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ORIGINAL INVESTIGATION

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# Intra-medial prefrontal cortex injection of quinpirole, but not SKF 38393, blocks the acute motor-stimulant response to cocaine in the rat

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**Abstract** *Rationale:* Considerable evidence suggests that the medial prefrontal cortex (mPFC) is an important region in mediating certain behavioral and neurochemical responses to cocaine. However, a role for cortical dopamine (DA) receptor subtypes in modulating these responses has yet to be elucidated. *Objectives:* This study investigated the effects of intra-mPFC administration of DA agonists on the acute motor-stimulant response to cocaine. In addition, in vivo microdialysis techniques were employed to determine the effects of intracortical injection on cocaine-induced extracellular DA concentrations in the nucleus accumbens (NAC). *Methods:* One week following bilateral cannulae implantation over the mPFC and the NAC (for dialysis experiments), male Sprague-Dawley rats received an intra-mPFC injection of saline, the DA D2-like agonist quinpirole (0.015, 0.05, 0.15, 0.5, 1.5, or 5.0 nmol per side) or the partial DA D1-like agonist SKF 38393 (0.5, 1.5, or 5.0 nmol per side) approximately 5 min before peripheral administration of saline or cocaine (15 mg/kg, i.p.). For dialysis experiments, only the highest dose of quinpirole was examined. *Results:* Pretreatment with quinpirole produced a dose-dependent decrease in cocaine-induced motor activity, with the highest doses resulting in a complete abolition of the acute motor-stimulant response to cocaine. In contrast, intra-mPFC administration of SKF 38393 was not shown, at the doses tested, to alter cocaine-induced motor activity. In agreement with the behavioral effects, intra-mPFC quinpirole injection (5 nmol per side) significantly blocked cocaine-induced DA overflow in the NAC. *Conclusions:* The results of the present study provide additional support that the mPFC is a neural substrate through which cocaine, in part, produces its motor-stimulant effects. In addition, these data suggest that modulation of cortical DA D2 receptors can block acute cocaine-induced behavioral (locomotor activity) and neurochemical (DA concentrations in the NAC) responses in the rat.

**Keywords** Medial prefrontal cortex · Quinpirole · SKF 38393 · In vivo microdialysis · Cocaine · Locomotor activity

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## Introduction

It has been postulated that the motor-stimulant response to cocaine underlies various components of drug-seeking and drug-taking behaviors that, in humans, often culminate in drug addiction (Wise and Bozarth 1987; Robinson and Berridge 1993). Moreover, the motor-stimulant response to cocaine is reported to result, in part, from drug-induced elevations in extracellular dopamine (DA) concentrations in the mesolimbic DA system (Kalivas and Stewart 1991; Kalivas et al. 1993; Robinson and Berridge 1993). Similarly, this system, which originates with DA cell bodies in the ventral tegmental area (VTA) and projects to various limbic regions, including the nucleus accumbens (NAC) (Oades and Halliday 1987), potently mediates the euphorigenic effects of cocaine (for review, see Koob and Bloom 1988). It is, however, becoming increasingly apparent that other DAergic systems in the brain may contribute to the psychomotor-stimulant (and presumably addictive) properties of cocaine (Beyer and Steketee 1999; Prasad et al. 1999).

The medial prefrontal cortex (mPFC) is permissively involved in mediating the motor-activating effects of psychostimulants. This is evidenced by studies demonstrating that the enhanced locomotor response elicited by repeated exposure to cocaine, a process termed behavioral sensitization, is reported to be induced following repeated electrical stimulation (or kindling) of the mPFC (Schenk and Snow 1994) and to be disrupted following ibotenic and quinolinic acid lesions of excitatory amino acid (EAA) neurons in the mPFC (Pierce et al. 1998;

Tzschentke and Schmidt 1998). Similarly, ibotenic acid lesions of the mPFC prevent the development of amphetamine- and cocaine-induced behavioral sensitization, as well as the accompanying neuroadaptations associated with cocaine sensitization (Wolf et al. 1995; Li et al. 1999). In addition to these findings, cortical 6-hydroxydopamine lesions are reported to enhance the acute motor-stimulant response to cocaine (Beyer and Steketee 1999) and amphetamine (Carter and Pycock 1980), as well as the locomotor effects of repeated amphetamine exposure (Banks and Gratton 1995). To this end, considerable evidence suggests that the ability of the mPFC to modulate the motor response to psychostimulants is widely attributed to cortical control over subcortical function (Carter and Pycock 1980; Banks and Gratton 1995; Karreman and Moghaddam 1996; Karler et al. 1998; Beyer and Steketee 1999).

The mPFC receives DAergic input from the VTA, giving rise to the mesocortical DA system, which provides a significant modulatory input to this region (Beckstead 1979; Oades and Halliday 1987). Both in vitro and in vivo studies indicate that DA transmission in the mPFC predominately functions to inhibit neuronal activity in this region (Bunney and Aghajanian 1976; Carter and Pycock 1980; Beyer and Steketee 1999). In this light, neuroanatomical studies suggest that DA neurons, originating in the VTA, project to and terminate on EAA cell bodies in the mPFC and serve to directly attenuate output from this region (Sesack and Bunney 1989; Cowen et al. 1994; Law-Tho et al. 1994; Grobin and Deutch 1998). In addition, studies confirm the existence of γ-aminobutyric acid (GABA)ergic interneurons in the mPFC that interact with both DA projections from the VTA and EAA cell bodies in the mPFC (Sesack and Bunney 1989; Cowen et al. 1994; Law-Tho et al. 1994; Grobin and Deutch 1998). Therefore, utilization of this pathway would allow for an indirect regulation of cortical excitatory output to regions innervated by the mPFC. Since cortical glutamatergic projections innervate subcortical regions including the NAC and the VTA (Sesack and Pickel 1992), enhanced DA transmission in the mPFC may serve to directly and/or indirectly inhibit local glutamate release and subsequent excitation of mesolimbic DA neurons. Lesion studies support this conclusion because DA depletion in the mPFC, in particular the infralimbic and prelimbic cortices, has been demonstrated to enhance cocaine-induced DA concentrations in the NAC (Beyer and Steketee 1999).

Collectively, the aforementioned data describe a role for cortical DA in mediating aspects of locomotor behavior and subcortical function; however, the involvement of specific DA receptor subtypes in the mPFC in mediating these responses has not yet been elucidated. Several reports indicate the presence of both D1-like and D2-like DA receptor subtypes on pyramidal neurons in the mPFC (Vincent et al. 1995), and activation of these receptors has been shown to modulate the excitatory output from the mPFC (Vezina et al. 1994; Grobin and Deutch 1998). In the present study, therefore, we investigated the potential involvement of specific cortical DA receptors in mediating the acute motor-stimulant response to cocaine. In order to do this, the effects of intra-mPFC injection of DA D1- and D2-like receptor agonists, SKF 38393 and quinpirole, respectively, were determined on the acute behavioral response to cocaine. In addition, microdialysis techniques were employed to determine the effects of intracortical microinjection on interstitial DA concentrations in the NAC.

## Materials and methods

### Subjects

Animal experiments were previously approved by the Louisiana State University Medical Center Animal Resources Advisory Committee and were performed in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. Adult male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Ind.) weighing 250–300 g at the time of surgery were used. All animals were housed individually in a temperature- and humidity-controlled, American Association for Accreditation of Laboratory Animal Care (AAALAC) international-accredited facility and maintained on a 12-h/12-h light/dark cycle (with lights on at 0600 hours). Food and water were provided ad libitum.

### Behavioral data collection

Locomotor activity was measured using a Macintosh classic-II computer interfaced with a Digiscan Micro-monitoring system (Omnitech Electronics, Columbus, Ohio.). This monitoring system was connected to each behavioral chamber (45×24×19 cm), which consisted of 16 evenly spaced light beams, located 4.5 cm above the bottom of the chamber. Each motor activity box was placed in a separate sound-attenuating chamber that included a 10-W light bulb and a fan to mask extraneous noise. Animals were placed in the experimental chambers 1 h prior to receiving injections, and motor activity was monitored during this time. Following injections, photocell counts were recorded for 2 h in 15-min time intervals.

### Intra-mPFC microinjections and acute cocaine

Rats were anesthetized with equithesin (3.3 ml/kg) and were placed in a David Kopf stereotaxic instrument (Tujunga, Calif.). All animals were bilaterally implanted with stainless-steel, 26-gauge cannulae (14 mm) that were directed 1 mm above the mPFC. The coordinates for these cannula tips were +3.2 mm anterior to bregma; ±0.6 mm from the midline; and –3.5 mm from the top of the skull, with the mandible bar set at 0.0 mm (Paxinos and Watson 1986). Cannulae were secured in position with dental acrylic and three stainless-steel screws mounted directly to the skull of the animal, and obturators (33 gauge, 14 mm) were inserted into the injection cannulae to maintain their patency. Following 1-week postoperative recovery, bilateral intra-mPFC microinjection of either saline (0.5 µl per side), the DA D2-like agonist quinpirole (0.015, 0.05, 0.15, 0.5, 1.5, and 5.0 nmol per side) or the DA D1-like agonist SKF 38393 (0.5, 1.5, and 5.0 nmol per side) were given 4–5 min before systemic administration of either saline (1.0 ml/kg, i.p.) or cocaine (15 mg/kg, i.p.). All intra-mPFC microinjections were administered via 33-gauge (15 mm) injectors attached to a Sage syringe pump (Orion Research Inc., Boston, Mass.) at a rate of 0.5 µl/min. A total volume of 0.5 µl per side was injected and both injectors remained in place for approximately 20 s following cessation of injection. Separate groups of animals were used for each dose of quinpirole or SKF 38393 tested, and all animals received each of the four treatment combinations (saline/saline, saline/cocaine, DA agonist/saline, DA agonist/cocaine) in a random order with a minimum of 3 days separating each drug exposure.

### In vivo microdialysis

For microdialysis studies, guide cannulae (20 gauge, 14 mm), in addition to intra-mPFC injectors (see above), were implanted 3 mm above the NAC and secured to the skull of the animal with dental acrylic. The coordinates for these cannulae were +1.4 mm anterior to bregma; ±1.4 mm from the midline; and –5.2 mm from the top of the skull, with the mandible bar set at 0.0 mm (Paxinos and Watson 1986). One week after surgery and approximately 16 h before the commencement of experiments, concentric-style dialysis probes, with a 2-mm active membrane, were inserted into the guide cannulae. The dialysis probes were attached to an infusion pump, and a liquid swivel attached to a counterbalance rod provided free mobility to all animals during the experiments. Following the adaption phase (overnight), microdialysis probes were perfused continuously at a rate of 2 µl/min with dialysis buffer [KCl 2.7; NaCl 140; $CaCl_2$ 1.2; $MgCl_2$ 1.2; phosphate-buffered saline (PBS) 0.2 (all in mM), pH 7.4] for at least 1 h before the start of dialysis experiments. Four, 20-min dialysis samples were collected before intra-mPFC injection of saline or quinpirole (5 nmol per side), which were administered 4–5 min prior to a systemic injection of saline or cocaine (15 mg/kg, i.p.). Dialysis samples were collected every 20 min following injections and were collected into 20 µl of mobile phase containing $1\times10^{-7}$ M internal standard dihydroxybenzylamine (DHBA). Next, samples were either stored at –80°C or immediately injected onto a high-performance liquid chromatography (HPLC) column. When possible, animals were used in two dialysis studies, with each NAC being dialyzed only once. Animals received different treatment combinations on each test day, which were separated by a minimum of 3 days.

### HPLC

Mobile phase [$NaH_2PO_4$ 75 mM, EDTA (disodium ethylenediamine tetraacetate) 0.01 mM, octanesulfonic acid 0.8 mM; and 11% acetonitrile v/v, pH 3.4 with $H_3PO_4$] was pumped, via a Rainin HP pump, through an octadecasilane reverse-phase column (Rainin) at a rate of 1.0 ml/min, as previously described (Steketee 1998). The electrochemical detection system consisted of three coulometric electrodes (preoxidation electrode –0.175 V, oxidation electrode 0.15 V, and preinjection port electrode 0.4 V). Dialysates, including the internal standard, were injected onto the column and compared with an external standard curve ranging from $10^{-14}$ mol to $10^{-11}$ mol. The minimum level of detection was 3 fmol/sample. These HPLC conditions allowed for determination of DA concentrations in the NAC.

### Histologies, drugs and statistics

All animals were euthanized via an overdose of sodium pentobarbital and were perfused by means of intracardiac infusion of PBS (0.2 mM) and 4% formaldehyde. Brains were rapidly removed and stored in 4% formaldehyde until time of sectioning on a vibratome (Technical Products International Inc., St. Louis, Mo.). Next, sections were mounted on gelatin-coated slides and stained with cresyl violet to allow visualization of cannulae placement under a light microscope. Animals with incorrect cannulae placement were excluded from the experiments.

Cocaine hydrochloride was purchased from Sigma Chemical Company (St. Louis, Mo.), and quinpirole hydrochloride (trans-(–)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g] quinoline hydrochloride) and SKF 38393 hydrochloride ((±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride) were purchased from Research Biochemicals Incorporated (Natick, Mass.). All drugs were diluted with isotonic saline.

Total motor activity is expressed as mean photocell counts per treatment session and was analyzed by a one-way repeated measures analysis of variance (ANOVA). Multiple comparisons were made by a Student-Newman-Keuls test. For microdialysis studies, DA data were converted to percentage of baseline to avoid interassay variability, and time courses of neurochemical and behavioral data were analyzed using a two-way ANOVA with one repeated measure (time).

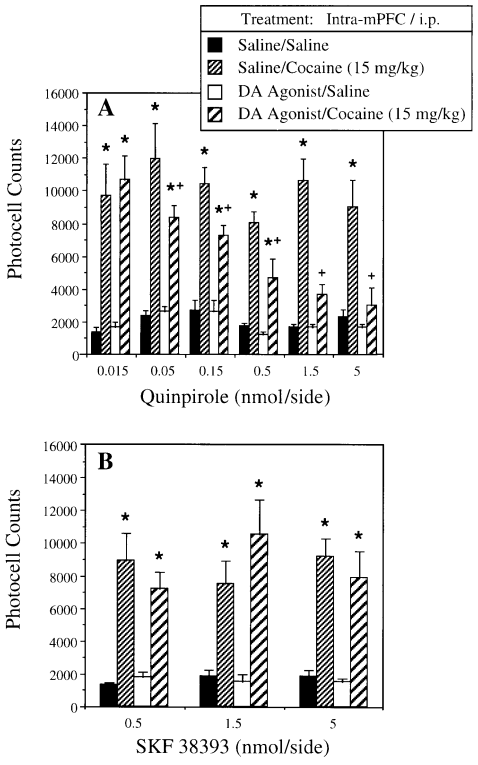



**Fig. 1A, B** Effects of intra-mPFC (medial prefrontal cortex) microinjection of (**A**) quinpirole and (**B**) SKF 38393 on the acute motor-stimulant response to cocaine (15 mg/kg, i.p.). Systemic cocaine produced a significant increase in motor activity which was suppressed following intracortical quinpirole injection. Data are represented as mean±SEM photocell counts per 2-h time interval (total locomotor activity); $n$=7 in all treatment groups except 0.15 nmol per side quinpirole ($n$=8), 0.05 nmol per side quinpirole ($n$=9), and 0.015 nmol/side quinpirole ($n$=9). Data were analyzed using a one-way repeated-measures analysis of variance and $F$ scores were as follows: **A** 0.015 nmol per side (between subjects $F_{8,35}$=0.615, $P$=0.758; within subjects $F_{3,35}$=20.115, $P$=0.0001), 0.05 nmol per side (between subjects $F_{8,35}$=0.551, $P$=0.808; within subjects $F_{3,35}$=17.104, $P$=0.0001), 0.15 nmol per side (between subjects $F_{7,24}$=0.252, $P$=0.967; within subjects $F_{3,31}$=21.582, $P$=0.001), 0.5 nmol per side (between subjects $F_{6,27}$=0.243, $P$=0.957; within subjects $F_{3,27}$=19.196, $P$=0.0001), 1.5 nmol per side (between subjects $F_{6,27}$=0.175, $P$=0.981; within subjects $F_{3,27}$=27.478, $P$=0.0001) and 5 nmol per side (between subjects $F_{6,27}$=0.497, $P$=0.803; within subjects $F_{3,27}$=12.150, $P$=0.0001). **B** 0.5 nmol per side (between subjects $F_{6,27}$=0.258, $P$=0.950; within subjects $F_{3,27}$=13.431, $P$=0.0001), 1.5 nmol per side (between subjects $F_{6,27}$=0.701, $P$=0.652; within subjects $F_{3,27}$=14.694, $P$=0.0001) and 5 nmol per side (between subjects $F_{6,27}$=0.428, $P$=0.852; within subjects $F_{3,27}$=17.209, $P$=0.0001). *$P$<0.05 compared with saline/ saline and +$P$<0.05 compared with saline/cocaine

Multiple comparisons were made using a modified least significant differences test (Milliken and Johnson 1984). In addition, significant differences of the microdialysis data, since normalized to percentage of baseline, were confirmed by conducting a Kruskal-Wallis test.

## Results

### Effects on behavior

The effects of intra-mPFC quinpirole (0.015, 0.05, 0.15, 0.5, 1.5, and 5.0 nmol per side) on the acute motor stim-

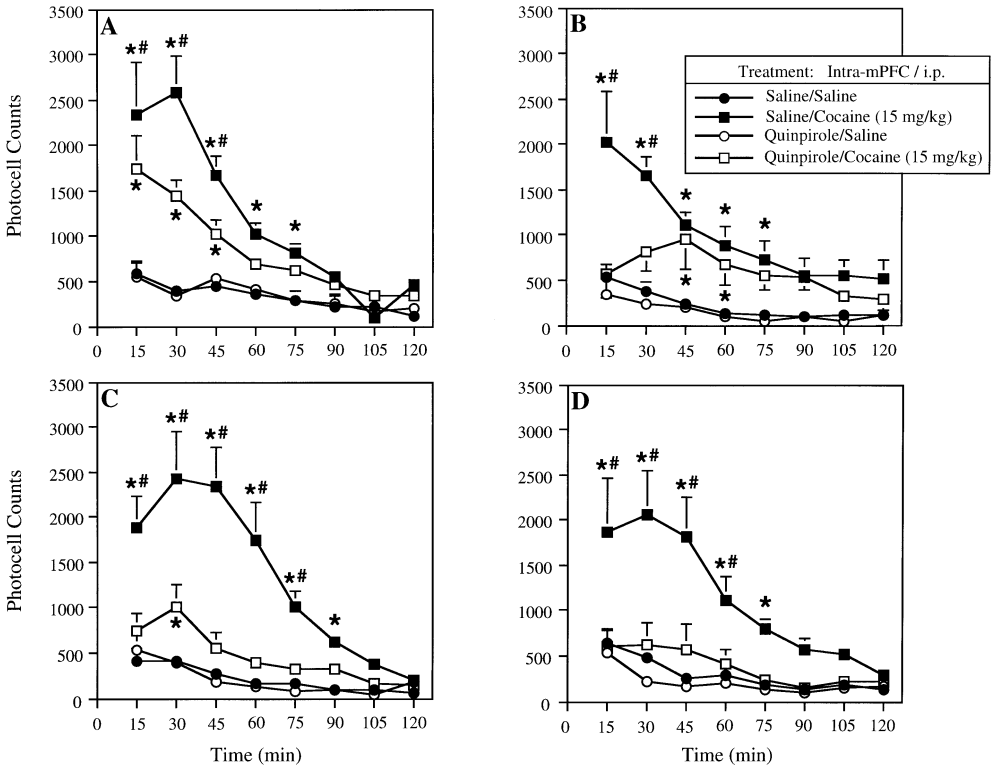



**Fig. 2A–D** A time course of the effects of intra-mPFC (medial prefrontal cortex) quinpirole injection on cocaine-induced horizontal motor activity. Quinpirole [0.15 (**A**), 0.5 (**B**), 1.5 (**C**), and 5.0 (D) nmol per side] pretreatment significantly blocked cocaine-induced motor activity during at least the first 30 min post-injection. Data illustrated correspond with that shown in Fig. 1, and all animals received each of the possible treatment combinations. Values represent mean±SEM photocell counts at each 15-min time interval. The *F* scores were: **A** 0.15 nmol per side (treatment $F_{3,28}$=14.093, *P*<0.0001; time $F_{11,308}$=25.931, *P*<0.0001; interaction $F_{33,308}$= 7.283, *P*<0.0001); **B** 0.5 nmol per side (treatment $F_{3,24}$=19.819, *P*<0.0001; time $F_{7,168}$=8.200, *P*<0.0001; interaction $F_{21,168}$=2.196, *P*=0.003). **C** 1.5 nmol per side (treatment $F_{3,24}$=28.644, *P*<0.0001; time $F_{7,168}$=17.116, *P*<0.0001; interaction $F_{21,168}$=4.895, *P*<0.0001). **D** 5 nmol per side (treatment $F_{3,24}$=11.330, *P*=0.0001; time $F_{7,168}$=12.595, *P*<0.0001; interaction $F_{21,168}$=3.195, *P*<0.0001). **P*<0.05 comparing all groups with saline/saline and #*P*<0.05 compared with quinpirole/cocaine using the methods of Milliken and Johnson (1984)

ulant response to cocaine is illustrated in Fig. 1A. Systemic cocaine (15 mg/kg, i.p.) produced a significant increase in motor activity that was completely abolished by high dose quinpirole (1.5 nmol and 5.0 nmol per side) pretreatment. Additionally, intermediate doses of quinpirole (0.05, 0.15, and 0.5 nmol/side) attenuated the motor-stimulant response to cocaine. It was also demonstrated that intra-mPFC quinpirole administration did not significantly alter, at any dose tested, basal motor activity levels, suggesting that the effects of quinpirole were not the result of a nonspecific suppression of motor activity.

The effects of intra-mPFC injection of SKF 38393 (0.5, 1.5, and 5.0 nmol per side) on the motor-stimulant response to cocaine is shown in Fig. 1B. Systemic cocaine (15 mg/kg, i.p.) resulted in an enhanced motor-stimulant response. However, unlike intra-mPFC quinpirole administration, intracortical pretreatment with SKF 38393 did not alter, at any dose tested, the acute motor-stimulant response to cocaine. Similar to quinpirole, SKF 38393 was not observed to significantly alter basal motor activity.

Examination of the time course of motor activity following systemic cocaine (Fig. 2) reveals that intra-mPFC quinpirole administration was effective in completely blocking horizontal activity during the first 75 min (quinpirole 1.5 nmol per side) and 60 min (quinpirole 5 nmol per side) post-injection. Additionally, motor activity induced by cocaine was attenuated during at least the first 30 min following administration of intermediate doses of quinpirole (Fig. 2A, B). Cocaine-induced locomotor activity was not inhibited, at any time point, by intracortical SKF 38393 (0.5, 1.5, and 5.0 nmol per side) injection (data not shown).

## In vivo microdialysis

Figure 3 shows the interstitial DA concentrations in the NAC, as estimated using in vivo microdialysis techniques, of animals receiving intra-mPFC quinpirole (5 nmol per side) prior to peripheral injection of cocaine (15 mg/kg, i.p.) or saline (1 ml/kg, i.p.). Systemic cocaine produced an increase in extracellular DA concentrations in the NAC, which was nearly completely blocked by cortical quinpirole pretreatment (20 min, H=16.342, *P*=0.001; 40 min, H=17.916, *P*<0.001; 60 min, H=13.858, *P*=0.003; 80 min, H=14.425, *P*=0.002; 100 min, H=8.366; *P*=0.039; 120 min, H=18.659, *P*=0.034). In these experiments, rats pretreated with intracortical

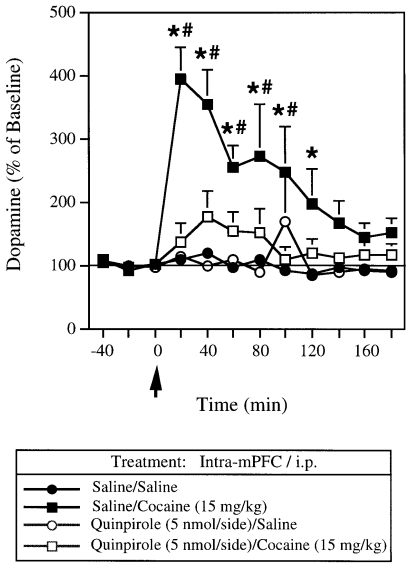


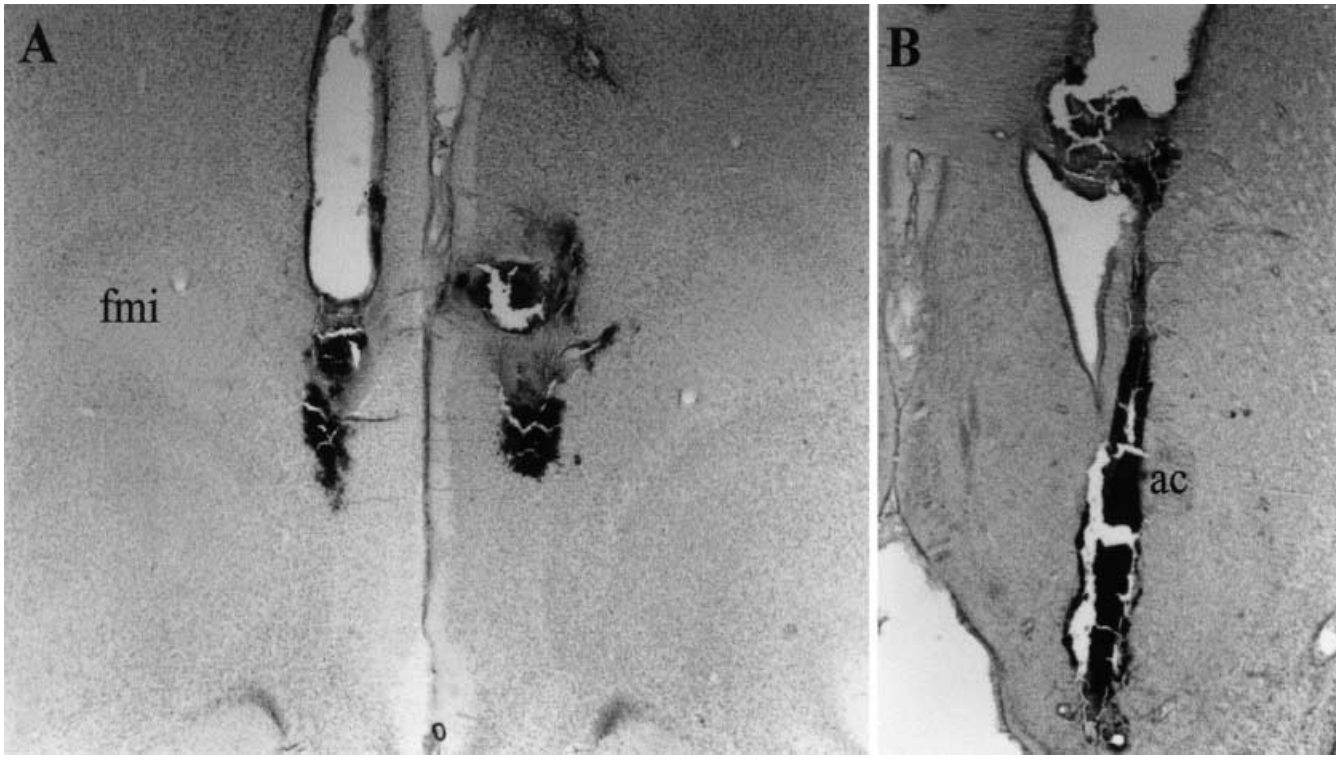

**Fig. 3** Effects of intracortical microinjection of quinpirole (5 nmol per side) on cocaine-induced (15 mg/kg, i.p.) dopamine (DA) transmission in the NAC. Intra-mPFC (medial prefrontal cortex) injection of quinpirole significantly blocked cocaine-induced DA transmission in the nucleus accumbens (NAC). The *arrow* indicates the time of intra-mPFC injection which was given 4–5 min prior to systemic injection. Neurochemical data are expressed as mean±SEM percentage of baseline. Raw basal DA concentrations were not statistically different (see results section for *F* score values) between treatment groups ($n$=8 in all groups except quinpirole/cocaine, $n$=9). The *F* scores were as follows: treatment $F_{3,29}$=13.591, $P$<0.0001; time $F_{11,319}$=6.277, $P$<0.0001; and interaction $F_{33,319}$=3.269, $P$<0.0001. *$P$<0.05 comparing all groups with saline/saline and #$P$<0.05 compared with quinpirole/cocaine. All multiple comparisons were performed according to the methods of Milliken and Johnson (1984)

quinpirole, prior to systemic cocaine administration, did not statistically differ from control (saline/saline) animals. Additionally, intra-mPFC quinpirole administration did not alter DA content in the NAC following peripheral saline injections, and baseline (i.e., pre-injection) DA concentrations in the NAC (saline/saline 15.6±2.9; saline/cocaine 27.2±3.5; quinpirole/saline 30.6±9.9; quinpirole/cocaine 21.3±6.2; all in fmol/20 min) were not significantly different between any of the treatment groups ($F_{3,29}$=1.086, $P$=0.370).

## Histology

In general, bilateral cannulae for intra-mPFC injections were found to be medial to the *forceps minor corpus collosum* (Fig. 4A), resulting in drug administration into the infralimbic and/or the prelimbic (or cingulate) cortices of the mPFC (Paxinos and Watson 1986). For microdialysis studies, the active membrane of the dialysis probe was located at or medial to the anterior commissure (Fig. 4B).

**Fig. 4 A** Representative photomicrograph showing placement of bilateral injector cannulae in the medial prefrontal cortex (mPFC). In general, cannulae implants were found medial to the *forceps minor corpus collosum* (*fmi*), resulting in drug administration in the infralimbic and/or the prelimbic (or cingulate) cortices of the mPFC (Paxinos and Watson 1986). Magnification ×20. **B** Representative micrograph of dialysis probe located in the nucleus accumbens (NAC). The active membrane of the dialysis probe was, in general, located at or medial to the anterior commissure (*ac*). In addition, greater than 50% of the active membrane was located in the boundaries of the NAC (including the core and the shell regions) as determined by (Paxinos and Watson 1986)



In most circumstances, greater than 50% of the active membrane was located in the boundaries of the NAC (including the core and the shell regions) as determined by Paxinos and Watson (1986). On occasion, a small portion of the dialysis probe was found to be dorsal or ventral to the NAC.

## Discussion

The present study provides evidence consistent with the hypothesis that cocaine-induced locomotor activity and DA transmission in the NAC is mediated, in part, by DAergic mechanisms in the mPFC. Specifically, the results demonstrate that intra-mPFC microinjection of the DA D2-like receptor agonist quinpirole blocked, in a dose-dependent manner, the acute motor-stimulant response to cocaine. Similar to the behavioral experiments, intra-mPFC quinpirole treatment resulted in a significant blockade of cocaine-induced DA transmission in the NAC. These latter findings are consistent with evidence demonstrating a role for the mPFC in regulating subcortical regions including the NAC (Carter and Pycock 1980; Beyer and Steketee 1999) and the striatum (Carter and Pycock 1980; Baca et al. 1998); areas confirmed to regulate certain facets of locomotor activity. Also, it appears that the reported behavioral effects are specific for cortical DA D2-like receptors, as intra-mPFC microinjection of SKF 38393, a DA D1-like receptor agonist, did not alter, at the doses tested, the acute locomotor effects of systemic cocaine administration. Although a direct correlation between cortical DA receptors and the motor-stimulant effects of cocaine in the rat, to our knowledge, has yet to be identified, the present results coincide with findings that cortical DA D2 receptors participate in various facets of cocaine reinforcement (Goeders et al. 1986).

The inhibitory behavioral effects of intracortical quinpirole reported in the present study are consistent with the local effects of DA agonists on psychostimulant-induced motor activity. Behavioral data have shown that intra-mPFC injections of the D2 agonist (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxytetraline (PPHT) (Karler et al. 1998) or amphetamine (Prasad et al. 1999), an indirect DA agonist, decrease amphetamine- and cocaine-induced stereotypy and motor activity in the mouse and the rat, respectively. Moreover, electrophysiological studies demonstrated that DA receptor activation by DA (Bunney and Aghajanian 1976) and DA D2 agonists (Sesack and Bunney 1989) suppresses activity of cortical neurons, suggesting that DAergic transmission in the mPFC has an inhibitory influence in this region. The ability of DA to inhibit cortical activity is presumed to occur via DAergic–GABAergic interactions in the mPFC (Linderfors et al. 1989). Indeed, neuroanatomical evidence suggests the existence of GABAergic axon terminals, dendrites, and perikarya in the mPFC (Sesack et al. 1995). Further, studies have demonstrated that D2 but not D1 agonists increase the spontaneous release of labeled GABA in cortical neuronal slices (Rétaux et al. 1991) and the concentrations of GABA in the mPFC as measured by in vivo microdialysis (Grobin and Deutch 1998). The mechanism by which D2 agonists increase cortical GABA levels is suggested not to be due to changes in intermediary metabolic pools of GABA (Grobin and Deutch 1998) or due to the reversal of the GABA transporter in this region (Grobin and Deutch 1998), but rather from DA agonist-induced depolarization of GABAergic interneurons (Yang et al. 1997; Zheng et al. 1997). In consideration of these findings, it is hypothesized that intracortical quinpirole administration produced a suppression of cocaine-induced behavioral and neurochemical responses via dampening the excitatory output from the mPFC, potentially an indirect result of GABAergic interneuron modulation of glutamatergic transmission in the mPFC (Penit-Soria et al. 1987).

Another equally important hypothesis to consider is that the inhibitory DAergic influence in the mPFC is mediated by a direct DA-glutamate interaction in this region. Thus, midbrain DA neurons, originating in the VTA, project to and synapse directly on cortical glutamatergic neurons (Seguela et al. 1988; Sesack et al. 1995), and have been reported to inhibit cortical EAA efferent projections (Cowen et al. 1994; Law-Tho et al. 1994; Grobin and Deutch 1998). Consequently, activation of cortical DA D2 receptors by quinpirole may directly inhibit glutamate cell bodies in the mPFC that would decrease neuronal activity in the mPFC and subsequent neuronal activity in subcortical regions; ultimately resulting in a decrease in cocaine-induced locomotor activity and NAC DA concentrations. Further studies exploring the potential relationship between cortical DA and GABA/glutamate are necessary to determine the importance of the interactions of transmitter systems in the mPFC during cocaine-mediated behaviors.

Another potential area of interest, although not investigated in the present study, would be to explore whether cortical modulation of the NAC is via a direct (cortico–accumben) or an indirect (cortico–VTA–accumben) interaction. The latter hypothesis is supported by a study from Taber and colleagues (1995), which demonstrated that electrical manipulation of the mPFC resulted in changes in DA transmission in the NAC that could be blocked by intra-VTA administration of glutamate receptor antagonists. Therefore, in that study, cortico–accumben interaction occurred specifically through midbrain DAergic projections from the VTA. This evidence is further supported by studies suggesting that EAA receptors located in the VTA, rather than those in the NAC, exhibit a tonic excitatory influence over DAergic overflow in the NAC (Karreman et al. 1996). In light of these findings, future studies need to be conducted to determine the putative involvement of the VTA in mediating the effects of intra-mPFC quinpirole administration on cocaine-induced DA transmission in the NAC.

In contrast to the effects of quinpirole, intra-mPFC injection of SKF 38393 did not alter, at any dose tested,

the acute motor stimulant response to cocaine. These findings compliment those of Karler and colleagues (1998) who reported that SKF 38393, unlike the D2 agonist PPHT, had no significant effect in blocking amphetamine-induced stereotypy in the mouse. However, the present data are dissimilar to those of Vezina et al. (1991), who demonstrated that injection of a D1 but not a D2 antagonist was successful in enhancing locomotor activity induced by intra-NAC administration of amphetamine. Furthermore, D1 receptor mechanisms in the mPFC have been implicated in mediating mesolimbic DA responses to stress (Doherty and Gratton 1996). The discrepancies between these studies and the present findings are not completely clear. It is conceivable that, in the present study, an effect of SKF 38393 on cocaine-induced motor activity was not observed due to the fact that SKF 38393 is only a partial agonist for DA D1 receptors (Setler et al. 1978). Therefore, we may have observed an effect on cocaine-induced motor activity following intra-mPFC injections of a full agonist for cortical DA D1 receptors. In addition, we investigated only three doses of SKF 38393 (5.0, 1.5, and 0.5 nmol per side). Perhaps, pretreatment with higher doses of SKF 38393 would have resulted in a significant effect on the behavioral responses to cocaine. Support for this hypothesis comes from electrophysiological data showing that doses of SKF 38393 much higher than DA D2 agonists were required to elicit a decrease in mPFC neuron firing (Parfitt et al. 1990), suggesting that cortical DA D1-like receptors may be less sensitive than other types of DA receptors in this region. We did, however, observe in a separate experiment a strong tendency for a decrease, although not significant, in basal motor activity evoked by SKF 38393 (5.0 nmol per side), potentially indicating that higher doses of SKF 38393 may have produced nonspecific effects on motor behavior (C.E. Beyer and J.D. Steketee, unpublished observation).

The dose-dependent decrease in cocaine-induced locomotor activity observed in the present study is likely the result of DA D2 receptor activation in the mPFC. However, Sesack and Bunney (1989) report that iontophoretic application of quinpirole only inhibited a small population of DA-sensitive neurons in the mPFC. Moreover, in their study, the inhibitory effects of quinpirole on cortical neurons was blocked by both stereoisomers of the D2 antagonist sulpiride (Sesack and Bunney 1989). It is suggested, therefore, that the pharmacological characteristics of quinpirole in the mPFC may be from effects on a receptor complex that is different from D2 receptors found in other regions of brain (Sesack and Bunney 1989). Along similar lines, it is noteworthy to mention that quinpirole is an agonist with much higher affinity for DA D3 and DA D4 receptors than the DA D2 receptor subtype (Tang et al. 1994). Although little evidence indicates the presence of DA D3 receptors in the mPFC, autoradiographic studies indicate the existence of cortical DA D4 receptors on GABAergic interneurons in the mPFC (Tarazi et al. 1997). Therefore, it is feasible to speculate that the results of the present study were due to the effects of quinpirole on DA D4 receptors in the mPFC. Or rather, the effects of quinpirole on decreasing the acute behavioral and neurochemical effects of cocaine may have resulted from the indistinguishable activation of both receptor subtypes. In order to test these hypotheses, we are conducting research in our laboratory to more accurately determine the contribution of cortical DA D2 and/or D4 receptors in modulating the motor-stimulant response to cocaine.

In conclusion, it was shown in this study that intra-mPFC pretreatment with the DA D2-like agonist quinpirole dose-dependently blocked the acute motor-stimulant response to cocaine. Intracortical quinpirole injection also significantly inhibited the ability of cocaine to increase extracellular DA concentrations in the NAC. These findings strongly support the recent hypothesis that the mPFC plays an integral role in contributing to the motor-stimulant response to cocaine (Beyer and Steketee 1999; Prasad et al. 1999) and suggest that DA D2 receptors in the mPFC may act to temper the function of subcortical areas during cocaine exposure. In this light, it would be interesting to speculate on possible pharmacological targeting of cortical D2 receptors to potentially modulate certain responses to cocaine. Finally, since the psychomotor-stimulant effects of cocaine have been suggested to underlie various components of drug dependence and drug craving (Wise and Bozarth 1987; Robinson and Berridge 1993), the results of the present study identify potential cellular processes that may contribute to the addictive properties of cocaine.

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## References

Baca SM, Lipska BK, Egan MF, Bachus SE, Ferguson JN, Hyde TM (1998) Effects of prefrontal cortical lesions on neuropeptide and dopamine receptor gene expression in the striatum-accumbens complex. Brain Res 797:55–64

Banks KE, Gratton A (1995) Possible involvement of medial prefrontal cortex in amphetamine-induced sensitization of mesolimbic dopamine function. Eur J Pharmacol 282:157–167

Beckstead R (1979) An autoradiographic examination of cortico-cortical and subcortical projections of the mediodorsal-projection (prefrontal) cortex in the rat. J Comp Neurol 184:43–62

Beyer CE, Steketee JD (1999) Dopamine depletion in the medial prefrontal cortex induces sensitized-like behavioral and neurochemical responses to cocaine. Brain Res 833:133–141

Bunney BS, Aghajanian GK (1976) Dopamine and norepinephrine innervated cells in the rat prefrontal cortex: pharmacological differentiation using microiontophoretic techniques. Life Sci 19:1793–1792

Carter CJ, Pycock CJ (1980) Behavioural and biochemical effects of dopamine and noradrenaline depletion within the medial prefrontal cortex of the rat. Brain Res 192:163–176

Cowen R, Sesack S, Van Bockstaele EJ, Branchereau P, Chan J, Pickel VM (1994) Analysis of synaptic inputs and targets of physiologically characterized neurons in rat frontal cortex:

combined intracellular recording and immunolabelling. Synapse 17:101–114
Doherty MD, Gratton A (1996) Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely-behaving rats. Brain Res 715:86–97
Goeders N, Dworkin S, Smith JE (1986) Neuropharmacological assessment of cocaine self-administration into the medial prefrontal cortex. Pharmacol Biochem Behav 24:1429–1440
Grobin AC, Deutch AY (1998) Dopaminergic regulation of extracellular γ-aminobutyric acid levels in the prefrontal cortex of the rat. J Pharmacol Exp Ther 285:350–357
Kalivas PW, Stewart J (1991) Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev 16:223–244
Kalivas PW, Sorg BA, Hooks MS (1993) The pharmacology and neural circuitry of sensitization to psychostimulants. Behav Pharmacol 4:315–334
Karler R, Calder LD, Thai DK, Bedingfield JB (1998) The role of dopamine and GABA in the frontal cortex of mice in modulating a motor-stimulant effect of amphetamine and cocaine. Pharmacol Biochem Behav 60:237–244
Karreman M, Moghaddam B (1996) The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by the ventral tegmental area. J Neurochem 66:589–598
Karreman M, Westerink BHC, Moghaddam B (1996) Excitatory amino acid receptors in the ventral tegmental area regulate dopamine release in the ventral striatum. J Neurochem 67: 601–607
Koob GF, Bloom FE (1988) Molecular and cellular mechanisms of drug dependence. Science 242:715–723
Law-Tho D, Hirsch J, Crepel F (1994) Dopamine modulation of synaptic transmission in rat prefrontal cortex: an in vitro electrophysiological study. Neurosci Res 21:151–160
Li Y, Hu X-T, Berney TG, Vartanian AJ, Stine CD, Wolf ME, White FJ (1999) Both glutamate receptor antagonists and prefrontal cortex lesions prevent the induction of cocaine sensitization and associated neuroadaptations. Synapse 34:169–180
Linderfors N, Brene S, Jerrera-Marchitz M, Persson H (1989) Region specific regulation of glutamic acid decarboxylase mRNA expression by dopamine neurons in rat brain. Exp Brain Res 77:611–620
Milliken GA, Johnson DE (1984) Analysis of messy data. Lifetime Learning, Toronto, Ontario
Oades RD, Halliday GM (1987) Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. Brain Res Brain Res Rev 12:117–165
Parfitt KD, Gratton A, Bickford-Wimer PC (1990) Electrophysiological effects of selective D1 and D2 dopamine receptor agonists in the medial prefrontal cortex of young and aged Fisher 344 rats. J Pharmacol Exp Ther 254:539–545
Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates, 2nd edn. Academic Press, New York
Penit-Soria J, Audinat E, Crepel F (1987) Excitation of rat prefrontal cortical neurons by dopamine: an in vitro electrophysiological study. Brain Res 425:363–374
Pierce RC, Reeder DC, Hicks J, Morgan ZR, Kalivas PW (1998) Ibotenic acid lesions of the dorsal prefrontal cortex disrupt the expression of behavioral sensitization to cocaine. Neuroscience 82:1103–1114
Prasad BM, Hochstatter T, Sorg BA (1999) Expression of cocaine sensitization: regulation by the medial prefrontal cortex. Neuroscience 88:765–774
Rétaux SM, Besson J, Penit-Soria J (1991) Opposing effects of dopamine D2 receptor stimulation on the spontaneous and the electrically evoked release of [3H]GABA on rat prefrontal cortex slices. Neuroscience 42:61–71
Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247–291
Schenk S, Snow S (1994) Sensitization to cocaine's motor activating properties produced by electrical kindling of the medial prefrontal cortex but not of the hippocampus. Brain Res 659:17–22
Seguela P, Watkins KC, Descarries L (1988) Ultrastructural features of dopamine axon terminals in the anteromedial and the suprarhinal cortex of adult rat. Brain Res 442:11–22
Sesack SR, Bunney BS (1989) Pharmacological characterization of the receptor mediating electrophysiological responses to dopamine in the rat medial prefrontal cortex: a microiontophoretic study. J Pharmacol Exp Ther 248:1323–1333
Sesack SR, Pickel VM (1992) Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol 320: 145–160
Sesack SR, Snyder CL, Lewis DA (1995) Axon terminals immunolabeled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex. J Comp Neurol 363:264–280
Setler PE, Sarau HM, Zirkle CL, Saunders HL (1978) The central effects of a novel dopamine agonist. Eur J Pharmacol 50: 419–430
Steketee JD (1998) Injection of SCH 23390 into the ventral tegmental area blocks the development of neurochemical but not behavioral sensitization to cocaine. Behav Pharmacol 9:69–76
Taber MT, Das S, Fibiger HC (1995) Cortical regulation of subcortical dopamine release: mediation via the ventral tegmental area. J Neurochem 65:1407–1410
Tang L, Todd RD, Heller A, O'Malley KL (1994) Pharmacological and functional characterization of D2, D3 and D4 dopamine receptors in fibroblast and dopaminergic cell lines. J Pharmacol Exp Ther 268:495–502
Tarazi FI, Kula NS, Baldessarini RJ (1997) Regional distribution of dopamine D4 receptors in rat forebrain. Neuroreport 8:3423–3426
Tzschentke TM, Schmidt WJ (1998) The development of cocaine-induced behavioral sensitization is affected by discrete quinolinic acid lesions of the prelimbic medial prefrontal cortex. Brain Res 795:71–76
Vezina P, Blanc G, Glowinski J, Tassin JP (1991) Opposed behavioral outputs of increased dopamine transmission in prefrontocortical and subcortical areas: a role for cortical D1 receptor. Eur J Neurosci 3:1001–1007
Vezina P, Blanc G, Glowinski J, Tassin JP (1994) Blockade of D-1 dopamine receptors in the medial prefrontal cortex produces delayed effects on pre- and postsynaptic indices of dopamine function in the nucleus accumbens. Synapse 16:104–112
Vincent S, Khan Y, Benes FM (1995) Cellular colocalization of dopamine D1 and D2 receptors in rat medial prefrontal cortex. Synapse 19:112–120
Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94:469–492
Wolf ME, Dahlin SL, Hu X-T, Xue C-J, White K (1995) Effects of lesions of prefrontal cortex, amygdala, or fornix on behavioral sensitization to amphetamine: comparison with *N*-methyl-D-aspartate antagonists. Neuroscience 69:417–439
Yang CR, Seamans JK, Goreleva N (1997) Mechanisms of dopamine (DA) modulation of GABAergic inputs to rat layer V-VI pyramidal prefrontal cortical (PFC) neurons in vitro. Soc Neurosci Abstr 23:1771
Zheng P, Bunney BS, Shi W-X (1997) Electrophysiological characterization and effect of dopamine on visually identified nonpyramidal neurons in the prefrontal cortex. Soc Neurosci Abstr 23:1212