Dopamine D1 Receptor Activation in the Medial Prefrontal Cortex Prevents the Expression of Cocaine Sensitization

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ABSTRACT

This study examined whether microinjection of the full D1 agonist, SKF 81297, or the D1 antagonist, SCH 23390, into the medial prefrontal cortex (mPFC) would alter the expression phase of cocaine sensitization. Male Sprague-Dawley rats were administered saline or cocaine (15 mg/kg, i.p.) once per day for seven consecutive days. After 8 to 17 days withdrawal, rats received a bilateral intra-mPFC microinjection of SKF 81297: either 0, 0.03, 0.1, or 0.3 μg/side; SCH 23390: either 0, 0.1, 0.3, or 1.0 μg/side; or a combination of 0.1 μg of SKF 81297 + 0.3 μg of SCH 23390, followed by an i.p. saline or cocaine (15 mg/kg, i.p.) injection. In naïve rats, vertical activity was elevated by the two lower doses of SKF 81297. A similar enhancement of cocaine-induced activity was observed in daily saline rats at the highest dose tested. In contrast, SKF 81297 suppressed the expression of sensitization to cocaine. This blockade of sensitization was prevented by coinfusion of SCH 23390. Infusion of SCH 23390 alone into the mPFC in daily saline and cocaine-pretreated rats demonstrated a suppression of cocaine-induced locomotion in daily saline-pretreated rats after the highest dose, but a slight augmentation of activity after the lowest dose in daily cocaine-pretreated rats. These results demonstrate a contribution by mPFC D1 receptors in the expression of cocaine sensitization and further suggest that the effects of D1 receptor activation in the mPFC occur in opposite directions in daily saline versus daily cocaine-pretreated rats.

Much evidence supports a role for the medial prefrontal cortex (mPFC) in drug abuse (Goeders and Smith, 1983; Isaac et al., 1989; McGregor and Roberts, 1995; Tzschentke and Schmidt, 1999). Studies in our laboratory (Sorg and Kalivas, 1993; Sorg et al., 1997; Prasad et al., 1999) and others (Wolf et al., 1995; Tzschentke and Schmidt, 1999, 2000; Beyer and Steketee, 2000) have focused on the role of the mPFC in the sensitization model of drug abuse. Sensitization is a well documented phenomenon in which repeated drugs of abuse, as well as other drugs or stress, produce amplified behavioral or neurochemical responses to later drug challenge (Antelman et al., 1986, 1992; Robinson and Becker, 1986; Kalivas and Stewart, 1991 for review).

The mPFC is involved in both the development and expression phases of sensitization to cocaine. Lesions of cell bodies in the mPFC prevent the development (Tzschentke and Schmidt, 1998, 1999, 2000; Li et al., 1999) and expression (Pierce et al., 1998) of cocaine sensitization. Also, lesions of dopamine terminals alone by 6-hydroxydopamine block the development of cocaine sensitization (Beyer and Steketee, 1999).

In the mPFC, behavioral sensitization is associated with a blunting of extracellular dopamine levels in response to further stimuli (cocaine or stress) (Sorg and Kalivas, 1993; Sorg et al., 1997; Chefer et al., 2000), and this diminished dopamine response is believed to contribute importantly to the expression of sensitization (Prasad et al., 1999). In our previous study, we determined that addition of local microinjection of d-amphetamine (AMPH) into the mPFC could block the expression of behavioral sensitization (Prasad et al., 1999). These findings suggested that dopamine and/or other monoamines are inhibitory on mPFC output neurons that regulate locomotor activity and that the blunted dopamine response to cocaine challenge observed in cocaine-sensitized rats may contribute to the expression of sensitized locomotor activity.

The relationship between mPFC dopamine and locomotion is believed to occur directly by dopamine's inhibitory action on excitatory amino acid (EAA) neurons in the mPFC and indirectly by dopamine-mediated increases in GABA 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 (Sesack et al., 1989). Direct EAA projections have been identified from the mPFC to the nucleus accum-
bens, as well as to dopamine and nondopaminergic neurons in the VTA, including GABAergic neurons projecting back to the mPFC (Carter, 1980; Sesack and Pickel, 1992; Carr et al., 1999; Carr and Sesack, 2000). Thus, dopamine and/or metabolite levels in the nucleus accumbens and striatum are regulated by mPFC EAA efferents (Taber et al., 1995; Doherty and Gratton, 1996; Karreman and Moghaddam, 1996). In addition, dopamine in the mPFC may control glutamate levels in these subcortical structures, and glutamate in the nucleus accumbens modulates locomotor output, contributing to cocaine-induced behavioral sensitization (Pierce et al., 1996; Reid and Berger, 1996; see also Wolf, 1998, for review).

Both D1 and D2 receptors in the mPFC have been shown to alter activity of mPFC neurons and behavioral output. The D2 receptor subtype alters electrical output of mPFC neurons (Sesack and Bunney, 1989; Parfitt et al., 1990; Gulledge and Jaffe, 1998), as well as cocaine-induced behavior (Beyer and Steketee, 2000). Several previous investigators reported that D1 receptors are important for altering behavioral output, including locomotor activity (Vezina et al., 1991), cocaine self-administration (McGregor and Roberts, 1995), and working memory function (Williams and Goldman-Rakic, 1995; Zahrt et al., 1997).

The goal of the present study was to directly activate or block D1 dopamine receptors in the mPFC to determine whether activation or inhibition of these receptors was sufficient to block or augment cocaine-induced locomotion, respectively, in daily cocaine-pretreated rats. Dorsal regions of the mPFC (dorsal anterior cingulate and prelimbic cortices) were targeted, because Pierce et al. (1998) previously demonstrated that ibotenic acid lesions of the dorsal, but not ventral, regions of the mPFC prevented the expression of cocaine sensitization. The full D1 agonist, SKF 81297, was microinjected into the mPFC just before saline or cocaine challenge. The D1 antagonist, SCH 23390, was used alone or in combination with SKF 81297 to determine the specificity of SKF 81297 effects.

Materials and Methods

Drugs. Cocaine hydrochloride was a gift from the National Institute on Drug Abuse. The dose of cocaine is reported as concentration of the salt and was prepared by dissolving in physiological saline. SKF 81297 hydrobromide and SCH 23390 hydrochloride were purchased from Research Biochemicals Inc. (Natick, MA). SKF 81297 was dissolved in sterile water, and SCH 23390 was dissolved in sterile saline. For experiments in which both drugs were coadministered, sterile water was used as the vehicle to dissolve the drug mixture.

Animals and Surgery. Adult male Sprague-Dawley rats weighing 260 to 300 g were obtained from Simonsen Laboratories (Gilroy, CA). All studies were conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The studies were approved by the Washington State University Laboratory Animal Care and Use Committee, and all possible efforts to reduce discomfort to the animals were made. Rats were housed in pairs before surgery, and individually after surgery, with free access to food and water in a temperature- and humidity-controlled room. Animals were maintained on a 12-h light/dark cycle, with lights on at 7:00 AM. Rats were anesthetized with an i.p. injection of Equithesin and placed in a stereotaxic apparatus. Stainless steel screws were inserted into the skull, and cannulae were affixed with dental acrylic cement. For intra-mPFC microinjections, 26-gauge bilateral cannulae were placed 3.2 mm anterior to bregma, 0.7 mm lateral to the midline and 2.5 mm below the skull. Obturators matching the length of guide cannulae were inserted into the cannulae. At least a 5-day postsurgery recovery was allowed before the beginning of experimentation.

Microinjection and Preparation of Drugs. SKF 81297 or SCH 23390 was dissolved in vehicle (see above) and microinjected into the mPFC. All microinjections were done by using a 33-gauge stainless steel needle connected to PE-20 tubing leading to a 1.0-μl Hamilton syringe. The 33-gauge needles were lowered 1 mm below the guide cannulae bilaterally, and a volume of 0.5 μl/side was delivered over a period of 90 s using an infusion pump. The needles were allowed to remain in place for 30 s following the injection. A microinjection of the vehicle (0.5 μl/side) was always given before the 1st day of testing the effect of drugs, and rats were adapted to the behavioral apparatus for 1 h before and 1 h after the microinjection procedure on this day. On the day of the experiment, animals were administered a microinjection and given an i.p. injection 5 min later.

Behavioral Measures. Locomotor activity was monitored by a photocell chamber (Omnitech Electronics) located in individual boxes with a light source (15 W bulb) and a fan. Horizontal activity was measured by interruption of eight photocells in each direction located 2 cm from the bottom of the cage. Vertical activity was measured by eight photocells in one direction located 18 cm from the bottom of the cage. Behavioral activity was collected in samples of 15 min for 1 h before and 2 h after saline/dopamine treatment.

Experimental Procedures. After 1 week of recovery from stereotaxic surgery, rats were treated with either saline (1 ml/kg, i.p.) or cocaine (15 mg/kg, i.p.) for 7 consecutive days. In addition, a third group of rats was left unhandled (=naive). Naive rats were given surgery and then left alone in their home cages for the same period of time as were the daily saline or cocaine-pretreated rats. Seven days following the last systemic injection, rats were adapted to behavioral boxes for 1 h and were given vehicle microinjection into the mPFC. Beginning the next day, and at intervals of at least 72 h, rats received a microinjection of one of the following doses of SKF 81297 (0, 0.03, 0.10, or 0.30 μg/side) or SCH 23390 (0, 0.10, 0.30, or 1.0 μg/side), followed by an i.p. saline (1 ml/kg, i.p.) or cocaine (15 mg/kg, i.p.) injection 5 min later. The doses of SKF 81297 were based on studies in which this drug was infused into the mPFC to examine working memory function in rats, spanning the dose range at which no effects or maximum effects were observed for the disruption of working memory (Zahrt et al., 1997). Doses of SCH 23390 were based on previous studies that examined behavioral output dependent on mPFC functioning (Vezina et al., 1991; Zahrt et al., 1997). Rats received a maximum of four microinjections, along with two saline and two cocaine injections given systemically, with saline or cocaine given on alternating test days. Only one dose of the drug was tested per rat. Rats were randomly assigned to one of four different treatment combinations. Most, but not all, rats received an i.p. saline injection with vehicle or drug, and an i.p. cocaine injection with vehicle or drug on four different test days.

Histology. At the completion of experiments, animals were anesthetized with sodium pentobarbital and perfused by intracardiac injection of phosphate-buffered saline, followed by 10% formalin in saline. Perfused brains were stored in 10% formalin until sectioned. Coronal sections (100 μm) were stained with neutral red, and placement of microinjection cannulae was determined by light microscopy.

Statistical Analysis of Data. Data were analyzed using a two-way ANOVA, with repeated measures over time in the case of time course data. For time courses, all preinjection data were analyzed separately from postinjection data. Because not all animals received all four injections due to cannulae blockade between microinjection days, a repeated-measures ANOVA was not conducted. Two-way ANOVA tests were followed by a Fischer’s least significant difference analysis in the case of a significant interaction (p < 0.05).
Results

Figure 1 shows all microinjection cannulae placements in the mPFC from the experiments reported herein. Cannulae in these studies were restricted to the prelimbic and dorsal anterior cingulate cortices. Animals whose placements were outside of these two brain regions were not included in the study.

Horizontal and vertical activities in response to acute systemic saline or cocaine injections in naïve rats are shown in Fig. 2A (total photocell counts over the 2-h postinjection period) and Fig. 2B (time course data) after various doses of SKF 81297. The results showed no effect of SKF 81297 infusion on horizontal or vertical activities after systemic saline injection (Fig. 2A, top panels). Acute cocaine-induced horizontal activity was not altered by any dose of SKF 81297. In contrast, a dose-dependent increase in vertical activity was found in these animals after the 0.03 μg (Fig. 2B) and the 0.1 μg/side dose (Fig. 2, A and B). However, the higher dose of 0.3 μg/side produced vertical activity levels similar to those found in vehicle controls.

Figure 3, A to C, shows horizontal and vertical activities in response to a systemic saline or cocaine challenge in rats pretreated with daily saline or cocaine. For horizontal activity, saline challenge revealed slightly reduced activity in cocaine-pretreated rats, compared with saline controls (Fig. 3A, top left panel). The behavioral sensitization observed in rats given vehicle into the mPFC was significantly suppressed by SKF 81297. Although there was a trend toward a decrease at the lowest dose, there was a significant blockade of sensitization in animals given the middle dose of SKF 81297 (0.1 μg/side). This decrease in cocaine-induced activity after 0.1 μg of SKF 81297 disappeared at the highest dose tested: 0.3 μg/side.

The time course data indicated no apparent blockade during the first 15-min time bin after cocaine challenge (Fig. 3C), although this effect was not observed in a later study (see Fig. 5B). Vertical activity in these animals showed similar trends as their horizontal activity, but the changes did not reach statistical significance (Fig. 3, A and C).

In contrast to the decrease in locomotor sensitization produced by SKF 81297 in daily cocaine-pretreated rats, animals given daily saline demonstrated a significant increase in horizontal activity after the highest dose of SKF 81297 and a cocaine challenge (Fig. 3, A and B). Rats also demonstrated the same trend when examining the time course of vertical activity, but the increase did not reach statistical significance (p = 0.08).

Shown in Fig. 4, A to C, are the responses to saline and cocaine challenge after microinjection of SCH 23390 into the mPFC. No significant differences were found after any dose of SCH 23390 when followed by a systemic saline challenge (Fig. 4A, top panels). After systemic cocaine challenge, SCH 23390 infusion into the mPFC produced a significant decrease in the time course for horizontal activity in daily saline-pretreated rats when the highest dose (1.0 μg) was given (Fig. 4B). In daily cocaine-pretreated rats, SCH 23390 produced a slight, but a significant, cocaine-induced increase in the time course for vertical activity at the 0.1 μg dose of SCH 23390 (Fig. 4C).

Figure 5, A and B, demonstrates the response to coadministration of SKF 81297 and SCH 23390. A 0.1 μg dose of SKF 81297 was chosen for this experiment because it was shown to significantly block expression of cocaine-induced sensitization (Fig. 3, A and C). The dose of 0.3 μg of SCH 23390, which had no effects on behavior when given alone (Fig. 4A), was chosen to antagonize the effects of SKF 81297. Figure 5A shows that there were no significant effects of SKF 81297 or coadministration with SCH 23390 after saline challenge (top panels). The suppression of cocaine sensitization by 0.1 μg of SKF 81297 was significantly blocked by coadministration of SCH 23390 (Fig. 5, A and B).

It should be noted that withdrawal times spanned from 8 to 17 days, and although there were no significant effects of day in vehicle-treated rats (not shown), there is some possibility that the effects of SKF 81297 or SCH 23390 may be different at 8 days, compared with 17 days withdrawal.

One additional finding was that naïve animals demonstrated a greater increase in cocaine-induced horizontal activity, compared with rats pretreated with daily saline. When all daily saline-pretreated groups from this study were considered together and compared with naïve animals (all receiving vehicle only), there was a significant increase in naïve rats versus daily saline-pretreated rats (p = 0.046). This result is in line with our previous findings, which found nonsignificant differences using smaller group sizes (Sorg et al., 1997; Prasad et al., 1999).

Discussion

The main findings from this study are: 1) D1 receptor activation by SKF 81297 in the mPFC suppressed the expres-
sion of behavioral sensitization to repeated cocaine; 2) this suppression was blocked by D1 receptor antagonist coinfusion into the mPFC; and 3) opposite responses to intra-mPFC infusion of SKF 81297 were found in naïve and daily saline-pretreated rats when compared with animals administered daily cocaine injections.

**mPFC Dopamine and Modulation of Locomotor Activity.** Studies examining the effects of acute, local microinjection of reversible drugs into the mPFC have supported an inhibitory effect of dopamine on stimulated locomotion by D1 (Vezina et al., 1991), D2 (Beyer and Steketee, 2000), or both D1 and D2 receptors (Duvauchelle et al., 1992; Broersen et al., 1999). In addition, inhibitory effects on novelty-induced locomotion by intra-mPFC application of the dopamine up-take inhibitor, GBR 12909, have been reported (Radcliffe and Erwin, 1996). In a previous study (Beyer and Steketee, 2000), intra-mPFC infusion of SKF 38393 did not produce any effect on cocaine-induced locomotion in naïve animals. The differences may be due to the doses used, the partial agonist effect of SKF 38393 versus the full agonist effect of SKF 81297, or the more dorsal regions of the mPFC targeted in our experiments.

We also did not observe the increase in stimulated locomotor activity after SCH 23390 microinjection as reported by Vezina et al. (1991). The discrepancy between our results and those of Vezina et al. (1991) may be explained by the difference in rats (daily saline-pretreated in our study versus naïve in the Vezina et al. study) and the differences in the mPFC subarea targeted for drug microinjection (prelimbic/infralimbic site by Vezina et al. versus the dorsal prelimbic/dorsal anterior cingulate regions in the present study). Also, Vezina et al. administered intra-nucleus accumbens AMPH, and behavioral activity driven by intra-nucleus accumbens AMPH may be regulated differently by cortical inputs, compared with systemic cocaine-induced activity.

In the present study, the effects of local SCH 23390 infusion into the mPFC were generally opposite to that of SKF 81297 infusion. In naïve and daily saline-pretreated rats, an augmentation in activity was observed after SKF 81297 infusion, whereas suppression of the locomotor response to cocaine challenge was found after infusion of SCH 23390 in daily saline-pretreated rats (the effects of this latter drug were not tested in naïve animals). Two explanations for the effects of the suppression by SCH 23390 and augmentation by SKF 81297 in daily saline-pretreated rats are offered. First, the effects could be due to diffusion of these drugs into the nucleus accumbens, where an increase in activity after D1 receptor stimulation and a decrease by D1 antagonism would be expected. However, no effects of these drugs were observed in animals given systemic saline challenge. In addition, opposite effects were found in daily cocaine-pretreated rats, making diffusion of these drugs into the nucleus accumbens an untenable explanation for the findings. Alternatively, the response to systemic cocaine after infusion of SKF 81297 in naïve and daily saline-pretreated rats may be due to activation rather than inhibition of excitatory projection neurons by mPFC dopamine. In this case, stimulation of D1 receptors with SKF 81297 would be expected to increase activity whereas SCH 23390 would suppress cocaine-induced activation. Yang and Seamans (1996) have reported that D1 receptor stimulation activates mPFC output neurons in naïve rats (see below).

**Fig. 2.** Effect of SKF 81297 on systemic saline- and cocaine-induced horizontal and vertical activities in naïve rats. A, mean ± S.E.M. of photocell counts for horizontal and vertical activities over a 2-h period after i.p. saline (top two panels) or i.p. cocaine (bottom two panels) administered 5 min after intra-mPFC microinjection of SKF 81297. B, time course showing mean ± S.E.M. of photocell counts for horizontal and vertical activities from animals given i.p. cocaine shown in panel A. N = 8 to 9/group for SKF 81297 doses; N = 24 for ”0” (vehicle) dose. Significant differences are as follows. For A: significant mPFC treatment effect for all doses, F(3,46) = 3.70; p = 0.018; for B: significant mPFC treatment × time interaction for vertical activity at the 0.03 µg dose, F(7,210) = 2.11; p = 0.043. There was also a near significant mPFC treatment effect for this dose (p = 0.054). At the 0.1 µg dose, there was a significant mPFC treatment effect (F(1,31) = 8.61; p = 0.006); there was also a significant mPFC treatment × time interaction (F(7,217) = 4.14; p = 0.0003). There was a significant time effect for all groups before and after systemic saline or cocaine injection. *p < 0.05, compared with a ”0” (vehicle) dose of SKF 81297.
The effects of SKF 81297 and SCH 23390 described above for daily saline-pretreated rats were not found in daily cocaine-pretreated rats. In fact, the opposite response to D1 receptor activation occurred in cocaine-sensitized animals. Dopamine may therefore be inhibitory on mPFC projection neurons in daily cocaine-pretreated rats because SKF 81297 suppressed the locomotor response to later cocaine challenge, whereas SCH 23390 slightly augmented this response, albeit only for vertical activity at the lowest dose tested. Interestingly, a recent report has described bidirectional effects of mPFC ibotinic acid lesions on systemic AMPH-induced locomotion, depending on whether open field testing occurred under conditions of high or low illumination (Lacroix et al., 2000). Under bright illumination, mPFC lesions attenuated the locomotor effect of systemic AMPH; but, under dim light, the response was potentiated in mPFC lesioned rats. These results suggest a state dependence of mPFC dopamine effects on locomotor output and may be related to a gating role for dopamine (see below).

Dose-Response Relationship. The observations that, in some cases, the lowest or middle dose of agonist/antagonist in the mPFC augmented or inhibited the locomotor response to cocaine but higher doses did not is intriguing. These results suggest that there may be opposing effects of these drugs in the integration of signals producing behavioral output, and therefore this brain region may be sensitive to optimal dopamine concentrations. Our previous study examining the effects of intra-mPFC AMPH infusion also demonstrated a U-shaped curve, similar to what was observed in the present study for SKF 81297 in cocaine-sensitized rats (Fig. 3A). In addition, Radcliffe and Erwin (1996) showed a clear U-shaped dose-response curve for novelty-induced locomotion after mPFC administration of the dopamine uptake inhibitor, GBR 12909.

Several studies in recent years examining the electrophysiological effects of dopamine on mPFC output neurons indicate that there is no simple relationship between mPFC dopamine concentration and activity of pyramidal neurons. In vitro studies have demonstrated a depolarizing or hyperpolarizing effect of dopamine, with both inhibition of spontaneous or stimulated firing, as well as reports of increased or unchanged firing (Penit-Soria et al., 1987; Yang and Seamas, 1996; see Gulledge and Jaffe, 1998, and references therein for further discussion of this issue). Gulledge and

**Fig. 3.** Effect of SKF 81297 on systemic saline- and cocaine-induced horizontal and vertical activities in daily saline and daily cocaine-pretreated rats. A, mean ± S.E.M. of photocell counts for horizontal and vertical activities over a 2-h period after i.p. saline (top two panels) or i.p. cocaine (bottom two panels) administered 5 min after intra-mPFC microinjection of SKF 81297. B, time course showing mean ± S.E.M. of photocell counts for horizontal and vertical activities from daily saline-pretreated animals given i.p. cocaine shown in panel A. C, time course showing mean ± S.E.M. of photocell counts for horizontal and vertical activities from daily cocaine-pretreated animals given i.p. cocaine shown in panel A. N = 7 to 11/group, with exception of the 0.03 μg dose in daily saline-pretreated rats, where N = 6. Significant differences are as follows. For A: significant daily treatment effect for horizontal activity in rats administered i.p. saline (F1,66 = 5.01, p = 0.028). Significant daily treatment × mPFC dose interaction for horizontal activity in rats administered i.p. cocaine (F3,63 = 4.24, p = 0.0086). For B: significant mPFC treatment effect for horizontal activity after 0.3 μg dose (F1,18 = 8.25, p = 0.010); significant mPFC treatment × time interaction (F3,126 = 5.80, p < 0.001). For vertical activity, there was a strong trend toward an mPFC treatment effect after the 0.3 μg dose (p = 0.080). For C: significant mPFC treatment effect for horizontal activity after the 0.1 μg dose (F1,15 = 5.75, p = 0.030). There was a significant time effect for all groups before and after systemic cocaine injection, with exception of daily saline rats given the 0.03 μg dose. A, *p < 0.05, comparing daily cocaine to daily saline-pretreated controls; †p < 0.05, compared with the “0” (vehicle) dose within the same daily pretreatment group. B, p < 0.05, compared with the vehicle.
Jaffe (1998) have reviewed the similarities and differences among these studies, and have concluded that perhaps there are complex time-dependent effects of dopamine related to tonic versus phasic activation of dopamine on mPFC pyramidal neurons.

Yang and Seamans (1996) described a modulatory role rather than an exclusively inhibitory or excitatory role for dopamine effects via D1 receptor activation. The mechanisms for D1 receptor effects occur through actions on opposing processes in pyramidal cells, including an increase in Na$^{+}$ conductance, inhibition of a K$^{+}$ conductance, and an opposing effect, attenuation of high-threshold Ca$^{2+}$ spikes. These investigators hypothesized that dopamine has an optimal range of concentrations required to facilitate activation of output neurons to subcortical structures by D1 receptor activation via influence on apical and basal dendrites. Their results support several studies in which optimal dopamine concentrations are required for maximal functioning of working memory in nonhuman primates and rodents (Williams and Goldman-Rakic, 1995; Cai and Arnsten, 1997; Zahrt et al., 1997). Working memory studies have demonstrated an inverted U-shaped curve after stimulation with dopamine agonists/antagonists, suggesting that there is a relatively narrow range of dopamine concentrations at which optimal working memory function occurs. Similarly, previous work (Radcliffe and Erwin, 1996) and the present study show a U-shaped curve for locomotor activity related to mPFC dopamine.

The modulatory effects of mPFC dopamine may be similar to those described in medium spiny neurons in the striatum. These neurons are present in bistable states: the “up” state (depolarized) or “down” state (hyperpolarized), in which D1 receptor activation reduces the response to stimulation when in the “down” state, but augments the response when in the “up” state, indicating a gating role for dopamine (Hernández-López et al., 1997).

Thus, when interpreting our results of dopamine D1 receptor agonist/antagonist infusion into the mPFC, several variables must be considered, including: direct and indirect effects of dopamine on pyramidal cell firing, the classification of pyramidal cell type influenced, the potentially new state of neurons after repeated psychostimulant exposure and withdrawal, such as the increase in neurons showing a bistable state within the mPFC (as well as within the nucleus accumbens) (Onn and Grace, 2000), and alterations in receptor number and/or efficacy—all of which could alter the respon-

Fig. 4. Effect of SCH 23390 on systemic saline- and cocaine-induced horizontal and vertical activities in daily saline and daily cocaine-pretreated rats. A, mean ± S.E.M. of photocell counts for horizontal and vertical activities over a 2-h period after i.p. saline (top two panels) or i.p. cocaine (bottom two panels) administered 5 min after intra-mPFC microinjection of SCH 23390. B, time course showing mean ± S.E.M. of photocell counts for horizontal and vertical activities from daily saline-pretreated animals given i.p. cocaine shown in panel A. C, time course showing mean ± S.E.M. of photocell counts for horizontal and vertical activities from daily cocaine-pretreated animals given i.p. cocaine shown in panel A. N = 7/group, with the exception of the 0.1 μg dose in daily cocaine-pretreated rats, where N = 6, and the “0” (vehicle) dose, where N = 19 to 21. Significant differences are as follows. For A: significant effect of daily pretreatment for horizontal activity in rats given i.p. cocaine ($F_{1,73} = 11.13, p = 0.0013$); and a significant effect of daily pretreatment for vertical activity in rats given i.p. cocaine ($F_{1,73} = 8.19, p = 0.0055$). For B: significant mPFC treatment × time interaction for horizontal activity during preinjection period after the 0.1 μg dose ($F_{3,75} = 3.17, p = 0.029$). Significant mPFC treatment effect for horizontal activity after the 1.0 μg dose ($F_{1,25} = 5.16, p = 0.032$); significant mPFC treatment × time interaction for vertical activity after the 0.1 μg dose ($F_{7,175} = 2.24, p = 0.033$). There was a significant time effect for all groups before and after systemic cocaine injection. *p < 0.05, compared with the vehicle.
siveness of mPFC neurons after repeated psychostimulant exposure.

In addition to the above considerations, there is discordance regarding which receptor subtype (D1 or D2) mediates dopamine-induced responses within the mPFC. It is conceivable that the diverse findings for dopamine effects on mPFC output neurons and behavior mediated by D1 (Vezena et al., 1991; Yang and Seamans, 1996; Zahrt et al., 1997; present study) versus the D2 receptor subtype (Sesack and Bunney, 1989; Parfitt et al., 1990; Gulledge and Jaffe, 1998; Beyer and Steketee, 2000) are at least partially due to state-dependent effects. In addition, the population(s) of neurons that are altered (e.g., D1 versus D2-containing, or neurons possessing both D1 and D2 receptors) after repeated drugs of abuse may shift the relative contribution of these receptor subtypes to the measured behavioral output.

Several possible explanations may be envisioned for how daily cocaine pretreatment could alter the response of mPFC neurons to dopamine. One possibility is that events downstream to D1 receptor activation alter the firing of mPFC output neurons. Bonci and Williams (1996) reported opposite effects of D1 receptor stimulation in dopamine cells in the VTA after repeated cocaine. In their studies, D1 receptor activation increased GABA<sub>\beta</sub>-mediated inhibitory postsynaptic potentials in dopamine neurons, but after repeated cocaine and morphine treatment, D1 receptor activation decreased the GABA<sub>\beta</sub>-mediated inhibitory postsynaptic potentials. This altered response was attributed to an increase in cAMP, which was transported and metabolized to extracellular adenosine and in turn inhibited GABA release via the adenosine receptor. Another possibility for the opposite effects of D1 stimulation in control and cocaine-pretreated rats is that repeated cocaine differentially alters discrete brain regions that send incoming signals to different sites on pyramidal cell bodies and dendrites. Such local influences may determine how D1 receptor activation influences input/output characteristics of mPFC neurons (Yang and Seamans, 1996). Finally, the tolerance of mPFC dopamine levels observed after daily cocaine or stress pretreatment (Sorg and Kalivas, 1993; Sorg et al., 1997; Chefer et al., 2000) may contribute to sensitization by providing decreased inhibitory signals to cortico-VTA and/or cortico-accumbens neurons, thus producing enhanced glutamate and/or dopamine levels in the nucleus accumbens.

Conclusions. In summary, the present studies found that D1 receptor activation within the mPFC by SKF 81297 was sufficient to block the expression phase of cocaine sensitization, and that this effect was prevented by coinfusion of the D1 antagonist, SCH 23390. Furthermore, the results indicate that the direction of the behavioral response to cocaine was state-dependent: D1 receptor stimulation produced an increase in cocaine-induced activity in naïve and daily saline-pretreated rats while it produced a decrease of cocaine-induced activity in daily cocaine-pretreated rats. The behavioral responses were dose-dependent such that there appeared to be a threshold effect, and the findings suggest that D1 receptor activation may affect opposing processes. More recent electrophysiological experiments determining mechanisms for dopamine effects on mPFC pyramidal neurons render interpretation of our findings more complex, and a simple description of increased or decreased dopamine receptor sensitivity/efficacy may not be adequate to explain the results. The cocaine-sensitized rat is expected to provide an important animal model for examining mechanisms by which to explore cortical control of behavioral responding to environmental stimuli, such as drugs of abuse and stress. Furthermore, the sensitization model may help to interpret the
implications of altered mPFC dopamine functioning in behaviors such as schizophrenia (Weinberger, 1995) and normal cognitive processes involved in working memory.

References


