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Fluoxetine Reduces Intravenous Cocaine Self-Administration in Rats

MARILYN E. CARROLL, SYLVIE T. LAC, MARISEL ASENCIO AND REBECCA KRAGH

Psychiatry Department, Box 392 UMHC, University of Minnesota Medical School, Minneapolis, MN 55455

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CARROLL, M. E., S. T. LAC, M. ASENCIO AND R. KRAGH. *Fluoxetine reduces intravenous cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV **35**(1) 237–244, 1990.—Rats self-administered intravenously delivered cocaine (0.2 mg/kg) under a fixed-ratio (FR) 4 schedule during 24-hr sessions. Water was freely available from both a drinkometer and a standard water bottle. After behavior had stabilized, the rats were injected with fluoxetine HCl at 10:00 a.m. and 4:00 p.m. for 5 consecutive days. Three groups of 5 rats each received a different dose of fluoxetine (2.5, 5 or 10 mg/kg) via the IV cannula. In three other groups of rats a glucose and saccharin solution (G+S) was substituted for water in the automatic drinking device and saline was substituted for cocaine. These three groups of rats received the same fluoxetine doses as the cocaine self-injecting groups. In two additional groups of 5 rats each, the cocaine dose was changed to 0.1 or 0.4 mg/kg, and 5 mg/kg fluoxetine injections were given. The two higher doses of fluoxetine (5 and 10 mg/kg) reduced cocaine infusions (0.2 mg/kg) by at least 50 percent on all 5 days of treatment, and cocaine infusions returned to baseline levels within 48 hr after fluoxetine treatments were terminated. Behavior maintained by the G+S solution was also reduced by the two higher fluoxetine doses; however, this reduction did not reliably occur until the last two days of fluoxetine administration. The G+S intakes returned to baseline levels within 24 hr after fluoxetine treatment. Fluoxetine also reduced cocaine infusions in the group of rats that received the lower unit dose of cocaine (0.1 mg/kg); however, it had almost no effect on behavior maintained by a higher cocaine dose (0.4 mg/kg). Food and water intake, responding on an inactive lever, and the number of saline infusions were not reliably altered by the fluoxetine treatments. These results suggest that fluoxetine alters the reinforcing effects of cocaine as well as a nondrug substance.

Cocaine Fluoxetine Intravenous Rats Self-administration Serotonin (5-HT)

REVIEWS of the literature indicate that dopamine receptors in the brain play a major role in the rewarding aspects of psychomotor stimulant drugs (35). A number of laboratory animal studies employing dopamine agonists and antagonists as well as neurotoxic lesions have indicated the importance of dopamine in the nucleus accumbens and frontal cortex. Recent laboratory animal studies (28) and clinical reports (12) indicate that another monoamine, serotonin, 5-hydroxytryptamine (5-HT), is also important in stimulant self-administration. Amphetamine self-administration in rats has been markedly reduced by pretreatment with L-tryptophan, a 5-HT precursor (20), fluoxetine, a 5-HT uptake blocker (19) and quipazine, a 5-HT receptor agonist (19). In contrast, reduction of cerebral 5-HT by neurotoxin lesions with 5,7-dihydroxytryptamine produced increases in amphetamine self-administration (21). Amphetamine self-administration was also increased by a serotonin antagonist, metergoline (22). The specific locus of action of 5-HT on stimulant drug self-administration has not yet been determined, nor has its relationship to dopamine-mediated cocaine effects. However, Lyness (20) has reported that injections of L-tryptophan that markedly reduce amphetamine self-administration fail to alter dopamine turnover in the nucleus accumbens. Others have shown that acute cocaine treatment inhibits the turnover of whole brain 5-HT (11).

Antidepressant medications that activate 5-HT neurons, such as sertraline, as well as those affecting dopamine and other neurotransmitters have been shown to have some efficacy in treating stimulant abuse (9, 12, 14, 27, 30–32). These drugs have been evaluated in relatively drug-free patients who have entered treatment for cocaine abuse, and they seem to aid in the prevention of relapse when combined with behavioral therapy. There are not yet any clear indications of what particular pharmacotherapies are most effective for treating specific stimulant abusers (13). Efforts have focused on relapse prevention, and little is known of how these pharmacologic treatments alter the maintenance of stimulant use or the initiation of abstinence. Since the neuronal basis for drug-reinforced behavior and withdrawal cravings are not well understood, animal models of cocaine abuse are useful for examining the effect of specific pharmacological treatments on different phases of the addiction process.

The purpose of the present study was to examine the effect of fluoxetine on cocaine-reinforced behavior in rats. Previous work has indicated that fluoxetine and related drugs markedly reduced amphetamine (19) and ethanol (40) self-administration in rats. In the present experiment several doses of fluoxetine were tested, and the cocaine dose was varied with fluoxetine dose held constant to determine whether there was a parallel or nonparallel shift in the cocaine dose-response curve. In other groups of rats a glucose and saccharin solution (G+S) was also established as a reinforcer, and high rates of behavior were maintained. Fluoxetine pretreatment was also given to these groups to determine whether the effects of this drug were specific to cocaine-reinforced behavior or to behavior maintained by nondrug reinforcers as well.

METHOD

Subjects

Eight groups containing 5 rats each completed this experiment. Approximately 15 rats did not complete the experiment due to overdose, infections or catheter blockage. These rats were replaced by new ones until each of the 8 groups contained 5 rats that completed the experiment. The rats were experimentally naive males from the Wistar strain (Harlan-Sprague Dawley, Madison, WI) with mean body weights (±S.E.) at the start of the experiment of 439.7 (±6.8). The rats were allowed free access to ground food (Purina Laboratory Chow) and water from both a water bottle and an automatic drinking device before the experiment began. Each rat was implanted with a chronic jugular catheter according to methods described previously (4,33), and they were then placed in their experimental chambers with free food and water where they recovered from surgery for 24–48 hr.

Apparatus

The experimental chambers and infusion system have been previously described in detail (3). The 18 stainless steel and Plexiglas chambers that were used were octagonal in shape with alternating Plexiglas and stainless steel walls. Each chamber contained two response levers (Coulbourn Instruments, Inc., Lehigh Valley, PA), a tongue-operated solenoid-driven drinking device (2) and a receptacle for ground food. Each of these devices was located on a separate stainless steel wall of the chamber. A stimulus light was mounted above each lever, and the light was illuminated for the duration of an infusion after the lever pressing requirements were completed. A light above the drinking device indicated the availability of a liquid. Above the food receptacle, a standard water bottle was mounted, with a drinking tube protruding into the chamber. The chamber was constantly illuminated by a 4.76-W house light, and the room was humidity- and temperature-controlled at 24°C. An infusion pump (Fluid Metering Inc., Oyster Bay, NY, Model rhsyockc) was located outside a wooden enclosure that contained the experimental chamber and was used for sound attenuation. Programming of experimental events and data recording was controlled by microcomputers (7) located in an adjacent room.

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Infusion solutions were mixed in sterile saline and contained in 500 ml reservoirs above the experimental chambers. Dose was controlled by infusion duration which was 1 sec/100 g body weight or approximately 4.4 sec depending upon the rat's weight. The volume per infusion was approximately 0.15 ml. Fluoxetine was donated by the Eli Lilly Company (Indianapolis, IN). Drug doses are expressed in terms of the salt. It was mixed in sterile saline and infusion volumes were held constant at 1 ml. Reagent grade glucose and saccharin were purchased from Sigma Chemical Co. (St. Louis, MO). The G+S solution consisted of 3% (wt./vol.) glucose and 0.125% (wt./vol.) saccharin which was mixed daily and presented to the rats at room temperature.

Procedure

After recovery from surgery the rats were allowed unlimited access to cocaine, ground food (Purina Laboratory Chow) and water. Session length was 24 hr beginning each day at 10:00 a.m. Cages were cleaned, intake measurements were made and food and liquids were replenished each day at 10:00 a.m. Sessions were conducted seven days per week. Cocaine deliveries (0.2 mg/kg) were contingent upon a response on the left lever. Each response on the right lever was counted, but had no programmed consequences. Each lick on the automatic drinking device initially resulted in delivery of 0.005 ml water. After cocaine infusions had stabilized for at least 5 days, the fixed ratio (FR) value for each infusion was increased from 1 to 2 and then 4. When behavior had again stabilized for at least 5 days, half of the rats were given a G+S solution instead of water in the automatic drinking device, and at the same time, saline replaced cocaine in the infusion reservoir. These rats served as controls for the cocaine-injecting rats to determine whether the effects of fluoxetine were specific to cocaine-reinforced behavior or to behavior maintained by a non-drug reinforcer (G+S) and/or saline infusions.

The food that was available to the groups self-administering cocaine and those self-administering G+S was limited to 20 g per day. Previous work had shown that rats self-injecting cocaine under similar conditions consume 15–20 g of ground food per day, while those self-injecting saline and drinking G+S consume 25–30 g per day (5). Thus, from the beginning of the experiment, food availability was held constant at 20 g across groups so that they would not differ with respect to feeding conditions or body weight. When cocaine- and G+S-reinforced behavior had stabilized for at least five days, fluoxetine injections were given through the IV cannula at 10 a.m. and 4 p.m. for 5 consecutive days. The two groups receiving either cocaine or G+S were further subdivided into three groups of five rats each that received three different doses of fluoxetine (2.5, 5, or 10 mg/kg/injection). Two additional groups of 5 rats were changed from 0.2 mg/kg unit doses to 2 other doses of cocaine (0.1 or 0.4 mg/kg/infusion), but they received fluoxetine injections of only the 5 mg/kg dose twice daily. The doses of fluoxetine were given twice daily to reduce the possibility of side-effects after a single higher unit dose. In all 8 groups after 5 days of fluoxetine injections, behavior was allowed to stabilize for at least 5 sessions. To minimize the chance of infection *(Pseudomonas aeruginosa)* and blocked catheters that have resulted in the past from frequent opening and injecting into the cannula system, saline control injections were not given for the 5 days preceding and the 5 days following fluoxetine injections. Previous research had shown that saline injections delivered twice daily had no effect on self-administration of cocaine (6), and the present data show that the lowest fluoxetine dose (2.5 mg/kg) had no effect on cocaine self-administration. Behavioral observations were made nonsystematically after the fluoxetine injections.

RESULTS

Figure 1 shows the effect of the three fluoxetine doses on cocaine infusions, inactive lever responses, water intake from the automatic drinking spout and food intake. At the 5 and 10 mg/kg doses fluoxetine produced decreases of at least 50 percent of baseline in cocaine-reinforced behavior. Cocaine-reinforced behavior was markedly reduced on the first day of fluoxetine injections and it generally remained suppressed all 5 days. Occasionally, during one of the fluoxetine treatment days, a rat showed a burst of cocaine-reinforced responding that equalled or exceeded baseline levels. When fluoxetine injections were discontinued, cocaine infusions returned to baseline levels within 24 hr, with the exception of one or two rats in each group for whom cocaine infusions remained suppressed for 48–72 hr. Responding on the inactive lever was generally low for most rats; the high rates shown in the 2.5 and 10 mg groups were due to one rat in each group. A few rats showed a burst of responding on the drug and/or inactive lever on the first day of fluoxetine injections. In the 2.5 group it was the same rat that showed a high rate of responding on the active and inactive lever. Water intake was not substantially altered by the fluoxetine injections. Food intake was substantially suppressed during the treatment with 2.5 mg/kg fluoxetine. Again, this was accounted for by one rat's lowered food intake. Such

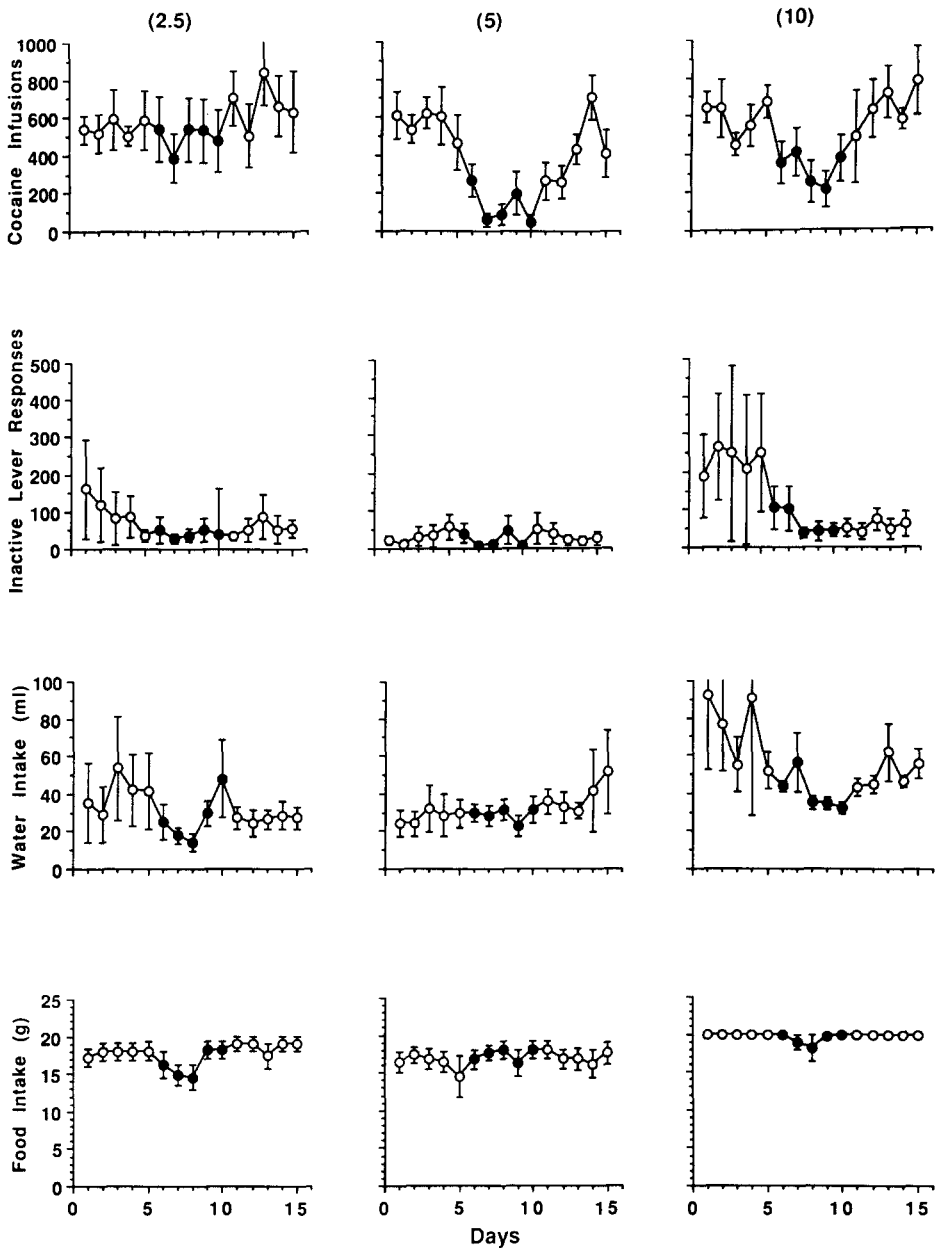

FIG. 1. Mean (± S.E.) cocaine infusions, inactive lever responses, water intake (ml) and food intake (g) are presented for 15 consecutive 24-hr sessions for groups of rats that self-injected cocaine and received water in their automatic drinking devices. Open symbols refer to sessions when no injections were administered. Filled symbols represent the sessions when fluoxetine injections were given twice daily. The 3 fluoxetine doses indicated in parentheses are presented in the left, center and right frames, respectively. Each point represents a mean of 5 rats.

periods of lowered food intake occasionally occur in rats with continuous access to cocaine. Thus, the finding was not likely to be due to the effects of fluoxetine since it was not found in any of the other groups, even those receiving high doses of fluoxetine. There were no observable behavioral changes (other than those noted in Fig. 1) associated with the fluoxetine injections.

As shown in Fig. 2, fluoxetine also reduced behavior reinforced by the G+S solution at the 5 and 10 mg doses. This suppression generally occurred during the last three days of the fluoxetine treatment. A comparison of G+S to water intake from the automatic drinking spouts (Fig. 1) indicated that G+S intake exceeded water intake by at least a factor of 5 and that the substance was functioning as a reinforcer. Responses on the inactive lever and saline infusions in the G+S-drinking groups

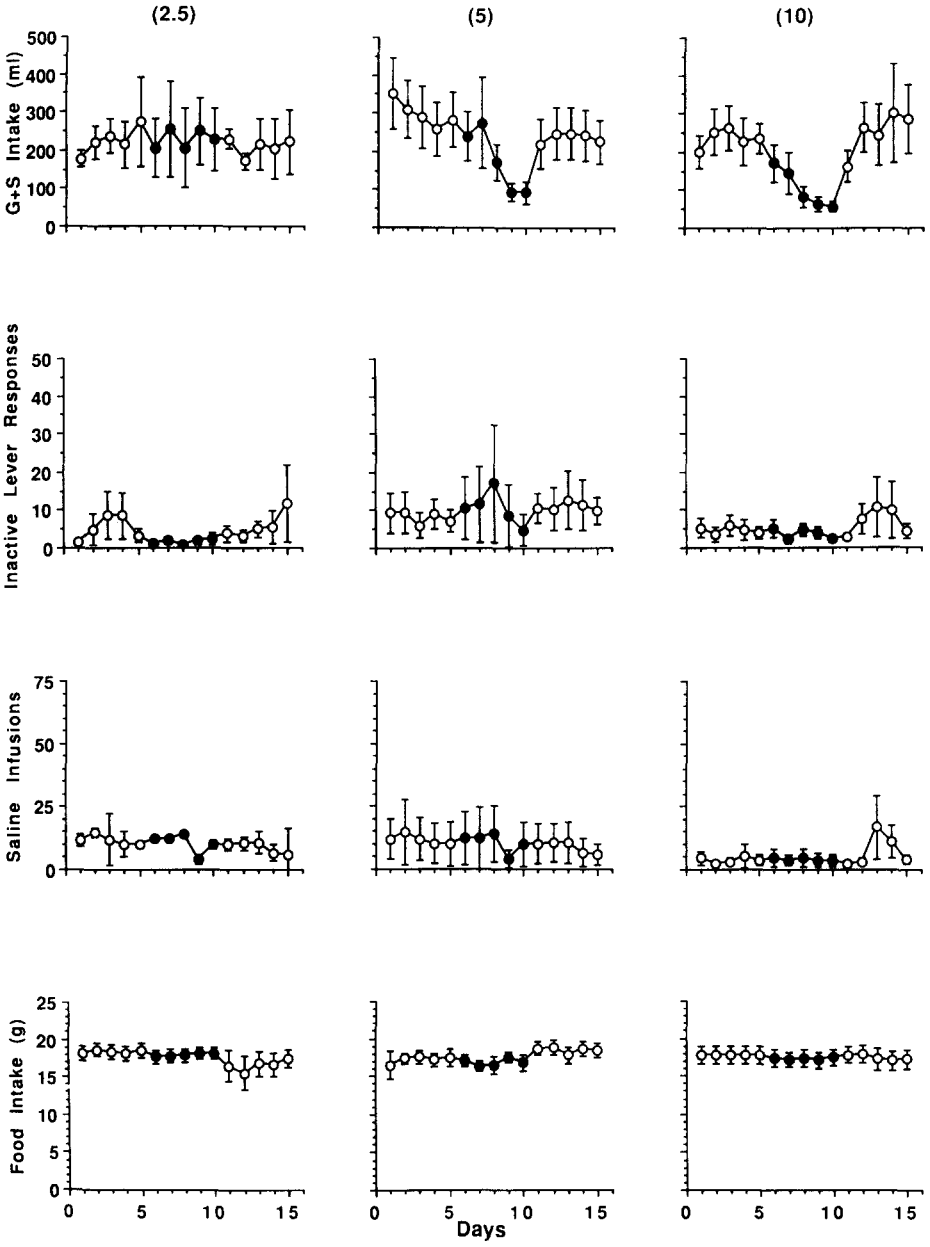

FIG. 2. Mean (±S.E.) G+S intake (ml), saline infusions, inactive lever responses and food intake (g) are presented for 15 consecutive 24-hr sessions for groups that had saline available for self-injection and that received G+S in their automatic drinking devices. Open symbols refer to sessions when no injections were administered. Filled symbols represent the sessions when fluoxetine injections were given twice daily. The 3 fluoxetine doses indicated in parentheses are presented in the left, center and right frames, respectively. Each point represents a mean of 5 rats.

were very low with the exception of one or two rats, and they were not systematically altered by the fluoxetine injections. Responding on the inactive lever was generally much lower in these groups than in the cocaine self-injecting groups (Fig. 1). Food intake was not altered by fluoxetine injections in any of the G+S self-administering groups, and it was comparable to the cocaine self-injecting groups receiving 5 and 10 mg/kg injections of fluoxetine. Water intake from the bottle with a standard drinking tube is not presented for any of the groups as it was almost negligible and did not vary as a function of fluoxetine dose or experimental condition (cocaine or G+S groups).

Figure 3 shows the time course of cocaine and G+S self-administration during the 24-hr sessions with respect to the times that fluoxetine injections were given (arrows). The data are presented as means of 5-day blocks: before, during and after fluoxetine injections. After about 1–12 hr into the session, there was no overlap between standard errors for the fluoxetine condition compared to baseline. There was no marked change in the rate

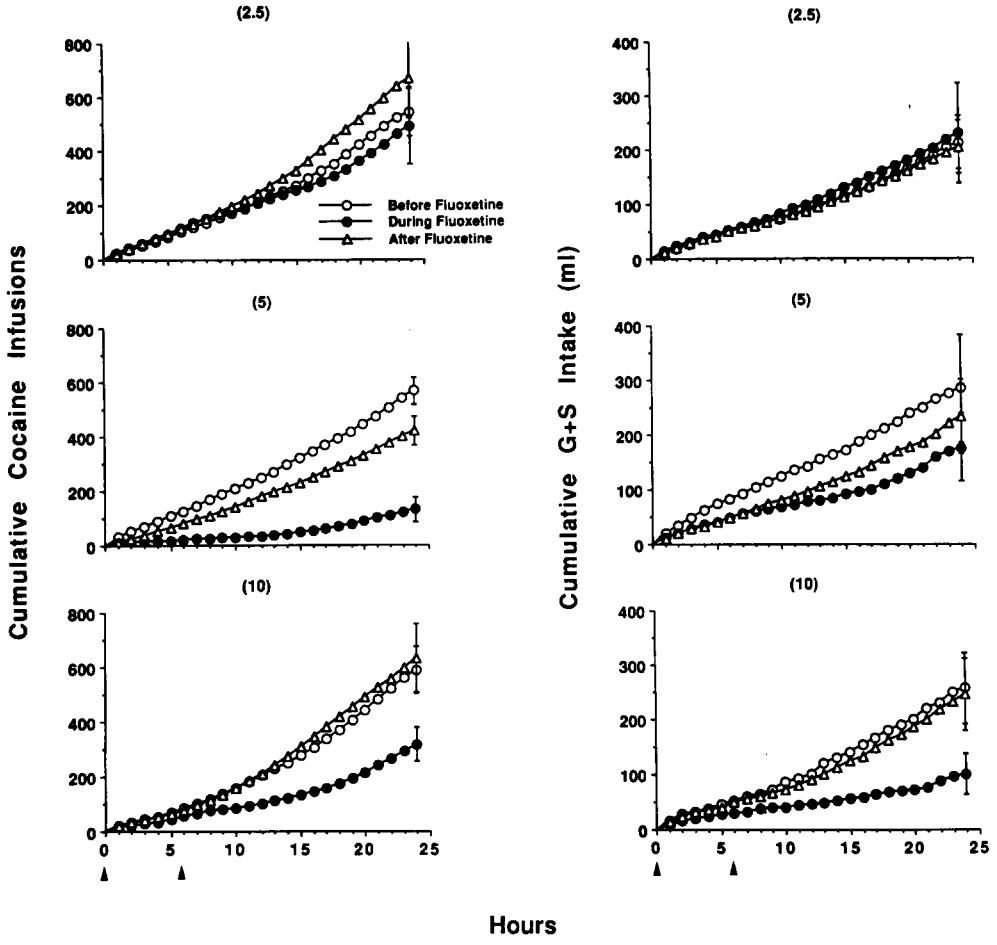

FIG. 3. Mean cumulative cocaine infusions and amount (ml) of G+S consumed (±S.E.) are presented over 24 1-hr periods as a function of fluoxetine dose (2.5, 5 and 10 mg/kg twice daily). Left frames refer to groups of rats that self-administered cocaine and received water in the drinking device. Right frames refer to groups that had saline available for self-injection and received G+S in the drinking device. Open circles represent the mean of 5 rats for the 5 days before fluoxetine (5 mg/kg twice daily) injections, filled circles indicate the mean of the 5 days when fluoxetine was injected, and open triangles refer to the 5 days after fluoxetine injections. Each point represents a mean for 5 rats for 5 days. Standard error bars refer to the mean standard errors across the 5 days. Fluoxetine doses, indicated in parentheses, are presented in the upper, middle and lower frames, respectively. Arrows refer to the times that fluoxetine injections were given in the 24-hr sessions.

of cocaine infusions after each fluoxetine injection. Approximately 8–10 hr after the second injection there was a noticeable increase in the rate of cocaine infusions suggesting that some recovery of the self-administration behavior was occurring during the last few hours of the session. The G+S self-administering groups showed a similar daily time course of changes in intake due to fluoxetine. However, the magnitude of the effect was smaller and variability was greater than the cocaine groups due to the fact that the data were averaged over 5 days and the suppression in intake began at variable times during fluoxetine treatment. The pre- and postfluoxetine functions were generally similar except for the 5 mg/kg fluoxetine group whose cocaine infusions did not return to the baseline condition until the fourth day after fluoxetine injections were terminated.

Figure 4 shows the effect of fluoxetine (5 mg/kg twice daily) on responding maintained by three cocaine doses (0.1, 0.2 and 0.4 mg/kg/infusion). The number of cocaine infusions as well as the intra- and intersubject variability of infusions decreased as the unit dose of cocaine was increased. Total daily cocaine intake increased slightly between the lowest and highest cocaine unit doses. Fluoxetine had similar suppressant effects on cocaine infusions in the groups receiving 0.1 and 0.2 mg/kg unit doses (left and center frames); however, the group receiving the highest cocaine unit dose (0.4 mg/kg) did not show reduced infusions due to fluoxetine. In all groups the postfluoxetine cocaine infusions were slightly lower than the mean infusions before fluoxetine due to the reduced infusions found in one or two rats during the first few days when fluoxetine injections were discontinued. Paired t-tests revealed a significant difference between the mean number of infusions during the 5-day block of sessions before fluoxetine injections and the 5-day block of fluoxetine injections at the 0.1, $t(4)=4.09$, $p<0.05$, and 0.2, $t(4)=5.39$, $p<0.05$, mg/kg and at the 0.4 mg/kg unit dose, $t(4)=3.24$, $p<0.05$. Similar comparisons of actual cocaine intake (mg/kg/24 hr) indicated significant differences before and during fluoxetine injections at the 0.1, $t(4)=4.09$, $p<0.05$, 0.2, $t(4)=5.39$, $p<0.05$, and 0.4, $t(4)=$

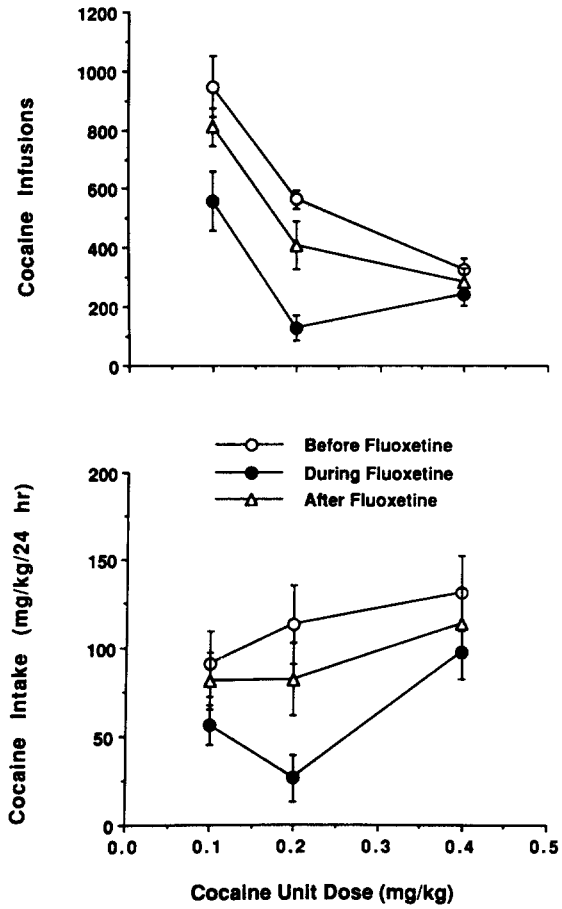

FIG. 4. Mean cocaine infusions (±S.E.) are presented in the upper frame and mean cocaine intake (mg/kg/24 hr) is presented in the lower frame as a function of cocaine unit dose (0.1, 0.2, and 0.4 mg/kg) before (open circles), during (filled circles) and after (triangles) 5 days of fluoxetine administration. Each point represents a mean of 5 rats during 5 days at each condition. The standard error bars refer to the mean standard errors of the 5 means (5 rats across the 5 days).

6.03, $p<0.05$, mg/kg doses. Within-subject comparisons of mean infusions and mean cocaine intake (mg/kg/24 hr) during the 5-day blocks before and after fluoxetine injections resulted in no significant differences (p's>0.05) except for number of infusions at the 0.2 mg/kg unit dose, $t(4)=5.37$, $p<0.05$, and mg/kg intake at the 0.4 mg/kg dose, $t(4)=2.91$, $p<0.05$. As described for Figs. 1 and 2, there were no differences in the other measures such as food and water intake, but there were transient increases in responding on the inactive lever the first day of fluoxetine injections.

DISCUSSION

Cocaine was clearly functioning as a reinforcer at the doses used in the present experiment, as responding maintained by the drug greatly exceeded that maintained by the vehicle, saline. The present results show that fluoxetine markedly reduced cocaine-reinforced behavior at two of the doses tested (5 and 10 mg/kg). This effect was attenuated somewhat when a higher cocaine unit dose (0.4 mg/kg) was provided for self-administration; however, total daily cocaine intake from all three cocaine unit doses was similar. Previous studies have shown that similar doses of fluoxetine reduced amphetamine (37) and alcohol (40) self-administration in rats. The present results and previous reports with amphetamine suggest that drugs such as fluoxetine may be effective in reducing drug abuse as well as in preventing relapse.

The present results may be subject to a number of possible interpretations. One hypothesis is that fluoxetine and other 5-HT-enhancing agents interfere with the reinforcing effects of drugs such as cocaine and nondrug substances. One form of interference may be to increase the reinforcing effect of these substances. If this were the case, the lower response rates as shown in the present experiment would be expected, and they were similar to the lower response rates that occur with higher doses of cocaine (see Fig. 4, "Before Fluoxetine," 0.4 mg/kg dose). This interpretation is also supported by reports of reduced IV amphetamine self-administration (19) decreased food intake (25,38), as well as reductions in intracranial self-stimulation (1, 8, 17, 18) after treatment with serotonin-enhancing agents. A second mechanism by which fluoxetine may have interfered with the reinforcing effects of cocaine is by blocking these effects. The expected result would be an initial increase or "extinction burst" in responding followed by a decline. This hypothesis was supported in the present finding that some rats exhibited a burst of responding on both active and inactive levers the first day that 5-HT was injected. Similar bursts of amphetamine-maintained responding have been reported after fluoxetine treatment (19). A third form of interference could occur and reduce cocaine intake if the fluoxetine injections had reinforcing effects of their own that partially substituted for the reinforcing effects of cocaine. The present experiment was not designed to examine the reinforcing effects of fluoxetine, and there are no published data to indicate that fluoxetine functions as a reinforcer for animals. Furthermore, there are no clinical reports of fluoxetine abuse in humans. However, recent data indicate that fluoxetine partially substitutes for cocaine as a discriminative stimulus cue in rats (34).

A second hypothesis regarding the fluoxetine-related decrease in cocaine- and G+S-maintained responding is that fluoxetine produced a nonspecific decrease in motor activity, although it was not reflected in eating and drinking behavior in the present experiment. Furthermore, responding on the inactive lever did not differ from baseline when fluoxetine was injected, except for an increase in some animals on the first day of fluoxetine injections. Other studies of drugs that are similar to fluoxetine (e.g., sertraline) suggest that serotonergic compounds specifically alter feeding and drug self-administration (15).

A final hypothesis is that fluoxetine produced a mild illness or malaise and acted as a direct punisher. Alternatively, the specific combination of cocaine and fluoxetine could have been punishing. It has been demonstrated earlier with other experimental designs that cocaine (29) and amphetamine (36) have both positive and negative elements. Fluoxetine (38) and 5-hydroxytryptophan (40) have been shown to produce an aversion to ethanol in rats; however, the ethanol was delivered orally and was not functioning as a reinforcer. Oral morphine consumption was also reduced by zimelidine, another 5-HT uptake inhibitor, and these results may be subject to a taste aversion interpretation (26). However, fluoxetine reduced alcoholic intake in male inpatient alcoholics (16), zimelidine reduced alcohol drinking and increased abstinence in male nondepressed heavy drinkers (24), and fluvoxamine improved episodic memory in patients with alcoholic amnesia (23). In these studies the subjects did not report aversive reactions to the drug treatments.

Aversion conditioning is implied by a slow return to baseline levels of drug intake when the fluoxetine or other treatments are discontinued. Previous studies show a delay of recovery to baseline levels of 1 or 2 days after dietary tryptophan supplements and amphetamine self-administration (28). Others have shown a two-day delay in the recovery of amphetamine self-administration

after fluoxetine treatments were discontinued (37). In the present study, cocaine-reinforced responding returned to baseline rates within the first or second day after fluoxetine treatment was terminated. Thus, it is possible that the suppression in cocaine and G+S self-administration was partially mediated by punishing effects of fluoxetine. Other evidence for an aversive or negative effect due to the combination of psychomotor stimulants with diet- or drug-induced increases in 5-HT is provided in an interesting discussion by Smith and co-workers (28).

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REFERENCES

1. Atrens, D. M.; Ungerstedt, U.; Lyunberg, T. Specific inhibition of hypothalamic self-stimulation by selective re-uptake blockers of either 5-hydroxytryptamine or noradrenaline. Psychopharmacology (Berlin) 52:177–180; 1977.
2. Beardsley, P. A.; Meisch, R. A. A precision drinking device for rats tested with water, etonitazene, and ethanol. Pharmacol. Biochem. Behav. 14:871–876; 1981.
3. Carroll, M. E.; Boe, I. N. Increased intravenous drug self-administration during deprivation of other reinforcers. Pharmacol. Biochem. Behav. 17:563–567; 1982.
4. Carroll, M. E.; France, C. P.; Meisch, R. A. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. J. Pharmacol. Exp. Ther. 217:241–247; 1981.
5. Carroll, M. E.; Lac, S. T.; Nygaard, S. L. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology (Berlin) 97:23–29; 1989.
6. Carroll, M. E.; Lac, S. T.; Walker, M. J.; Kragh, R.; Newman, T. Effects of naltrexone on intravenous cocaine self-administration in rats during food satiation and deprivation. J. Exp. Pharmacol. Ther. 238:1–7; 1986.
7. Carroll, M. E.; Santi, P. A.; Rudell, R. L. A microcomputer system for the control of behavioral experiments. Pharmacol. Biochem. Behav. 14:415–417; 1981.
8. Cazala, P. Effects of Lilly 110140 (Fluoxetine) on self-stimulation behavior in the dorsal and ventral regions of the lateral hypothalamus in the mouse. Psychopharmacology (Berlin) 71:143–146; 1980.
9. Dackis, C. A.; Gold, M. S. Pharmacological approaches to cocaine addiction. J. Subst. Abuse Treat. 2:139–145; 1985.
10. Fletcher, P. J. The effects of d-fenfluramine on saccharin intake and preference and on food and water intake. Pharmacol. Biochem. Behav. 29:687–691; 1988.
11. Friedman, E.; Gershon, S.; Rotrosen, J. Effects of acute cocaine treatment on the turnover of 5-hydroxytryptamine in the rat brain. Br. J. Pharmacol. 54:61–64; 1975.
12. Gawin, F. H. Chronic neuropharmacology of cocaine: Progress in pharmacotherapy. J. Clin. Psychol. 49(Suppl.):11–16; 1988.
13. Gawin, F. H.; Ellinwood, E. H., Jr. Cocaine and other stimulants: Actions, abuse and treatment. N. Engl. J. Med. 318:1173–1182; 1988.
14. Giannini, A. J.; Malone, D. A.; Giannini, M. G.; Price, W. A.; Loiselle, R. H. Treatment of depression in chronic cocaine and phencyclidine abuse with desipramine. J. Clin. Pharmacol. 16: 211–214; 1986.
15. Gill, K.; Filion, Y.; Amit, Z. A further examination of the effects of sertraline on voluntary ethanol consumption. Alcohol 5:355–358; 1988.
16. Gorelick, D. A. Effect of fluoxetine on alcohol consumption. Alcoholism 10:113; 1986.
17. Heel, R. C.; Morley, P. A.; Borgden, R. N.; Carmine, A. A.; Speight, T. M.; Avery, G. S. Zimelidine: A review of its pharmacologic properties and therapeutic efficacy in depressive illness. Drugs 24:169–206; 1982.
18. Katz, R. J.; Carroll, B. J. Intracranial reward after Lilly 110140 (fluoxetine HCl): Evidence for an inhibitory role for serotonin. Psychopharmacology (Berlin) 51:189–193; 1977.
19. Leccese, A. P.; Lyness, W. H. The effects of putative 5-hydroxytryptamine receptor active agents on d-amphetamine self-administration in controls and rats with 5,7-dihydroxytryptamine median forebrain bundle lesions. Brain Res. 303:153–162; 1984.
20. Lyness, W. H. Effect of L-tryptophan pretreatment on d-amphetamine self-administration. Subst. Alcohol Actions/Misuse 4:305–312; 1983.
21. Lyness, W. H.; Friedle, N. M.; Moore, K., E. Increased self-administration of d-amphetamine after destruction of 5-hydroxytryptamine neurons. Pharmacol. Biochem. Behav. 12:937–941; 1980.
22. Lyness, W. H.; Moore, K. E. Increased self-administration of *d*-amphetamine by rats pretreated with metergoline. Pharmacol. Biochem. Behav. 18:721–724; 1983.
23. Martin, P. R.; Adinoff, B.; Bone, G. A. H.; Stapleton, J. M.; Eckardt, M. J.; Linnoila, M. Fluovoxamine (F) treatment of alcoholic chronic organic brain syndromes (COBS). Clin. Pharmacol. Ther. 41:211; 1987.
24. Naranjo, C. A.; Sellers, E. M.; Roach, C. A.; Woodley, D. V.; Sanchez-Craig, M.; Sykora, K. Zimelidine-induced variations in alcohol intake by nondepressed heavy drinkers. Clin. Pharmacol. Ther. 35:374–381; 1984.
25. Reid, L. R.; Wong, D. T.; Threlkeld, P. G. Reduction of food intake with daily administration of a selective inhibitor of serotonin uptake, fluoxetine. Fed. Proc. 45:609; 1986.
26. Rockman, G. E.; Amit, Z.; Borque, C.; Brown, Z. E.; Ogren, S. O. Reduction in voluntary morphine consumption following treatment with zimelidine. Arch. Int. Pharmacodyn. Ther. 244:123–129; 1980.
27. Sinclair, J. D. The feasibility of effective psychopharmacological treatments for alcoholism. Br. J. Addict. 82:1213–1223; 1987.
28. Smith, F. L.; Yu, D. S.; Smith, D. G.; Lecesse, A. P.; Lyness, W. H. Dietary tryptophan supplements attenuate amphetamine self-administration in the rat. Pharmacol. Biochem. Behav. 25:849–855; 1986.
29. Spealman, R. D. Behavior maintained by termination of a schedule of self-administered cocaine. Science 204:1231–1232; 1979.
30. Tennant, F. S.; Rawson, R. A. Cocaine and amphetamine dependence treated with desipramine. In: Problems of Drug Dependence, 1982. National Institute of Drug Abuse Research Monograph, 43 DHHS Pub. No. (ADM) 83-1264. Washington, DC: Supt. of Docs., U.S. Govt. Printing Office; 1983:351–355.
31. Tennant, F. S.; Sagherian, A. A. Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch. Int. Med. 147:109–112; 1987.
32. Tollefson, G. D. Serotonin and alcohol: Interrelationships. Psychopathology 22(Suppl.):1–78; 1989.
33. Weeks, J. R. Long term intravenous infusion. In: Myers, R. D., ed. Methods in psychobiology. vol. 2. London: Academic Press; 1972: 155–168.
34. Winters, T. A.; Slifer, B. L. Discriminative stimulus properties of cocaine. Is there mediation by serotonin? FASEB J. 3:295; 1989.
35. Wise, R. A.; Bozarth, M. A. A psychomotor stimulant theory of addiction. Psychol. Rev. 4:469–492; 1987.
36. Wise, R. A.; Yokel, R. A.; Dewit, H. Both positive reinforcement and conditioned aversion from amphetamine and apomorphine in rats.

Science 191:1273–1274; 1976.
37. Yu, D. S. L.; Smith, F. L.; Smith, D. G.; Lyness, W. H. Fluoxetine-induced attenuation of amphetamine self-administration in rats. Life Sci. 39:1383–1388; 1986.
38. Zabik, J. E.; Binkerd, K.; Roache, J. D. Serotonin and ethanol aversion in the rat. In: Naranjo, C. A.; Sellers, E. M., eds. Research advances in new psychopharmacological treatments for alcoholism. New York: Elsevier; 1985:87–105.
39. Zabik, J. E.; Roache, J. D. 5-Hydroxytryptophan-induced conditioned taste aversion to ethanol in the rat. Pharmacol. Biochem. Behav. 18:785–790; 1983.
40. Zabik, J. E.; Roache, J. D.; Sidor, R.; Nash, J. F., Jr. The effects of fluoxetine on ethanol preference in the rat. Pharmacologist 24:204; 1982.