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Citalopram enhances cocaine's subjective effects in rats

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Abstract

Serotonin-selective reuptake inhibitors (SSRIs) have been shown to enhance the locomotor stimulatory, discriminative-stimulus, and convulsive effects of cocaine in rodents. A pharmacokinetic mechanism for the interaction is supported by increases in the brain levels of cocaine by fluoxetine treatment. Furthermore, the locomotor-stimulant effects of cocaine in rodents are enhanced by fluoxetine and fluvoxamine, SSRIs known to inhibit cocaine-metabolizing cytochrome P450 enzymes, whereas citalopram, an SSRI that does not inhibit P450 enzymes, does not enhance cocaine's locomotor-stimulant effects. Citalopram, however, attenuated the discriminative-stimulus effects of cocaine in squirrel monkeys trained to discriminate cocaine from saline, though it enhanced the discriminative-stimulus effects of a low dose of cocaine in rats trained to discriminate high and low doses of the drug. This study investigated the effects of citalopram on cocaine's discriminative-stimulus effects in rats trained more simply to discriminate cocaine from saline. Citalopram alone produced predominantly saline-appropriate responding, but when administered before cocaine, citalopram dose-dependently shifted the cocaine dose-response curve leftward. The present findings suggest that enhancement of cocaine's discriminative-stimulus effects may occur through a mechanism different from that underlying enhancement of cocaine's locomotor effects or that another action of citalopram selectively blocks locomotor enhancement.

Keywords

citalopram; cocaine; drug discrimination; rats

Introduction

Serotonin selective reuptake inhibitors (SSRIs) enhance some of the behavioral effects of cocaine. For example, fluoxetine has been reported to enhance the discriminative-stimulus effects of cocaine in squirrel monkeys (Schama *et al.*, 1997), the locomotor stimulant and discriminative-stimulus effects of cocaine in rats (Cunningham and Callahan, 1991; Callahan and Cunningham, 1997; Herges and Taylor, 1998; Bubar *et al.*, 2003; Fletcher *et al.*, 2004), and convulsive effects of cocaine in mice (Ritz and George, 1997). Such findings have been interpreted as support for the notion that serotonin systems play a modulatory role in the behavioral effects of cocaine.

A more recent study, however, suggests that some SSRIs enhance the behavioral effects of cocaine by increasing brain levels of cocaine, perhaps by inhibiting cocaine metabolism (Fletcher *et al.*, 2004). In that study, fluoxetine enhanced the locomotor-stimulating effects

of cocaine in rats depleted of brain serotonin suggesting that serotonin is not important in producing the effect. Furthermore, both fluoxetine and fluvoxamine, SSRIs known to inhibit cocaine-metabolizing cytochrome P450 enzymes (Pellinen *et al.*, 1994; Hemeryck and Belpaire, 2002), enhanced the locomotor-stimulating effects of cocaine, whereas citalopram, an SSRI with little or no activity on those enzymes (Brosen and Naranjo, 2001; Hemeryck and Belpaire, 2002), did not alter cocaine's locomotor-stimulating effects (Fletcher *et al.*, 2004). In addition, Fletcher *et al.* (2004) found that rats pretreated with fluoxetine before cocaine administration had higher levels of cocaine in brain than rats pretreated with saline. Together these results suggest that whether an SSRI enhances the effects of cocaine depends on whether it inhibits cocaine metabolism and does not involve increased serotonin levels.

The suggestion of a metabolic interaction is complicated by the finding that citalopram can attenuate the discriminative-stimulus effects of cocaine in squirrel monkeys (Spealman, 1993; Rowlett *et al.*, 2004) and enhance the discriminative-stimulus effects of a low dose of cocaine in rats trained in a more complex discrimination of low and high doses of cocaine (Kleven and Koek, 1998). These findings suggest a possible species difference in the interaction of citalopram and cocaine; however, the different procedures make that conclusion tentative. The effects of citalopram on cocaine's discriminative-stimulus effects have not been reported in rats trained to discriminate cocaine from saline. Thus, it is unclear whether the results with citalopram and cocaine obtained in monkeys will also be obtained with rats, which was the focus of the present study.

Method

Subjects

Individually housed, male Sprague–Dawley rats, approximately 200 days of age at start, served. Rats were maintained at 85% of unrestricted-feeding weights, and water was freely available in cages in the housing room (12-h light/dark cycle).

Apparatus

Sessions were conducted in two-lever operant conditioning chambers (modified ENV 007, Med Associates, Inc., St. Albans, Vermont, USA) housed within sound-attenuating cubicles (ENV-018, Med Associates, Inc.). A downward force on the lever (approximately 0.4 N) through approximately 11 mm, defined a response and produced an audible click. The chambers contained pairs of light-emitting diodes above each lever, a lamp at the top of the front panel for ambient illumination, and a food receptacle behind an approximate 5×5 cm opening centered in the front panel. A dispenser (ENV-203, Med Associates, Inc.) behind the front panel delivered 45-mg food pellets (Bio-Serv, Inc., Frenchtown, New Jersey, USA) into the receptacle. White noise masked extraneous sounds.

Procedure

Subjects were trained in daily sessions to discriminate 10 mg/kg cocaine from saline, injected 5-min earlier using a two-lever food-reinforcement procedure as described in detail previously (Katz *et al.*, 2004). Briefly, after cocaine injection responses on one lever were reinforced with food after 20-consecutive responses (fixed ratio 20; FR 20) by delivery of a food pellet. Following saline, responses on the other lever were reinforced according to the FR 20 schedule.

Testing began when 85% or more responses were emitted on the appropriate lever for the first FR completed, and for the entire session during at least two saline and two cocaine sessions. Thereafter test sessions occurred when responding met the criteria on the preceding

two sessions. Conditions during test sessions were identical to training sessions except that 20 consecutive responses on either lever were reinforced.

Drugs

(–)-Cocaine hydrochloride (Sigma-Aldrich St. Louis, Missouri, USA) and citalopram hydrobromide (Sigma-Aldrich; Tocris Bioscience, Ellsville, Missouri, USA) were dissolved in 0.9% NaCl or water and administered intraperitoneally, (1 ml/kg) 5 or 30 min, respectively, before sessions.

Data analysis

Linear regression was used to calculate ED₅₀ values (dose producing 50% cocaine-appropriate responding) using the linear portion of the dose-effect curve (Snedecor and Cochran, 1967). Parallel-line bioassay techniques (Finney, 1964) assessed the degree of change (relative potency) in the cocaine dose-effect curve produced by citalopram. The relative potency is considered significant if the 95% confidence limits exclude the value 1.0.

Results

Cocaine dose-dependently increased the percentage of cocaine-appropriate responses (Fig. 1, top panel, filled circles) with an ED₅₀ value of 2.38 mg/kg (Table 1). Across the range of doses studied, there were no significant effects ($P>0.05$) of cocaine on response rates (Fig. 1, bottom panel, filled circles).

Citalopram, when administered before cocaine vehicle, produced predominantly saline-appropriate responding at the doses tested (Fig. 1, top panel, open symbols above 'C'). Citalopram pretreatment shifted the dose-effect curve for the discriminative-stimulus effects of cocaine to the left (Fig. 1, top panel, compare open to filled points). The leftward shifts produced by citalopram were dose-related with the highest dose producing a greater shift. The effects of citalopram are reflected in the dose-related decrease in cocaine ED₅₀ values, and relative potency estimates, which were statistically significant (Table 1). There were no significant effects ($P>0.05$) of cocaine dose on response rate when cocaine was administered with citalopram (Fig. 1, bottom panel, open diamonds and squares).

Discussion

As showed earlier, cocaine dose-dependently increased drug-appropriate responding in rats trained to discriminate cocaine from saline. Citalopram alone produced predominantly saline-appropriate responding, but when combined with cocaine, citalopram produced significant, dose-dependent increases in the potency of cocaine to produce its discriminative-stimulus effects. This finding is consistent with earlier findings that citalopram enhances the discriminative-stimulus effects of a low dose of cocaine in rats trained to discriminate a low from a high dose of cocaine (Kleven and Koek, 1998), but is in contrast to results in squirrel monkeys showing an attenuation of cocaine's discriminative-stimulus effects by citalopram (Spealman, 1993; Rowlett *et al.*, 2004). These results further support a species difference in the interaction of citalopram and cocaine, however procedural differences, though less likely as contributing factors, cannot be completely excluded at this time.

The enhancement of cocaine's discriminative-stimulus effects by citalopram is also in contrast to addition research in rats showing a lack of effect of citalopram on cocaine-induced locomotion (Fletcher *et al.*, 2004). As noted in that study, unlike fluoxetine and fluvoxamine, citalopram has little, if any inhibitory effect on the cytochrome P450 enzymes which contribute to the metabolism of cocaine through oxidative mechanisms (Brosen and

Naranjo, 2001; Hemeryck and Belpaire, 2002). Though, it is not currently known whether citalopram affects other oxidative or hydrolytic metabolic pathways for cocaine (e.g., Kloss *et al.*, 1983; Jatlow, 1988), it appears unlikely in light of the finding that citalopram does not also enhance the locomotor-stimulant effects of cocaine (Fletcher *et al.*, 2004). A metabolic basis for the interaction would presumably have altered all of the effects of cocaine. It is also possible that the shorter pretreatment time used in this study (30λmin) may have contributed to differences in the present interactions and those reported by Fletcher *et al.* (60λmin) for stimulation of locomotor activity. This appears unlikely in light of microdialysis data indicating prolonged effects of citalopram (Reith *et al.*, 1997).

The finding that citalopram does not enhance cocaine's locomotor effects at a dose that in the current study enhanced the subjective effects of cocaine raises several possibilities. One is that the mechanism underlying discriminative-stimulus enhancement does not contribute to cocaine's locomotor effects. Thus, SSRIs that enhance both cocaine's locomotor and discriminative-stimulus effects may do so through different mechanisms. Alternatively, it may be that a common mechanism underlies enhancement of cocaine's locomotor and discriminative-stimulus effects, but that some other action of citalopram selectively blocks locomotor enhancement. The fact that the major SSRIs have affinity for differing off-target sites (Carrasco and Sandner, 2005) may account for differences in their interactions with cocaine. For example, fluoxetine has affinity for serotonin 2C receptors (Palvimäki *et al.*, 1999), which have been implicated in modulation of cocaine's discriminative-stimulus and locomotor effects (Walsh and Cunningham, 1997; Fletcher *et al.*, 2006).

In summary, the present results show that citalopram enhances the discriminative-stimulus effects of cocaine in rats. Differences in the effects of combinations of citalopram and cocaine in squirrel monkeys and rats indicate a species difference. Differences in the effects of the combinations on cocaine-like discriminative-stimulus effects and on stimulation of locomotor activity suggest the possibility that an off-target action of citalopram interferes with the enhancement of the locomotor effects only, or a different sensitivity to serotonergic modulation of the discriminative-stimulus effects of cocaine and its stimulation of locomotor activity. Future research might focus on the basis for these differing effects of the drug combinations, and additionally on the effects of extended exposure to citalopram, which is typical of its clinical use.

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Fig. 1.

Effects of citalopram on cocaine's discriminative-stimulus (top panel) and response-rate altering effects (bottom panel). Ordinates, percentage of responses on the cocaine-appropriate lever (top panel) and percentage of control response rate (bottom panel). Abscissa, dose of cocaine (C, saline control injection). The effects of cocaine alone are indicated by filled circles, the effects of citalopram and cocaine combinations are indicated by open triangles and open squares. Error bars represent $\pm$ standard error of the mean. Each symbol represents the average of six to ten rats except at 0.3 mg/kg cocaine ($n = 4$), 10 mg/kg citalopram and 0.3 mg/kg of cocaine ($n=4$), and 10 mg/kg citalopram and 10 mg/kg cocaine ($n=3$).

Table 1
Individual and relative potencies of cocaine alone and in combination with citalopram on the percentage of cocaine-appropriate responding with 95% confidence limits in parentheses

Drug	ED ₅₀ (mg/kg) (95% CLs)	Relative potency (95% CLs)
λCocaine	2.38 (1.93–2.88)	
With 10λmg/kg citalopram	1.56 (1.02–2.23)	0.65 (0.93–0.45)
With 17λmg/kg citalopram	1.03 (0.77–1.32)	0.42 (0.57–0.31)

CLs, confidence limits.