Dopamine D_5 Receptors in Nucleus Accumbens Contribute to the Detection of Cocaine in Rats

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Dopamine D_1/D_5 receptor antagonism has been shown to block the euphoric and stimulatory effects of cocaine in humans and rats. In the present study, rats trained to discriminate the presence of cocaine (10 mg/kg) from its absence were used to analyze the functional contribution of D_1 (D_1R) versus D_5 (D_5R) receptors in the nucleus accumbens, an important neural site for the actions of cocaine. Bilateral microinfusion into the nucleus accumbens of an antisense oligonucleotide directed at the D_5R (0.75 nmol/0.3 μl per side, two times per day for 3 d) elicited a downward shift in the dose–effect curve for cocaine with a suppression of peak efficacy; the dose of cocaine estimated to elicit 50% drug-lever responding (ED_{50}) was 6.71 mg/kg when assessed 12 hr after the D_5R antisense oligonucleotide compared to the control ED_{50} of 1.83 mg/kg and to the ED_{50} of 1.75 mg/kg established 7 d after the last D_5R antisense oligonucleotide infusion. The D_1R antisense and scrambled oligonucleotide (0.75 nmol/0.3 μl per side, two times per day for 3 d) were both ineffective. Thus, using drug discrimination techniques that model the subjective effects of cocaine, we show that responsiveness to cocaine is dramatically attenuated after interference with the process of translation of the D_5R mRNA to its protein product. These findings suggest that D_5R is a functionally important target site for the indirect actions of cocaine and that rigorous investigations of the function of D_5R may help guide the discovery of strategies for pharmacotherapy in cocaine dependence.

Key words: behavior; cocaine; D_1 receptor; D_5 receptor; D1a receptor; D1b receptor; discriminative stimulus effects; dopamine

Cocaine abuse continues to impose serious medical, psychological, and criminal challenges for society. A thorough understanding of the neural basis underlying the effects of cocaine is critical to the development of science-based treatment protocols for cocaine dependence. One primary target for the actions of cocaine is the mesocorticolimbic dopamine circuit (Callahan et al., 1997; McBride et al., 1999), which has been implicated in reward, emotional, and motivational processes, as well as in psychosis and mania (Kalivas and Nemeroff, 1988). Dopamine acts at D_1- and D_2-like receptors, each of which is comprised of at least two receptor subtypes. The D_1-like receptor family includes the D_1 receptor (D_1R; also known as D1a) and D_5 receptor (D_5R; also known as D1b), which are separate gene products, exhibiting differential anatomical localization, but pharmacologically indiscriminable transduction pathways and agonist/antagonist profiles (Baldessarini and Tarazi, 1996). Oral administration of the D_1R/D_5R antagonist ecopipam (SCH 39166) was shown to significantly attenuate the euphoric and stimulatory effects of cocaine in humans (Romach et al., 1999). This recent observation in humans is consistent with findings that systemic administration of the D_1R/D_5R antagonist SCH 23390 blocked the locomotor stimulant, discriminative stimulus and reinforcing effects of cocaine in rodents (Callahan et al., 1991; Caine and Koob, 1994; Tella, 1994). In addition, intra-accumbens microinfusion of SCH 23390 completely antagonized the interoceptive (Callahan et al., 1997) and reinforcing effects of systemically administered cocaine (Caine et al., 1993; McGregor and Roberts, 1993). However, because SCH 23390, as well as other nonselective D_1-like receptor antagonists, has almost equal affinity for D_1R and D_5R, the contribution of each receptor subtype to the behavioral effects of cocaine has received little attention. In fact, because of the lack of selective ligands, the relative functional contributions of the D_1R versus D_5R remain uncharacterized *in vivo*. With the cloning of both the D_1R and D_5R genes (Monsma et al., 1990; Sunahara et al., 1991), the application of molecular biological tools to this question has been possible, in the forms of analysis of D_1R knock-out mice (Xu et al., 1994) and the use of antisense oligonucleotides directed at the translation initiation sequences of the rat D_1R and D_5R genes (Zhang et al., 1994; Dziewczapolski et al., 1998).

In the present study, we used the drug discrimination technique as a rodent model of the subjective effects of cocaine in humans (Schuster and Johanson, 1988; Drummond et al., 1995). In this assay, saline or cocaine (10 mg/kg) is injected and the rat must press one of two levers in the operant chamber to obtain a water reinforcer based on the recognition of the preceding injection. For example, when completion of the fixed ratio of 20 presses on the cocaine-associated lever follows the cocaine injection, the animal is "correct", and a water reinforcer is delivered. On saline

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sessions, completion of a fixed ratio of 20 presses on the saline-appropriate lever is reinforced with water. To analyze the relative role of D_1R versus D_5R in the discriminative stimulus effects of cocaine (10 mg/kg), a cumulative dose–response relationship (Schechter, 1997) for cocaine was established before and after microinfusion of antisense oligonucleotides directed at either D_1R or D_5R mRNA into the shell of the nucleus accumbens, which has been shown to be particularly sensitive to the actions of cocaine (Pontieri et al., 1995; McBride et al., 1999). We found that a selective and reversible loss of recognition of cocaine resulted from intra-nucleus accumbens pretreatment with the D_5R (but not D_1R) antisense oligonucleotide.

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MATERIALS AND METHODS

Animals. Adult male Sprague Dawley rats ($n = 34$; Harlan, Houston, TX) weighing between 300 and 350 gm at the beginning of the study were used. The rats were housed in pairs in a colony room that was maintained at a constant temperature (21–23° C) and humidity (40–50%); lighting was maintained on a 12 hr light/dark cycle (7:00 A.M.-7:00 P.M.). The amount of water each animal received during drug discrimination studies was restricted to that given during operant training sessions, after test sessions (10–15 min), and on weekends (36 hr). All experiments were conducted during the light phase (between 9:00 A.M. and 3:00 P.M.). All experiments were performed in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

Apparatus. The procedures were conducted in commercially available, two-lever operant chambers (model 80001; Lafayette Instrument, Lafayette, IN). Each chamber, housed in a light- and sound-attenuating cubicle (model 80015; Lafayette Instrument), was equipped with a water-filled dispenser mounted equidistant between two response levers on one wall. A 28 V house light provided illumination, and a blower supplied ventilation and masking noise. An interface (MedAssociates, St. Albans, VT) connected the chambers to a computer that controlled and recorded all experimental events.

Procedures. Standard two-lever, water-reinforced drug discrimination procedures were used (Cunningham et al., 1985). Rats were injected intraperitoneally with cocaine (10 mg/kg) or saline (1 ml/kg) 15 min before daily sessions. During this phase, only the stimulus-appropriate (drug or saline) lever was present. Training began under a fixed ratio 1 (FR 1) schedule of water reinforcement, and the FR requirement was incremented until all animals were responding reliably under an FR 20 schedule for each experimental condition. Both levers were then presented simultaneously, and rats were required to respond on the stimulus-appropriate lever to obtain reinforcement ("discrimination" training).

Test protocols. When rats demonstrated individual accuracies of at least 80% correct responses before the first reinforcer for 10 consecutive sessions, test sessions were initiated, and training sessions were run during the intervening days to maintain discrimination accuracy. Because only a narrow time frame was available in which to assess oligonucleotide-evoked alterations, we used a cumulative dose–response procedure (Schechter, 1997). The series began with an injection of saline and introduction to the operant chamber 10 min later. After completion of 20 responses on either lever (occurring within a few seconds), a single reinforcer was delivered, and the house lights were turned off; as the rat was removed from the chamber, the first dose of cocaine (0.625 mg/kg) was administered. Access to the operant chamber occurred 10 min later, and rats were again removed after accumulation of 20 responses on either lever. The series continued with another injection of cocaine (0.625 mg/kg) and testing; thus, the sequential cocaine dosing schedule was 0 (saline), 0.625, 0.625, 1.25, 2.5, and 5 mg/kg tested at 10 min intervals to achieve doses of 0, 0.625, 1.25, 2.5, 5, and 10 mg/kg of cocaine. The dose–response curve for cocaine established using the cumulative dosing procedure did not differ from that initially determined (after acquisition) with bolus injections of cocaine (0.625, 1.25, 2.5, 5, or 10 mg/kg) administered 15 min before rats were tested for lever selection (data not shown) (Callahan et al., 1991). After testing, the rats were returned to the colony and allowed *ad libitum* access to water for 10 min beginning 30 min after the end of each test.

Surgery and cannulae implantation. Rats were anesthetized with an intramuscular injection of 8.6 mg/kg of xylazine, 1.5 mg/kg of acepromazine, and 43 mg/kg of ketamine in physiological saline (0.9% NaCl). Bilateral guide cannulae (26 gauge) were stereotaxically implanted 2 mm above the nucleus accumbens shell (anteroposterior, −1.7 mm from bregma; mediolateral, ±0.75 mm; dorsoventral, −6 mm) (Paxinos and Watson, 1998). After surgery, animals were injected twice with penicillin (10,000 U/kg, i.m.) and were allowed a 1 week recovery period during which each rat was handled and weighed daily.

Microinfusion protocols. After recovery, discrimination training was reinstated for several weeks, and the cumulative dose–response curve for cocaine was reestablished and did not differ from that established before surgery (data not shown); the postsurgical dose–response curve served as control in the present experiment. During that period, rats were handled for 10–15 min each day for 5 d to familiarize them with the microinfusion procedure. Intracranial infusions (0.75 nmol/0.3 μl per side, two times per day for 3 d) were administered through 33 gauge internal cannulae that extended 2 mm below the tips of guide cannulae into the shell of the nucleus accumbens. The injection volume of 0.3 μl per side was infused over a 3 min period at 0.1 μl per min using a micropump (HoneyBee Pump; BAS, West Lafayette, IN). Injection cannulae remained in place for an additional 1 min to allow for diffusion away from the cannulae tips. Twelve hours and 7 d after the intracranial infusion procedure was completed, the cumulative dose–response curve for cocaine was reestablished. At the completion of the study, rats were killed by an overdose of chloral hydrate (800 mg/kg, i.p.), and tissue sections were processed for localization of cannulae. Only those animals whose cannulae were within the shell of the nucleus accumbens were included for statistical analysis (D_1R rats, $n = 7$; D_5R rats, $n = 8$; SCR rats, $n = 8$). No significant tissue damage was evident after histological examination of sections.

Drugs. Cocaine HCl (National Institute of Drug Abuse, Rockville, MD) was dissolved in saline (0.9% NaCl). Antisense oligonucleotides (Life Technologies, Gaithersburg, MD) were designed against the translation initiation sequences of the rat D_1R (5′-TAGGAGCCATCTTCCAG-3′) and D_5R sequences (5′-CAGCATGTCGCGCTGAGT-3′). A scrambled oligonucleotide (SCR; 5′-ATACTTCACGCCGATGG-3′) was designed that had thermodynamic properties similar to these antisense oligonucleotides. Based on a FastA search of GenBank, these oligonucleotides did not have significant homologies with any relevant, known cDNA sequences. The HPLC-purified oligonucleotides were dissolved in sterile saline.

Statistical analyses. Performance in the drug discrimination task was expressed as the percentage of drug-appropriate responses to total responses before delivery of the first reinforcer, and the response rate was calculated as the total number of responses on either lever divided by the number of minutes taken to complete the FR 20. Only data from animals that completed the FR 20 during the test sessions were used. A two-way ANOVA for repeated measures was used to analyze the effects of oligonucleotide pretreatment and cocaine dose on the percentage of drug-lever responding and response rate. Because treatments with D_1R antisense and scrambled oligonucleotide were not associated with any significant main effects or interactions, the results of these ANOVAs are not presented. The methods of Litchfield and Wilcoxon (1949) were used to estimate the dose of cocaine predicted to elicit 50% cocaine-appropriate responding (ED_{50}) and its 95% confidence intervals (Tallarida and Murray, 1986).

RESULTS

Assessment of the dose–effect curve for cocaine 12 hr after the last injection of the antisense oligonucleotide targeted to the D_5R (0.75 nmol/0.3 μl per side, two times daily for 3 d) indicated that the recognition of cocaine was significantly impaired (Fig. 1*B, gray squares*) in comparison to the control dose–effect curve for cocaine (Fig. 1*B, open circles*). Two-way ANOVA indicated a significant effect of treatment ($F_{(2,21)} = 3.94$; $p = 0.035$), dose ($F_{(5,105)} = 34.3$; $p = 0.001$) and a significant treatment × dose interaction on cocaine-lever responding ($F_{(10,105)} = 3.07$; $p = 0.002$); no significant differences were observed for the response rate measure. A complete recovery was observed as shown by the fact that the cumulative dose–effect curve for cocaine assessed 7 d after the termination of the D_5R antisense oligonucleotide treatment (Fig. 1*B, filled triangles*) did not differ from the control dose–effect curve. The cocaine dose estimated to elicit 50% drug-lever responding (ED_{50}) was 6.71 mg/kg when assessed 12 hr after the D_5R antisense oligonucleotide compared to the control ED_{50} of 1.83 mg/kg and to the ED_{50} established 7 d after the last D_5R antisense oligonucleotide infusion (1.75 mg/kg; Table 1). The effects elicited by the D_5R antisense oligonucleotide appear to be specific, because neither the D_1R antisense (Fig. 1*A*) nor the scrambled oligonucleotide (Fig. 1*C*) altered the discriminative stimulus effects of cocaine (Table 1).

DISCUSSION

Impairment of the translation of D_5R mRNA to its protein product in the nucleus accumbens resulted in the failure of trained rats to recognize the subjective effects of systemically

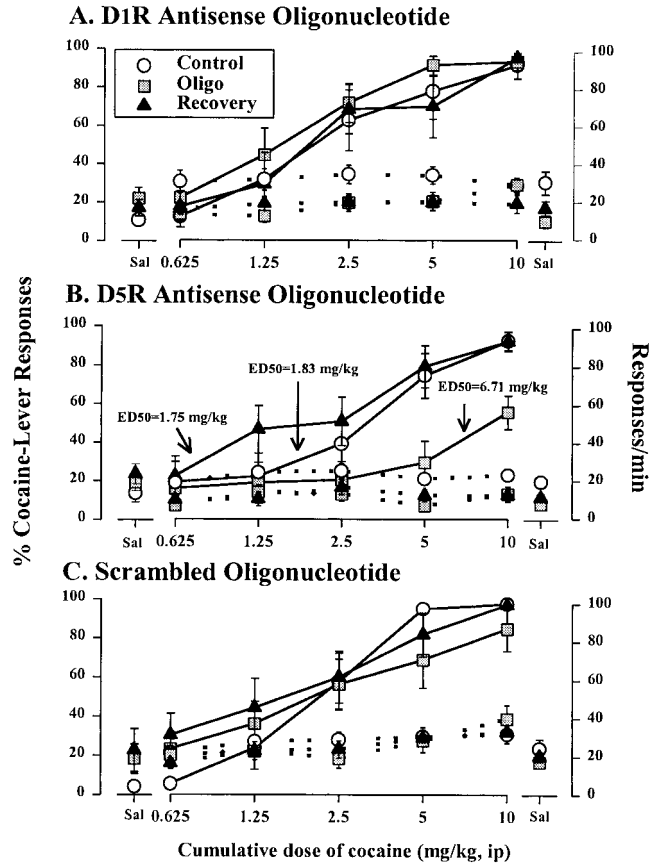

Figure 1. D_5R antisense oligonucleotide pretreatment evokes a rightward shift in the dose–response relationship for cocaine. The cumulative dose–response curve for cocaine (intraperitoneally) is shown for rats before the start of oligonucleotide infusion (*Control; open circles*), 12 hr (*Oligo; gray squares*), and 7 d after the last infusion of the oligonucleotide (*Recovery; filled triangles*). *Symbols* connected by *solid lines* denote the mean percentage of cocaine-appropriate responses during the test session (±SEM; *left ordinate*); *symbols* connected by *dotted lines* denote the mean response rate per minute (±SEM; *right ordinate*). For comparison, the percentage of cocaine-lever responding (*SAL, left of each panel*) and response rate (*SAL, right of each panel*) observed after saline test administered immediately before the start of cumulative dose–response testing are included. Pretreatment with the D_1R (*A*) and SCR (*C*) did not significantly alter cocaine-lever responding or response rates (results of analyses not shown).

Table 1. Pretreatment with D_1R and D_5R antisense and SCR oligonucleotides: ED_{50} values for cocaine

Oligonucleotide	Control ED_{50} (CI)	Treatment ED_{50} (CI)	Recovery ED_{50} (CI)
D_1R	1.81 (0.85–3.84)	1.67 (0.79–3.55)	1.80 (0.92–3.51)
D_5R	1.83 (0.86–3.94)	6.71 (3.28–13.76)	1.75 (0.81–3.79)
SCR	1.67 (0.92–2.99)	1.75 (0.84–3.63)	1.65 (0.82–3.34)

The dose (mg/kg) predicted to elicit 50% drug-lever responding and its 95% confidence intervals (CI) were calculated using the methods of Litchfield and Wilcoxon (Tallarida and Murray, 1986).

administered cocaine. Our findings suggest that actions at D_5R may underlie the efficacy of D_1-like receptor antagonists to block the euphoric and stimulatory effects of cocaine in humans (Romach et al., 1999) and animals (Callahan et al., 1991; Caine and Koob, 1994; Tella, 1994), particularly those effects mediated by the nucleus accumbens (Caine et al., 1993; McGregor and Roberts, 1993; Callahan et al., 1997). However, although our findings support an important role for D_5R in the behavioral effects of cocaine, the failure of the D_1R antisense oligonucleotide to modify the stimulus effects of cocaine does not categorically rule out a role for D_1R; even in the face of a knockdown of D_1R, a population of spare D_1R in the nucleus accumbens might be capable of maintaining normal D_1R function.

A D_1R antisense oligonucleotide similar to that used in the present study was shown to inhibit both grooming behavior evoked by the D_1R-like agonist SKF 38393 in intact mice (Zhang et al., 1994) and SKF 38393-evoked rotational behavior in either mice (Zhang et al., 1994) or rats (Dziewczapolski et al., 1998) with unilateral 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway. An opposite role for D_5R in the control of locomotor activity was suggested by the recent finding that SKF 38393-evoked rotational behavior in 6-OHDA-lesioned rats was facilitated after intracerebroventricular infusion of a D_5R antisense oligonucleotide (Dziewczapolski et al., 1998). In the present study, an important role for the D_5R in mediating the stimulus effects of cocaine is suggested by the selective loss of recognition of cocaine after pretreatment with the D_5R antisense oligonucleotide into the nucleus accumbens shell and a subsequent complete recovery. We did not analyze presumed loss of D_1R and D_5R protein after oligonucleotide administration because of the limited availability of selective D_1R and D_5R antibodies and the noted lack of correlation between functional parameters and reductions in protein levels. For example, both behavioral and physiological responses have been shown to be altered after knockdown conditions in the absence of significant changes in receptor density (Wahlestedt et al., 1993; Zhou et al., 1994). In fact, a previous study had demonstrated that D_1R and D_5R antisense oligonucleotide administration significantly altered behaviors evoked by the D_1R/D_5R agonist SKF 38393 in the absence of a detectable loss of receptor protein (Dziewczapolski et al., 1998). In contrast, a recent analysis of D_1R and D_5R-like immunoreactivity in the ventral tegmental area after intraparenchymal infusion of a similar D_1R or the identical D_5R antisense oligonucleotide to those used here identified a significant loss of D_1R and D_5R protein in this region, respectively (Frye and Vongher, 1999).

Our evidence indicates that the D_5R in nucleus accumbens plays an important role in the actions of cocaine. The abundance of D_5R mRNA and protein in the striatal complex of rats and primates, however, has been described as relatively low (Tiberi et al., 1991; Meador-Woodruff et al., 1992; Bergson et al., 1995; Ariano et al., 1999; Luedtke et al., 1999). Interestingly, selective protein–protein coupling between the D_5R and $GABA_A$-ligand-gated channel has been identified and shown to enable mutually inhibitory functional interactions in cultured hippocampal cells (Liu et al., 2000). Such an interaction may underlie the observation that stimulation of a D_1-like receptor modulates $GABA_A$ receptor-mediated synaptic activity in striatal neurons (Yan and Surmeier, 1997). Furthermore, numerous recent observations suggest that GABAergic control of striatal function is integral in the neural response to cocaine administration (Gerasimov et al., 1999; Jung et al., 1999; Resnick et al., 1999). Thus, the attenuation of cocaine-induced behavior seen after D_5R knockdown may be amplified by an operational disruption of the coupled function between D_5R and $GABA_A$ receptor channels, allowing the apparently limited number of D_5R in striatal regions to play an important role in the control of behavior.

In summary, using drug discrimination techniques that model the subjective effects of cocaine, we show that responsiveness to cocaine is dramatically attenuated by knockdown of the D_5R in the nucleus accumbens. These findings suggest that D_5R is a functionally important target site for the indirect actions of cocaine. Based on the known parallel between the discriminative stimulus properties of cocaine in animals and its interoceptive effects in humans as well as the prominent role of interoceptive stimuli in the initiation and maintenance of drug-seeking behav-

ior (Schuster and Johanson, 1988; Drummond et al., 1995), the present data suggest that rigorous investigations of the role of D_5R in drug dependence and psychiatric disorders are warranted and may help guide the discovery of D_5R-targeted strategies for effective pharmacotherapies.

REFERENCES

Ariano MA, Wang J, Noblett KL, Larson ER, Sibley DR (1999) Cellular distribution of the rat D1B receptor in central nervous system using anti-receptor antisera. Brain Res 746:141–150.

Baldessarini RJ, Tarazi FI (1996) Brain dopamine receptors: a primer on their current status, basic and clinical. Harv Rev Psychiatry 3:301–325.

Bergson C, Mrzljak L, Smiley JF, Pappy M, Levenson R, Goldman-Rakic PS (1995) Regional, cellular, and subcellular variations in the distribution of D_1 and D_5 dopamine receptors in primate brain. J Neurosci 15:7821–7836.

Caine SB, Koob GF (1994) Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. J Pharmacol Exp Ther 270:209–218.

Caine SB, Heinrichs SC, Williams CE, Coffin VL, Koob GF (1993) D-1 receptor antagonist injected into the accumbens shell or central amygdala increases cocaine self-administration. Soc Neurosci Abstr 1856:1993.

Callahan PM, Appel JB, Cunningham KA (1991) Dopamine D_1 and D_2 mediation of the discriminative stimulus properties of *d*-amphetamine and cocaine. Psychopharmacology 103:50–55.

Callahan PM, De La Garza II R, Cunningham KA (1997) Mediation of the discriminative stimulus properties of cocaine by mesocorticolimbic dopamine systems. Pharmacol Biochem Behav 57:601–607.

Cunningham KA, Callahan PM, Appel JB (1985) Dopamine D_1 receptor mediation of the discriminative stimulus properties of SKF 38393. Eur J Pharmacol 119:121–125.

Drummond DC, Tiffany ST, Glautier S, Remington B (1995) Addictive behaviour: cue exposure theory and practice. West Sussex, England: Wiley.

Dziewczapolski G, Menalled LB, Garcia MC, Mora MA, Gershanik OS, Rubenstein M (1998) Opposite roles of D_1 and D_5 dopamine receptors in locomotion revealed by selective antisense oligonucleotides. NeuroReport 9:1–5.

Frye CA, Vongher JM (1999) GABA(A), D1, and D5, but not progestin receptor, antagonist and anti-sense oligonucleotide infusions to the ventral tegmental area of cycling rats and hamsters attenuate lordosis. Behav Brain Res 103:23–34.

Gerasimov MR, Ashby Jr CR, Gardner EL, Mills MJ, Brodie JD, Dewey SL (1999) Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. Synapse 34:11–19.

Jung BJ, Dawson Jr R, Sealey SA, Peris J (1999) Endogenous GABA release is reduced in the striatum of cocaine-sensitized rats. Synapse 34:103–110.

Kalivas PW, Nemeroff CB (1988) The mesocorticolimbic dopamine system. New York: New York Academy of Sciences.

Litchfield JT, Wilcoxon F (1949) A simplified method of evaluating dose effect experiments. J Pharmacol Exp Ther 96:99–113.

Liu F, Wan Q, Pristupa ZB, Yu XM, Wang YT, Niznik HB (2000) Direct protein-protein coupling enables cross-talk between dopamine D5 and gamma-aminobutyric acid A receptors. Nature 403:274–280.

Luedtke RR, Griffin SA, Conroy SS, Jin X, Pinto A, Sesack SR (1999) Immunoblot and immunohistochemical comparison of murine monoclonal antibodies specific for the rat D1a and D1b dopamine receptor subtypes. J Neuroimmunol 101:170–187.

McBride WJ, Murphy JM, Ikemoto S (1999) Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav Brain Res 101:129–152.

McGregor A, Roberts DCS (1993) Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement. Brain Res 624:245–252.

Meador-Woodruff JH, Mansour A, Grandy DK, Damask SP, Civelli O, Watson Jr SJ (1992) Distribution of D_5 dopamine receptor mRNA in rat brain. Neurosci Lett 145:209–212.

Monsma FJ, Mahan LC, McVittie LD, Gerfen CR, Sibley DR (1990) Molecular cloning and expression of a D1 dopamine receptor linked to adenylyl cyclase activation. Proc Natl Acad Sci USA 87:6723–6727.

Paxinos G, Watson C (1998) The rat brain in stereotaxic coordinates. Sydney: Academic.

Pontieri FE, Tanda G, Di Chiara G (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc Natl Acad Sci USA 92:12304–12308.

Resnick A, Homanics GE, Jung BJ, Peris J (1999) Increased acute cocaine sensitivity and decreased cocaine sensitization in GABA(A) receptor beta3 subunit knockout mice. J Neurochem 73:1539–1548.

Romach MK, Glue P, Kampman K, Kaplan HL, Somer GR, Poole S, Clarke L, Coffin V, Cornish J, O'Brien CP, Sellers EM. (1999) Attenuation of the euphoric effects of cocaine by the dopamine D1/D5 antagonist ecopipam (SCH 39166). Arch Gen Psychiatry 56:1101–1106.

Schechter MD (1997) Discrete versus cumulative dosing in dose-response discrimination studies. Eur J Pharmacol 326:113–118.

Schuster CR, Johanson C-E (1988) Relationship between the discriminative stimulus properties and subjective effects of drugs. Psychopharmacology 4:161–175.

Sunahara RK, Guan H-C, O'Dowd BF, Seeman P, Laurier LG, Ng G, George SR, Torchia J, Van Tol HHM, Niznik HB (1991) Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. Nature 350:614–619.

Tallarida RJ, Murray RB (1986) Manual of pharmacologic calculations with computer programs, Ed 2. New York: Springer.

Tella SR (1994) Differential blockade of chronic versus acute effects of intravenous cocaine by dopamine receptor antagonists. Pharmacol Biochem Behav 48:151–159.

Tiberi M, Jarvie KR, Silvia C, Falardeau P, Gingrich JA, Godinot N, Bertrand L, Yang-Feng TL, Fremeau Jr RT, Caron MG (1991) Cloning, molecular characterization, and chromosomal assignment of a gene encoding a second D_1 dopamine receptor subtype: differential expression pattern in rat brain compared with the D_{1A} receptor. Proc Natl Acad Sci USA 88:7491–7495.

Wahlestedt C, Golanov E, Yamamoto S, Yee F, Ericson H, Yoo H, Inturrisi CE, Reis DJ (1993) Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions. Nature 363:260–263.

Xu M, Moratalla R, Gold LH, Hiroi N, Koob GF, Graybiel AM, Tonegawa S (1994) Dopamine D1 receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. Cell 79:729–742.

Yan Z, Surmeier DJ (1997) D5 dopamine receptors enhance Zn^{2+}-sensitive GABA(A) currents in striatal cholinergic interneurons through a PKA/PP1 cascade. Neuron 19:1115–1126.

Zhang S-P, Zhou L-W, Weiss B (1994) Oligodeoxynucleotide antisense to the D_1 dopamine receptor mRNA inhibits D_1 dopamine receptor-mediated behaviors in normal mice and in mice lesioned with 6-hydroxydopamine. J Pharmacol Exp Ther 271:1462–1470.

Zhou L-W, Zhang S-P, Qin Z-H, Weiss B (1994) *In vivo* administration of an oligodeoxynucleotide antisense to the D_2 dopamine receptor messenger RNA inhibits D_2 dopamine receptor-mediated behavior and the expression of D_2 dopamine receptors in mouse striatum. J Pharmacol Exp Ther 268:1015–1023.