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Fluoxetine does not alter the ability of dopamine D₁ and D₂ agonists to substitute for cocaine in squirrel monkeys

Paul L. Soto and Jonathan L. Katz

Abstract

Fluoxetine has been shown to enhance several behavioral effects of cocaine, including its discriminative-stimulus effects. An interaction between increased serotonergic and dopaminergic actions produced by blockade of serotonin and dopamine reuptake, is one possible mechanism for the enhancement. The present study investigated the effects of fluoxetine on the cocaine-like discriminative-stimulus effects of the D₂-like agonists quinpirole and (-)-NPA, and the D₁-like agonist SKF 82958 in squirrel monkeys trained to discriminate cocaine. The direct dopaminergic agonists, injected 5 min before testing, produced maximal levels of cocaine-appropriate responding of 50% (0.3 mg/kg, SKF 82958), 67% (0.003 mg/kg, (-)-NPA), and 77% (0.1 mg/kg, quinpirole) with ED₅₀ values of 0.43, 0.003, and 0.06 mg/kg, respectively. Fluoxetine at doses up to 10 mg/kg (also 5 min before testing) did not alter the effectiveness or the potency of any of the dopamine agonists in substituting for cocaine. The present failure of fluoxetine to consistently alter the cocaine-like discriminative effects of the dopamine agonists is consistent with the notion that the mechanism underlying the enhancement of the effects of cocaine by fluoxetine is not simply an interaction between enhanced serotonergic and dopaminergic activation as it is not obtained with direct-acting dopamine receptor agonists.

Keywords

cocaine; serotonin; dopamine receptor subtypes; fluoxetine; quinpirole; (-)-NPA; SKF 82958; drug discrimination; squirrel monkey

Although the importance of dopamine uptake inhibition in the discriminative-stimulus and other behavioral effects of cocaine is well-established, research has also demonstrated that selective serotonin reuptake inhibitors (SSRIs) can modulate the effects of cocaine. For example, the SSRI, fluoxetine, does not by itself substitute for cocaine but enhances the discriminative effects of cocaine in squirrel monkeys (Schama et al. 1997) and rats (Callahan and Cunningham, 1997; Cunningham and Callahan, 1991; Simon and Appel, 1997). The mechanism by which fluoxetine modulates the effects of cocaine may be an interaction between enhanced serotonin levels produced by fluoxetine, and enhanced dopamine levels produced by cocaine. That hypothesis implies that fluoxetine should also enhance the behavioral effects of direct dopamine agonists. Another possibility is that fluoxetine enhances the discriminative effects of cocaine by increasing brain levels of cocaine via a pharmacokinetic interaction (Fletcher et al., 2004; Tella and Goldberg, 1993).

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That hypothesis implies that fluoxetine should not enhance the behavioral effects of direct dopamine agonists.

The present study examined interactions of fluoxetine and several direct dopamine agonists in squirrel monkeys trained to discriminate injections of cocaine from saline. The dopamine direct-acting agonists were ones that were selective for either D₁- or D₂-like dopamine receptors (see Table 1 for order of drug exposure). The D₁-like agonist, SKF 82958, was selected because of its high efficacy in stimulating adenylyl cyclase (Izenwasser and Katz, 1993; Keabian and Calne, 1979), a defining feature of D₁-like receptor activation, and because of its relatively high potency in substituting for cocaine (e.g., Chausmer and Katz, 2002; Spealman et al., 1991). For D₂-like agonists, quinpirole and (-)-NPA were selected. Quinpirole has previously been shown to produce either full substitution (Barrett and Appel, 1989; Callahan et al., 1991; Terry et al., 1994) or a high level of partial substitution for cocaine relative to other D₂-like agonists (Spealman et al., 1991; Witkin et al., 1991). (-)-NPA is another efficacious D₂-like agonist that has previously been shown to be among the most potent D₂-like agonists in substituting for cocaine (Witkin et al., 1991).

Methods

Subjects

Squirrel monkeys, housed individually in stainless steel primate cages, served as subjects. All monkeys had substantial previous exposure to cocaine and other dopamine transporter inhibitors. The subjects were fed (Purina Monkey Chow supplemented with Teklad Monkey Diet; Ralston Purina, St. Louis, MO; Teklad Premier Laboratory Diets, Madison, WI) daily at least 1 hour after experimental sessions. Daily feed amounts were calculated such that subjects were maintained at approximately 85% of free feeding weights. During their daily enrichment subjects were given small amounts of fruit, vegetables, or grain. Water was continuously available in the individual home cages, and there was a 12-h light/dark cycle (lights on: 06:00) in the housing room.

Apparatus

Sessions were conducted with subjects seated in small-primate restraint chairs (modified ENV-601A, Med Associates, Inc. St. Albans, VT) housed within sound-attenuating cubicles (ENV-018, Med Associates, Inc.). The chairs were constructed of Plexiglas with a stainless-steel front panel on which two levers were mounted 9.53 cm apart, and 8.89 cm above the waist restraint of the chair. Mounted above each lever was an array of three stimulus lights. A food receptacle (ENV-200 R2M, Med Associates, Inc.) was behind a 5.08 cm × 5.08 cm opening in the front panel centered between the two levers facing the subject. Behind the front panel was a dispenser (ENV-203, Med Associates, Inc.) which delivered 190-mg banana-flavored food pellets (Bio-Serv, Inc., Frenchtown, NJ) to the food receptacle. Also mounted behind the front panel was a relay that provided a feedback click for each lever press. Inside the sound-attenuating cubicle, behind the restraint chair was a fan that provided ventilation and a speaker that delivered white noise in order to mask extraneous sounds.

Procedure

Subjects were trained in daily sessions (Monday through Friday) to discriminate intramuscular (i.m.) injections of cocaine (0.3 mg/kg) from saline using a two-lever food reinforcement procedure. Subjects were trained to depress both levers with each response reinforced (fixed-ratio 1 or FR 1 schedule) by delivery of a food pellet. During initial training, only the stimulus lights directly above the active lever were illuminated. Once responding on both levers was established, lights above both levers were illuminated, and subjects were injected 5 min before each session with either saline or 0.3 mg/kg cocaine.

Responses on only one lever were reinforced following saline injections and responses on the other lever were reinforced following cocaine injections. Over the course of daily sessions the FR schedule was gradually changed so that 30 consecutive responses were required for food presentation. Responding on the cocaine-appropriate lever during sessions following saline injections, or on the saline-appropriate lever during sessions following cocaine injections reset the FR schedule requirement on the appropriate lever. The assignment of saline- and cocaine-appropriate levers was counterbalanced across subjects. A post-reinforcement timeout period was gradually increased across several training sessions, from 0.1 to 20 s. During timeout periods all stimulus lights were off and responses had no scheduled consequences other than producing feedback clicks. Cocaine (C) and saline (S) sessions were arranged in a double-alternation sequence (...CCSSCCSS...).

Training continued until subjects met the training criteria of greater than 85% of responses (over the entire session and before the first food presentation) on the appropriate lever for at least two saline and two cocaine sessions. Once responding reached criterion levels, test (T) sessions were interspersed between cocaine or saline repeats of the double alternation sequence (e.g., ...SCTCSTSC...). Test sessions only occurred when responding met criteria on the preceding two sessions. During test sessions, subjects were given different doses of cocaine, quinpirole, (-)-NPA, or SKF 82958 alone or in combination with different doses of fluoxetine 5 min prior to the session. Stimulus conditions during test sessions were identical to training sessions except that 30 consecutive responses on either lever were reinforced.

Data Analysis

Overall response rate and the percentage of responses occurring on the cocaine-appropriate lever for the entire session were calculated for each subject and the mean for the group was plotted as a function of drug dose. Linear regression on the pooled individual subject data were used to calculate ED₅₀ values (dose producing 50% cocaine-appropriate responding) using the linear portion of the dose-effect curves (Snedecor and Cochran, 1967). ED₅₀ values were judged to be significantly different when their 95% confidence limits did not overlap. The data were analyzed using all the collected data for each subject and after applying an exclusion criterion that excluded the percentage of cocaine-appropriate responding at a particular drug dose if the subject's response rate was less than 0.02 responses per minute. Conclusions did not differ when all the data were used versus after applying the exclusion criteria and therefore results obtained by including all the subjects' data are presented

To assess changes in the effectiveness of the dopamine agonists produced by co-administration of fluoxetine, separate one-way repeated measures ANOVAs were conducted for each dopamine agonist on the percentage of cocaine-appropriate responding obtained in each subject at the dose producing the average maximum effect.

Results

Cocaine and each of the dopamine agonists dose-dependently increased cocaine-appropriate responding (Figure 1, top panel). Cocaine produced full substitution at doses of 0.3 and 1.0 mg/kg. In contrast, the D₂-like agonists only partially substituted, with quinpirole and (-)-NPA producing maximal amounts of substitution of 77% and 67%, respectively (Table 2). The D₁-like agonist SKF 82958 produced a maximum of 50% cocaine-appropriate responding (Table 2). Fluoxetine failed to produce any substantial cocaine-appropriate responding (Figure 1, top panel). All of the drugs were studied over a range of doses from those having little or no effect to those that either fully substituted or decreased response rates to below 50% of control (Figure 1, bottom panel).

Fluoxetine failed to alter the potency of the D₂-like agonist (-)-NPA as a substitute for the discriminative-stimulus effects of cocaine (Figure 2, top panel) as judged by overlapping 95% confidence limits for ED₅₀ values obtained from each combination of fluoxetine and (-)-NPA (Table 2). Further, the effectiveness of (-)-NPA in substituting for cocaine was not significantly altered by fluoxetine ($F_{3,12} = 0.370$, $p = 0.776$), and neither was the potency of (-)-NPA to reduce response rate (Figure 2, bottom panel; Table 2).

Fluoxetine produced a trend towards an enhancement of the effects of 0.03 mg/kg of quinpirole (Figure 3, top panel), however the effect was not significant as evidenced by overlapping 95% confidence limits for ED₅₀ values for quinpirole alone and each fluoxetine-quinpirole combination (Table 2). Neither did fluoxetine significantly increase the maximal substitution of quinpirole for cocaine ($F_{3,9} = 2.156$, $p = 0.163$; Table 2). Finally, fluoxetine did not significantly alter the potency of quinpirole to reduce response rates (Figure 3, bottom panel; Table 2).

Similar to the results obtained with the D₂ agonists, the cocaine-like discriminative stimulus effects of SKF 82958 were not changed by co-administration of fluoxetine (Figure 4, top panel). ED₅₀ values for combinations of fluoxetine and SKF 82958 compared to SKF 82958 alone were not significantly different (Table 2, column 3) and the effectiveness of SKF 82958 in substituting for cocaine was not changed ($F_{4,12} = 0.161$, $p = 0.954$). Fluoxetine did, however, significantly alter the effects of SKF 82958 on response rates (Figure 4, bottom panel) although this change was due virtually in its entirety to effects at a single dose of fluoxetine (10 mg/kg) that had response rate suppressive effects when administered alone.

Discussion

The present study was designed to determine if the cocaine-like discriminative-stimulus effects of D₁- and D₂-like agonists are enhanced by the specific serotonin reuptake inhibitor, fluoxetine. The D₂-like agonists, quinpirole and (-)-NPA partially substituted for cocaine, and the D₁-like agonist, SKF 82958 produced approximately 50% cocaine-appropriate responding. The levels of substitution of D₁- and D₂-like agonists for cocaine obtained in the current study are consistent with previous studies (e.g. Barrett and Appel, 1989; Spealman et al., 1991; Witkin et al., 1991). Also, consistent with previous studies is the finding that fluoxetine alone failed to produce significant substitution for cocaine (e.g. Baker et al., 1993; Kleven et al., 1990). Fluoxetine did not appreciably alter the cocaine-like discriminative-stimulus effects of any of the three direct-acting dopamine agonists. Further, fluoxetine did not significantly alter the effects of any of the studied dopamine agonists on response rates, except when 10 mg/kg of fluoxetine was combined with SKF 82958.

The present lack of an interaction between fluoxetine and direct-acting dopamine agonists differs from previous reports that fluoxetine can alter the discriminative-stimulus and other effects of the indirect dopamine agonist cocaine. As noted above, fluoxetine has been shown to enhance the discriminative-stimulus effects of cocaine in squirrel monkeys (Schama et al., 1997) and rats (Callahan and Cunningham, 1997; Cunningham and Callahan, 1991; Simon and Appel, 1997). Additionally, fluoxetine enhances the locomotor and convulsive effects of cocaine in rodents (Bubar et al., 2003; Fletcher et al., 2004; Ritz and George, 1987). The failure of fluoxetine to enhance the cocaine-like discriminative-stimulus effects of either the D₁- or D₂-like agonists in a manner similar to that reported for cocaine may be because the indirect agonist cocaine produces a stimulation of both D₁- and D₂-like receptors. Accordingly, fluoxetine might enhance the discriminative effects of combinations of D₁- and D₂-like agonists more consistently than it did for the individual agonists alone. A greater enhancement of combinations of D₁- and D₂-like agonists seems unlikely however, as combinations of D₁- and D₂-like agonists do not produce more substitution than either drug

does alone (Katz and Witkin, 1992; Spealman et al., 1991), though that experiment is yet to be conducted.

The lack of a robust enhancement by fluoxetine by dopamine agonists is consistent with a pharmacokinetic interaction between cocaine and fluoxetine. Pretreatment with fluoxetine results in higher levels of cocaine in plasma and brain (Fletcher et al., 2004; Tella and Goldberg, 1993) and fluoxetine, but not citalopram, enhances the locomotor-stimulating effects of cocaine (Fletcher et al., 2004) suggesting that an enhancement of cocaine's effects is not generally obtained with drugs that increase serotonin levels. Further, fluoxetine enhances cocaine-induced locomotor activity in rats depleted of brain serotonin (Fletcher et al., 2004), suggesting that serotonin is not necessary for the effect. Further, while fluoxetine has been shown to enhance the discriminative-stimulus effects of cocaine, citalopram attenuates, rather than enhances, the discriminative-stimulus effects of cocaine in squirrel monkeys (Rowlett et al., 2004; Spealman, 1993 but see Kleven and Koek, 1988) again suggesting that increases in serotonin do not consistently enhance cocaine's effects. Thus, whatever the mechanism of the interaction, it presently appears to differ for the two serotonin uptake inhibitors most extensively studied or possibly depend on species.

Finally, fluoxetine has been demonstrated to increase extracellular dopamine in the prefrontal cortex of rats (Tanda et al., 1994). Fluoxetine-produced increases in extracellular dopamine may contribute to its effectiveness in enhancing the discriminative-stimulus effects of cocaine. However, that mechanism might also be expected to increase the effectiveness of direct dopamine agonists. Clearly, several questions remain unanswered regarding the mechanism underlying fluoxetine-produced enhancement of cocaine's discriminative-stimulus effects.

In summary, the current results replicate previous findings that D₁- and D₂-like dopaminergic agonists do not fully reproduce the discriminative-stimulus effects of cocaine, and further demonstrate that fluoxetine does not consistently enhance the cocaine-like discriminative-stimulus effects of D₁- and D₂-like agonists. The failure of fluoxetine to consistently enhance the cocaine-like discriminative-stimulus effects of the dopaminergic agonists studied here is consistent with the notion that the enhancement of the effects of cocaine by fluoxetine is not due to a combination of enhanced serotonergic and dopaminergic actions, and is consistent with a pharmacokinetic interaction between fluoxetine and cocaine. Regardless of the exact nature of the mechanism underlying fluoxetine's enhancement of cocaine's behavioral effects, it does not appear to be one that generalizes to the cocaine-like discriminative-stimulus effects of direct-acting dopaminergic agonists.

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Figure 1.

Percentage of responses on the cocaine-appropriate lever (top panel) and response rate expressed as a percentage of saline response rate (bottom panel) following administration of various doses of cocaine (saline control response rate = 3.13 responses/sec), fluoxetine (saline control rate = 3.87 responses/sec), quinpirole (saline control rate = 4.11 responses/sec), (-)-NPA (saline control rate = 3.53 responses/sec), or SKF 82958 alone (open squares; saline control rate 3.82 responses/sec). Each data point represents the effects in four to seven monkeys.

Figure 2.

Percentage responses on the cocaine-appropriate lever (top panel) and response rate expressed as a percentage of saline response rate (bottom panel) following administration of various doses of (-)-NPA alone (saline control rate = 3.53 responses/sec), or (-)-NPA in combination with 1 mg/kg (saline control rate = 3.14 responses/sec), 3 mg/kg (saline control rate = 3.36 responses/sec), and 10 mg/kg (saline control rate = 3.17 responses/sec) fluoxetine. Each data point represents the effects in four to six monkeys.

Figure 3.

Percentage of responses on the cocaine-appropriate lever (top panel) and response rate expressed as a percentage of saline response rate (bottom panel) following administration of various doses of quinpirole alone (saline control rate = 4.11 responses/sec) or quinpirole in combination with 1 mg/kg (saline control rate = 3.99 responses/sec), 3 mg/kg (saline control rate = 3.66 responses/sec), and 10 mg/kg (saline control rate = 4.25 responses/sec) fluoxetine. Each data point represents the effects in four to six monkeys except 3 mg/kg fluoxetine plus 0.001 mg/kg quinpirole ($n = 3$) and 10 mg/kg fluoxetine plus 0.003 mg/kg quinpirole ($n = 3$).

Figure 4.

Percentage responses on the cocaine-appropriate lever (top panel) and response rate expressed as a percentage of saline response rate (bottom panel) following administration of SKF 82958 alone (saline control rate = 3.87 responses/sec), or SKF 82958 in combination with 1 mg/kg (saline control rate = 2.85 responses/sec), 3 mg/kg (saline control rate = 3.61 responses/sec), and 10 mg/kg (saline control response rate = 3.46 responses/sec) fluoxetine. Each data point represents the effects in four or five monkeys except 10 mg/kg fluoxetine plus 0.1 mg/kg SKF 82958 (n = 3).

Order of drug exposures for individual monkeys. In some cases, selected doses of drugs were administered after the initial exposure to a particular drug.

Table 1

Order of Drug Exposures									
110-93	11-88	1-84	34B-03	476-90	49A-03	8-91	HS-5		
SKF82958	SKF82958	(-)-NPA	Fluoxetine	SKF82958	Quinpirole	Fluoxetine	(-)-NPA	Quinpirole	Fluoxetine
Quinpirole	Quinpirole	Quinpirole	(-)-NPA	(-)-NPA	Fluoxetine	Quinpirole	Quinpirole	Quinpirole	Fluoxetine
(-)-NPA	(-)-NPA	SKF82958	Quinpirole	Fluoxetine	(-)-NPA	(-)-NPA	SKF82958	Fluoxetine	SKF82958
		Fluoxetine	SKF82958	Quinpirole					

Table 2

Maximal effects and potencies of dopamine agonists alone and in combination with fluoxetine in substituting for cocaine and reducing response rate. 95% confidence limits (CLs) are given in parentheses.

Drug	Cocaine-like Discriminative-Stimulus Effects			Response Rates	
	Dopamine Agonist ED ₅₀ Values (mg/kg)	Maximum Effectiveness (%Cocaine Responding)	Dopamine Agonist ED ₅₀ Values (mg/kg)		
(-)-NPA Alone	0.0029 (0.0011–0.0142)	66.8 ± 10.8 @ 0.003 mg/kg	n.s.		
(-)-NPA + Fluoxetine 1.0	0.0042 (0.0021–0.0188)	58.5 ± 7.2 @ 0.01 mg/kg	0.0011 (0.0001–0.0027)		
(-)-NPA + Fluoxetine 3.0	0.0073 (0.0031–0.1092)	48 ± 13 @ 0.01 mg/kg	n.s.		
(-)-NPA + Fluoxetine 10.0	0.0048 (0.0026–0.0144)	59.7 ± 8.3 @ 0.01 mg/kg	n.s.		
Quinpirole Alone	0.06 (0.04–0.08)	76.8 ± 7 @ 0.1 mg/kg	0.02 (0.00–0.52)		
Quinpirole + Fluoxetine 1.0	0.08 (0.03–0.39)	62.6 ± 5.8 @ 0.1 mg/kg	0.01 (0.00–0.04)		
Quinpirole + Fluoxetine 3.0	0.07 (0.02–0.53)	72.2 ± 21.3 @ 0.3 mg/kg	0.01 (0.00–0.02)		
Quinpirole + Fluoxetine 10.0	0.03 (0.01–0.16)	64.4 ± 0.8 @ 0.1 mg/kg	0.01 (0.00–0.04)		
SKF82958 Alone	0.43 (0.18–29.43)	49.8 ± 20.4 @ 0.3 mg/kg	0.10 (0.06–0.18)		
SKF82958 + Fluoxetine 0.3	n.s.	37.9 ± 18.1 @ 0.3 mg/kg	0.08 (0.05–0.13)		
SKF82958 + Fluoxetine 1.0	0.65 (0.24–290.49)	38.4 ± 14 @ 0.3 mg/kg	0.10 (0.06–0.16)		
SKF82958 + Fluoxetine 3.0	n.s.	26.6 ± 21.3 @ 0.3 mg/kg	0.07 (0.02–0.14)		
SKF82958 + Fluoxetine 10.0	n.s.	38 ± 23.5 @ 0.3 mg/kg	n.s.		

n.s. non-significant linear regression