that KCl and amphetamine can release dopamine independent of cell firing (Kuczenski, 1983). Thus, tolerance of the dopamine response to acute cocaine treatment (present study) or footshock stress (Sorg and Kalivas, 1993) may be discernible only when dopamine release is primarily impulse-dependent.

To determine whether local infusion of cocaine as a challenge treatment would mimic the effects of a systemic cocaine challenge, various doses of cocaine were infused through the dialysis probe in the mPFC. In contrast to what was found after a systemic cocaine challenge, local cocaine infusion produced a trend in the opposite direction. Cocaine infusion at the lowest dose (1 μM) produced a significant increase in percentage of basal levels accumulated over the last 1-hr postinfusion period in daily cocaine- vs. saline-pretreated rats. No differences existed between the two groups after the higher two doses, although the middle dose (10 μM) also tended toward an increase in cocaine-pretreated animals.
The observations that local cocaine infusion at 1) a dose below that known to cause anesthetic effects (<10 μM) (Yasuda et al., 1984) and 2) at levels approximating brain cocaine levels after a 15 mg/kg injection (Nicolaysen et al., 1988) does not mimic the dopamine response after a systemic cocaine challenge suggests that afferent regulation of mesocortical dopamine neurons is altered. It is likely that the site of modification is afferent projections to dopamine neurons, because tolerance is observed only after challenge with stimuli that are primarily dependent on impulse flow (cocaine or stress) and not with amphetamine or local KCl infusion, whose effects on dopamine release are at least partially independent of impulses. Several neurotransmitters that regulate dopamine neurons in the VTA (Kalivas, 1993) may be involved.

Although daily saline injections were given to rats to control for the handling and injection procedures associated with cocaine injections, the response of mPFC dopamine levels in unhandled (naive) animals was also examined. Previously, naive animals demonstrated a dopamine response to acute footshock stress that was between that of saline- and cocaine-pretreated rats, with saline-pretreated animals showing the most robust increase in mPFC dopamine levels (Sorg and Kalivas, 1993). Also, in the converse experiment, a cocaine challenge elicited a similar increase in mPFC dopamine in both naive rats and rats given repeated daily footshock, whereas daily sham shock-pretreated animals demonstrated the most robust increase. Previous work has demonstrated that handling of rats alters several responses related to the mesocorticlimbic dopamine system (Robinson et al., 1987; Peris et al., 1990; Meiergerd et al., 1996). A possible explanation for enhanced responsiveness of the mesocortical dopamine system in daily saline-pretreated animals is that this manipulation may produce a sensitization of mPFC dopamine to subsequent cocaine. Evidence points to a role for mPFC dopamine in the acquisition of a coping response (D'Angio et al., 1988; Deutch and Young, 1995). Therefore, rats given repeated daily handling and injections of saline may represent fully adapted animals that exhibit the greatest response to a subsequent novel stimulus such as cocaine or footshock. The lack of adaptation to the handling and injection procedures in naive rats or maladaptation in daily cocaine-pretreated rats may suppress this coping response. Although the mPFC dopamine responses to a cocaine challenge were similar in naive and daily cocaine-treated rats, this finding does not imply that naive and daily cocaine-treated animals are identical with regard to the mPFC. For example, recent in vitro data indicate that the rate of dopamine uptake in the mPFC is increased in daily cocaine-pretreated rats, compared with saline-pretreated or naive animals (Meiergerd et al., 1996).

Repeated cocaine treatment in rodents has served as an animal model for cocaine-induced psychosis and schizophrenia. The present data may have implications for the observed hypodopaminergic function in the prefrontal cortex of individuals presenting with negative symptoms of schizophrenia (Kahn and Davis, 1995). Another animal model of psychosis has been developed in which the ventral hippocampus is lesioned in rats (Lipska and Weinberger, 1993). One of the manifestations of such lesions is decreased mPFC dopamine turnover (Lipska et al., 1992). Thus, it has been posited that idiopathic and drug-induced psychoses alter the function of subcortical sites via altered cortical regulation. The site of initiation may be different with idiopathic psychosis occurring as a result of hippocampal damage, whereas cocaine- or stress-induced psychosis may be initiated via altered prefrontocortical function (P. W. Kalivas and B. A. Sorg, submitted).

Summary and conclusions. The results from the present study suggest that 1) mesoprefrontal dopamine neurons in cocaine-sensitized rats demonstrate tolerance to the effects of subsequent systemic cocaine, but not systemic amphetamine, compared with saline controls, 2) the tolerance is not due to decreased releasability of dopamine from mPFC terminals, as determined by local mPFC infusion of KCl or amphetamine through the dialysis probe, and 3) local infusion of cocaine through the dialysis probe into the mPFC does not mimic the effects of systemic cocaine but tends toward the opposite response. The present results, together with previous observations (Sorg and Kalivas, 1993), suggest that tolerance of mPFC dopamine is detected only when the expression depends primarily on impulse-mediated increases in extracellular dopamine concentrations. The inability to mimic systemic cocaine effects with local mPFC cocaine infusion further supports the idea that tolerance of mPFC dopamine response in systemic cocaine injection is mediated by afferents to mesocortical dopamine neurons. The suppression of the mPFC dopamine response in the present study us. the sensitization of this pathway previously reported in amphetamine-sensitized animals indicates that the mPFC dopamine response to subsequent stimuli may depend on the sensitizing stimulus. Differential responsiveness of mesocortical neurons to amphetamine and cocaine may lead to clues regarding mechanisms triggering the development of dopamine neuron sensitization.

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