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Effects of Monoamine Reuptake Inhibitors on Cocaine Self-Administration in Rats

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TELLA, S. R. *Effects of monoamine reuptake inhibitors on cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV **51**(4) 687–692, 1995.—The objective of this study was to investigate the effects of acute administration of monoamine reuptake inhibitors on cocaine self-administration in rats. Pretreatment with GBR 12909 (1–5.6 mg/kg, IV), a dopamine-selective reuptake inhibitor, produced a dose-dependent and large reduction in the self-administration of cocaine (1 mg/kg/infusion). The 3- and 5.6-mg/kg doses of GBR 12909 produced downward shifts in the dose–response curves for cocaine (0.3–3 mg/kg/infusion) self-administration. Unlike GBR 12909, the norepinephrine-selective reuptake inhibitors, desipramine and nisoxetine, at a 10-mg/kg dose produced small, but significant, reductions in the self-administration of cocaine (1 mg/kg/infusion). The 10-mg/kg dose of fluoxetine, a serotonin-selective reuptake inhibitor, produced a small, but not significant, reduction in the self-administration of cocaine. The 10-mg/kg dose of desipramine, nisoxetine, or fluoxetine produced brief respiratory distress and motor abnormalities immediately following IV injections, thereby suggesting that this dose is close to the toxic range for all three drugs. Desipramine, nisoxetine, or fluoxetine at nontoxic doses of 1 and 3 mg/kg had no significant effects on cocaine self-administration. These data indicate that the acute enhancement of endogenous dopaminerigc activity by pretreatment with dopamine reuptake inhibitor reduces the total intake of cocaine, thus supporting the hypothesis that the dopamine is critically involved in the reinforcing properties of cocaine. The data also suggest that the acute enhancements in the endogenous norepinephrine or serotonin systems by nontoxic doses of norepinephrine- or serotonin-selective reuptake inhibitors do not appear to alter the reinforcing properties of cocaine.

Cocaine Self-administration Monoamine reuptake inhibition Dopamine Norepinephrine Serotonin

DOPAMINERGIC activation has been proposed as the major mechanism for reinforcing effects of psychomotor stimulants such as cocaine and amphetamines (21,25,48). Cocaine inhibits the reuptake of dopamine by binding to the dopamine transporter and thus enhances dopaminergic function in central nervous system. However, cocaine at doses that block dopamine reuptake also inhibits the reuptake of other monoamines such as norepinephrine and serotonin and thus enhances their function (24,42,43,47). The roles of central norepinephrine and serotonin systems in cocaine's behavioral effects that are related to its abuse potential are less clearly understood. For example, the manipulation of the endogenous serotonergic system by dietary L-tryptophan loading (7,30) or by neurotoxic lesions of serotonin (28) have been reported to alter the reward value of cocaine as assessed by intravenous self-administration. However, the pretreatments with antagonists of different serotonin receptors such as 5-HT_3 (GR38032F, MDL 72222, ondansetron), 5-HT_2 (ketanserin), and 5-HT_1 and 5-HT_2 (methysergide) have been shown to be ineffective in altering cocaine self-administration (11, 26,38). It has been reported that the adrenoceptor antagonists, phenoxybenzamine or phentolamine (12,46) do not alter cocaine self-administration.

Using drug discrimination testing procedures, it has been reported that neither the adrenoceptor antagonists, prazosin and phentolamine (4,52), nor the serotonin receptor antagonists, ICS 205-930, MDL 72222, ritanserin, and ondansetron (27,34,37), alter the discriminative stimulus properties of co-

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caine. However, substitution studies indicate that desipramine (1,9) and nisoxetine (52) produce partial generalization to cocaine in animals trained to discriminate cocaine from saline, whereas fluoxetine (9,22,32,35,54) does not generalize to cocaine. A pretreatment study indicates that both norepinephrine- and serotonin-selective reuptake inhibitors markedly potentiate the discriminative stimulus effects of cocaine (9). The degree of potentiation produced by fluoxetine and desipramine of the discriminative stimulus effects of cocaine appeared to be equal to that produced by a dopamine-selective reuptake inhibitor, GBR 12909 (9). This may indirectly indicate that in this testing procedure, involving a pretreatment schedule, serotonergic and adrenergic systems are as important as dopaminergic systems in cocaine's behavioral effects. However, it is not clear whether this hypothesis also holds true in a self-administration testing model. Although previous pretreatment studies using norepinephrine-selective reuptake inhibitor, desipramine (14,23,29,36), fail to support such a hypothesis, some of the previous studies (6,45) using serotonin-selective reuptake inhibitor, fluoxetine, reported an alteration in cocaine self-administration. A similar pretreatment study using dopamine-selective reuptake inhibitors to my knowledge has not been reported. The objective of this study was to investigate whether acute pretreatment with various monoamine reuptake inhibitors alters the rewarding effects of cocaine as assessed by intravenous self-administration methods. Such a study may also be of clinical importance in view of the fact that various monoamine reuptake inhibitors are currently being considered or have been proposed for the clinical treatment of cocaine addiction (2,10,15,16,39,51).

METHOD

Subjects and Surgical Procedure

Male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, DE) weighing 360–430 g (at the beginning of the study) were used. The rats were individually housed in a temperature- and humidity-controlled room under a 12L : 12D schedule.

Daily food intake was restricted until body weights gradually stabilized at 80–85% of their free-feeding body weight. The rats were then trained to press a lever for food pellets (45 mg) in standard operant boxes (Med Associates Inc., East Fairfield, VT) equipped with two levers. Responding on one of the levers resulted in reinforcement, while responding on the other lever was recorded but did not result in reinforcement. Rats were initially reinforced on a FR1 schedule and after every 50 such reinforcements, the FR was increased by 1 until FR10 was reached. These food training sessions lasted 60 min. Following the completion of this training, rats were fed their daily food requirement of 20 g standard rat chow as a single meal. After the recovery of their body weight, a small plastic pedestal was surgically mounted on the animal skull using dental cement and stainless steel screws under pentobarbital anesthesia (50–60 mg/kg, IP). This plastic pedestal served as a device to connect to a swivel spring through which external tubing was passed to connect to the venous catheter during experimental sessions. Seven days following the head mount surgery, the animals were implanted with polyvinyl chloride catheters into the femoral or jugular veins under halothane anesthesia (2–3 % in medical grade oxygen). The IV catheter was passed subcutaneously and exited at the midscapular region. Animals were allowed to recover for a minimum of 7 days prior to the initiation of cocaine self-administration sessions.

Cocaine Self-Administration

Animals were placed in operant boxes and the venous catheters were connected to the external tubing which in turn were connected to 10-ml syringes filled with cocaine solution. The syringes were placed in infusion pumps (Pump 22, Harvard Apparatus, South Natick, MA), which were interfaced with the computer. The syringe pump was programmed to deliver cocaine (6.66 mg/ml) solution over 1 s when activated. The infusion volume was appropriately (0.055–0.065 ml) adjusted to each animal to deliver a cocaine dose of 1 mg/kg/infusion. When a change in cocaine dose was required, the concentration of cocaine in syringes was appropriately altered. Access to cocaine was on a FR10 schedule with a 20-s signalled time-out during which responding had no programmed consequence. Self-administration sessions were 2 h in duration and were conducted once daily Monday through Friday. The experimental sessions were controlled by Soft 700 Med PC software (Med Associates Inc.). Experiments with test drugs were performed when rats responded with less than 10% variability form the mean of 3 consecutive control days. Once a stable responding has been achieved, animals were injected with various doses of GBR 12909 (1–5.6 mg/kg, IV), desipramine (1–10 mg/kg, IV), nisoxetine (1–10 mg/kg, IV), fluoxetine (1–10 mg/kg, IV), or their vehicles 5 min prior to the initiation of self-administration sessions.

Drugs

(−)-Cocaine hydrochloride (Mallinkrodt, St. Louis, MO) and desipramine hydrochloride (Sigma Chemical Co., St. Louis, MO) were dissolved in sterile saline, whereas nisoxetine hydrochloride, fluoxetine hydrochloride (Eli Lilly Co., Indianapolis, IN), and GBR 12909 {1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]-4-[3-phnylpropyl]piperazine dihydrochloride} (Research Biochemicals International, Natick, MA) were dissolved in sterile water. Doses are expressed as the salt. Pretreatment drugs were injected IV in a volume of 1 ml/kg.

Data Analysis

The number of cocaine infusions on the test drug days was compared with the total number of infusions on the corresponding preceding control days using analysis of variance (ANOVA) followed by a Tukey test for individual comparisons (59). The time course data was analyzed using ANOVA followed by CONTRASTS for determining individual effects. All the data are expressed as mean ± SE.

RESULTS

Figure 1 shows the effects of various doses of GBR 12909, desipramine, nisoxetine, or fluoxetine on the time course of cocaine infusions (1 mg/kg/infusion) during the 2-h self-administration tests. Pretreatment with GBR 12909 produced a dose-dependent and a large reduction, $F(5, 25) = 18.7, p < 0.001$, in the total number of cocaine infusions. The time course response curves indicate that a significant reduction in the intake of cocaine occurred for the most part of the 2-h session when animals were pretreated with 5.6-mg/kg doses of GBR 12909 (Fig. 1). In view of the large reduction in cocaine intake by GBR 12909, the effects of GBR 12909 were also

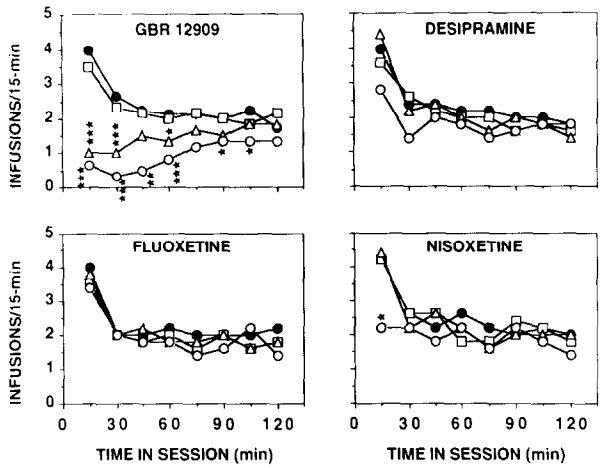

FIG. 1. Effects of GBR 12909, desipramine, nisoxetine, and fluoxetine on the time course of cocaine infusions (1 mg/kg/infusion) during 15-min time blocks of 2-h self-administration sessions. The open squares represent the 1-mg/kg dose, the open triangles represent the 3-mg/kg dose of test drugs, and the open circles represent the 10-mg/kg dose for desipramine, nisoxetine, and fluoxetine and the 5.6-mg/kg dose for GBR 12909. The closed circles indicate a representative control day data. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ compared to the data on corresponding time blocks.

tested against two other doses (0.3 or 3 mg/kg/infusion) of cocaine. Changing the dose of cocaine resulted in a dose-dependent alteration in the number of cocaine infusions self-administered (Fig. 2). When animals were on 3-mg/kg/infusion dose of cocaine, four out of six animals required a daily priming injection of cocaine to initiate the self-administration behavior. Pretreatment with GBR 12909 consistently reduced the total number of cocaine infusions when tested against both 0.3 mg/kg/infusion, $F(5, 20) = 28.31$, $p < 0.001$, and 3 mg/kg/infusion, $F(5, 20) = 40.28$, $p < 0.001$, doses of cocaine. GBR 12909 (3 and 5.6 mg/kg) clearly produced a downward shift in the cocaine dose-response curve (Fig. 2). When a high dose (5.6 mg/kg) of GBR 12909 was tested against cocaine's dose of 3 mg/kg/infusion, two out of six animals convulsed immediately after the first infusion of cocaine, thereby suggesting that this dose combination is toxic to some animals.

The norepinephrine-selective reuptake inhibitors, desipramine, $F(5, 20) = 6.98$, $p < 0.01$, or nisoxetine, $F(5, 20) = 3.31$, $p < 0.05$, at a 10-mg/kg dose produced a small, but significant, reduction in the total number of cocaine infusions. Although the 10-mg/kg dose of fluoxetine, a serotonin-selective reuptake inhibitor, produced a small reduction in the total number of cocaine infusions, this reduction was not statistically significant, $F(5, 20) = 1.64$, $p = 0.19$. At a dose of 10 mg/kg all three of these drugs produced mild and brief respiratory distress and motor abnormalities, thereby suggesting that this dose is close to the toxic range. Therefore, doses greater than 10 mg/kg were not tested in the present study. Examination of the time course of the data indicates that the reduction in cocaine self-administration produced by desipramine and nisoxetine occurred mainly within the first 30 min of the session (Fig. 1). Neither desipramine, nisoxetine, nor fluoxetine when administered at nontoxic doses (1 and 3 mg/kg) altered cocaine self-administration (Fig. 1).

DISCUSSION

There is a large body of evidence indicating that the reinforcing effects of cocaine are due to its ability to block the reuptake of endogenous dopamine leading to enhanced activation of dopamine receptors. A number of previous studies have shown that the pharmacological blockade of dopamine receptors alters cocaine self-administration in a pattern similar to that of reducing the dose of cocaine infused. Following antagonist treatment, the animals respond with increased rates for cocaine self-administration (5,12,13,18,20,50). This increased rate of responding is considered as a compensatory phenomenon in which animals work at higher rates to maintain the desired level of reward. The extrapolation of such an argument would be that the enhancement of endogenous dopamine function may decrease the rate of responding for cocaine self-administration. Consistent with such an analogy are the present findings that the pretreatment with GBR 12909, a dopamine-selective reuptake inhibitor, markedly reduces cocaine self-administration and produces a downward shift in the cocaine dose-response function. This is also consistent with a number of previous substitution studies that GBR 12909 is reliably self-administered by animals that are previously trained to self-administer cocaine (3,17,49). These data are in agreement with the hypothesis that the inhibition of dopamine reuptake plays a main role in cocaine's rewarding properties (25,47).

Unlike GBR 12909, the norepinephrine-selective reuptake inhibitors, desipramine or nisoxetine, at 1 and 3 mg/kg, did not alter cocaine self-administration. However, both desipramine and nisoxetine at a high dose of 10 mg/kg produced a small, but significant, reduction in the intake of cocaine during the 2-h session. However, this dose of desipramine and nisoxetine produced mild respiratory distress and motor abnormalities in animals, thereby suggesting that this dose is close to the toxic range. It is likely that the reductions in the intake of cocaine produced by desipramine and nisoxetine may be due to this mild illness of animals. This may also possibly explain the fact that the reduction produced by a 10-mg/kg dose of desipramine and nisoxetine occurred early in the session. The lack of such reduction throughout the

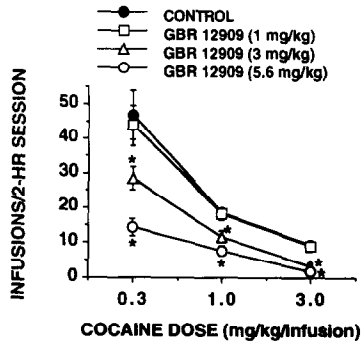

FIG. 2. Effect of pretreatment with GBR 12909 (1-5.6 mg/kg) on the mean number of cocaine infusions for various doses of cocaine in 2-h self-administration tests. Pretreatment with 3 and 5.6 mg/kg, but not 1 mg/kg, doses of GBR 12909 produced a clear downward shift of the cocaine dose-response curve. $n = 6$ for the 1- and 3-mg/kg/infusion doses of cocaine, whereas $n = 5$ for the 0.3-mg/kg/infusion dose of cocaine. $*p < 0.01$ compared to the corresponding control day data.

subsequent portion of the session may be that the animals recovered from the brief illness by this time and then self-administered cocaine at normal rates. Whatever may be the mechanism for reduction at this high dose, acute enhancement of endogenous norepinephrine function by administering nontoxic doses of desipramine or nisoxetine does not appear to alter the reinforcing properties of cocaine. This is consistent with the similar conclusions of previous studies on the effect of desipramine on cocaine self-administration in humans and animals (14,23,29,36). Similarly, it has been reported that adrenoceptor antagonists phenoxybenzamine and phentolamine do not alter cocaine self-administration (12,46). The above findings collectively indicate that the inhibition of norepinephrine reuptake by cocaine may not be critical for its reinforcing properties.

However, a number of previous studies do indicate some involvement of adrenergic mechanisms in cocaine's behavioral effects. For example, on drug discrimination testing, though adrenoceptor agonists and antagonists do not alter the discriminative stimulus properties of cocaine (4,8,52), desipramine (1,9) and nisoxetine (52) have been shown to produce partial generalization to cocaine. Desipramine has been shown to potentiate cocaine's discriminative stimulus properties in rats (9) and has been shown to enhance some of cocaine's behavioral effects in humans (14). Further, cocaine produces complete generalization in animals trained to discriminate nisoxetine from saline (53). Prazosin, an $alpha_1$-adrenoceptor antagonist, has been shown to antagonize both the rate-increasing and rate-decreasing effects of cocaine on responding in pigeons and squirrel monkeys (57). Nisoxetine (58), prazosin (4,53), and idazoxan (19), an $alpha_2$-adrenoceptor antagonist, have all been shown to attenuate the locomotor-stimulant effects of cocaine. It is possible that these experimental studies, implicating adrenergic mechanisms in cocaine's behavioral responses, may be dealing with the reward-related as well as the reward-unrelated responses.

Similar to desipramine and nisoxetine, the serotonin-selective reuptake inhibitor fluoxetine, at 1- and 3-mg/kg doses, did not alter cocaine self-administration. Although fluoxetine at a high dose (10 mg/kg) produced a small reduction in cocaine self-administration in the present study, this reduction was not significant. This small, statistically insignificant reduction produced by the 10-mg/kg dose of fluoxetine may be due possibly to the mild illness produced by this high dose. These findings indicate that the acute enhancement of endogenous serotonin function by administering the reuptake inhibitor fluoxetine at nontoxic doses does not modify the reinforcing properties of cocaine. This is in agreement with a previous report describing the lack of effect of fluoxetine on cocaine self-administration in rats (40). Consistent with this, it has been reported that the acute antagonism of serotonin 5-HT_3 (GR38032F, MDL 72222, ondansetron), 5-HT_2 (ketanserin), and 5-HT_1 and 5-HT_2 receptors (methysergide) by administering appropriate antagonists does not alter cocaine self-administration (11,26,38).

Contrary to the above, there are a number of studies suggesting an inhibitory role for serotonin in cocaine's reinforcing effects. For example, using a progressive ratio schedule of reinforcement it has been reported that the bilateral neurotoxic lesions of the serotonergic system of the median forebrain bundle or amygdala by 5,7-dihydroxytryptamine (28) increase the breaking points, whereas enhancement of endogenous serotonergic function by pretreatment with fluoxetine (45) or L-tryptophan (30) decreases the breaking points. One possible factor for these differences could be the use of two different experimental procedures, such as a fixed ratio in the present study vs. a progressive ratio schedule of reinforcement used by these investigators, and that these two may measure different aspects of cocaine self-administration (31). However, using a fixed ratio schedule, it has been reported that pretreatment with fluoxetine (6) or L-tryptophan (7), unlike the present data, attenuated cocaine self-administration in rats. The treatment schedule in these studies consisted of prolonged administration of drugs for a few days as opposed to the acute single dose administration of fluoxetine used in the present study. Thus, it is possible that the longer treatment schedule used by these investigators may have altered the basal status of some important neuronal functions and thus indirectly influenced cocaine self-administration. The present results are consistent with those of Porrino et al. (40), who used a fixed ratio schedule and acute single dose IP administration of fluoxetine. Thus, it is likely that the length of fluoxetine treatment schedule may be one of the important variables determining the outcome. Consistent with this interpretation are two recent studies reporting a reduction in cocaine intake by treating animals for a few days with serotonin receptor antagonists (33,34). For example, it has been reported that the 5-HT_2 receptor antagonist, ritanserin, reduced the oral self-administration of cocaine when administered SC once daily for 7 days in rats; thus, this drug did not alter cocaine discriminative stimulus properties when administered as an acute single dose (34). Similarly, amperozide, a 5-HT_2 receptor antagonist, when administered SC once daily for 3 days, reduced the oral self-administration of cocaine (33).

On drug discrimination testing, fluoxetine potentiates (9) the discriminative stimulus properties of cocaine, while serotonin receptor antagonists ICS 205-930, MDL 72222, ritanserin, and ondansetron do not alter them (27,34,37). Serotonin reuptake inhibitors do not alter the locomotor effects of cocaine (44), whereas the serotonin receptor antagonists ICS 205-930, MDL 72222, and zacopride inhibit the locomotor effects of cocaine (41,55). However, as pointed out earlier, these experimental procedures may likely be dealing with the responses that are related to reinforcing properties as well as responses that may not be critically important for cocaine's reinforcing properties.

A recent pretreatment study indicates that norepinephrine-, serotonin- and dopamine-selective reuptake inhibitors markedly potentiate the discriminative stimulus effects of cocaine to a nearly equal degree (9). This may indirectly indicate that in this testing procedure, involving a pretreatment schedule, serotonergic and adrenergic systems are as important as dopaminergic systems in cocaine's behavioral effects. However, it is not clear from this study whether this potentiation is due to an enhancement of a specific interoceptive stimulus related to the rewarding property of cocaine or due to an enhancement of some other interoceptive stimuli unrelated to the rewarding property of cocaine. The data from the present study indicate that pretreatment with the dopamine-, but not norepinephrine- and serotonin-selective reuptake inhibitors markedly potentiate the reward property of cocaine as assessed by the self-administration testing. Thus the earlier reported marked potentiation of the discriminative stimulus effects of cocaine by norepinephrine and serotonin-selective reuptake inhibitors (9) may be due to the enhancement of some interoceptive stimuli unrelated to the rewarding property of cocaine. Although these reuptake inhibitors have been reported to transiently elevate the plasma levels of cocaine (56), the magni-

tudes of these elevations do not appear to parallel their abilities to enhance the discriminative stimulus effects of cocaine (9).

In summary, the present data suggest that the acute enhancement of endogenous dopaminergic activity by pretreatment with dopamine-selective reuptake inhibitor dose-dependently reduces cocaine self-administration. The acute enhancement of endogenous noradrenergic and serotonergic systems by selective reuptake inhibitors at nontoxic doses does not alter the reinforcing properties of cocaine. However, norepinephrine-selective reuptake inhibitors, at high doses, produce a small, but significant, reduction in cocaine intake, presumably by causing a mild and brief illness of animals.

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