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Serotonergic Properties of Cocaine: Effects on a 5-HT_2 Receptor-Mediated Behavior and on Extracellular Concentrations of Serotonin and Dopamine

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ESSMAN, W. D., A. SINGH AND I. LUCKI. *Serotonergic properties of cocaine: Effects on a 5-HT_2 receptor-mediated behavior and on extracellular concentrations of serotonin and dopamine.* PHARMACOL BIOCHEM BEHAV **49**(1) 107–113, 1994.—The present study examined the ability of cocaine to produce behavioral and neuropharmacological effects through serotonin (5-HT) systems. Pretreatment with fluoxetine or cocaine potentiated the head-shake response to the 5-HT precursor, 5-hydroxytryptophan (5-HTP; 75 mg/kg), a behavior mediated by the activation of 5-HT_2 receptors. This effect was antagonized by the selective 5-HT_2 receptor antagonist ketanserin (1 mg/kg). In contrast, pretreatment with the selective norepinephrine uptake inhibitor desipramine (10 mg/kg) or the selective dopamine (DA) uptake inhibitor GBR 12909 (32 mg/kg) failed to potentiate the head-shake response. The effects of cocaine on extracellular concentrations of DA and 5-HT in the nucleus accumbens were examined using in vivo microdialysis in a separate group of anesthetized rats. Cocaine (10 mg/kg) increased the extracellular concentrations of DA and 5-HT by 300–350% over baseline levels. Cocaine's ability to increase the head-shake response and to increase extracellular concentrations of 5-HT may be due to its ability to block 5-HT uptake.

Cocaine Head-shake response Microdialysis Serotonin Dopamine 5-HT_2 Receptor

COCAINE binds with high affinity to transporter sites for dopamine (DA), serotonin (5-HT), and norepinephrine (NE) (38–40) and inhibits the uptake of these monoamines into presynaptic neurons (18,41,42). Previous studies investigating the mechanism of action of cocaine have generally ascribed its behavioral effects to the inhibition of DA uptake (20,40). The associated enhancement of dopaminergic neurotransmission has been implicated as a substrate for the reinforcing, psychomotor stimulant, and discriminative stimulus effects of cocaine and is, therefore, considered the principle mediator of cocaine's abuse potential (19).

Metabolic, neuroendocrine, and electrophysiological studies have provided evidence that cocaine can produce distinct neuropharmacological effects through interactions with 5-HT uptake sites (10,11,15,21–23,31), suggesting that cocaine may function as an indirect 5-HT agonist. However, few studies have demonstrated behavioral effects of cocaine that are mediated through serotonergic mechanisms. In general, most studies assessing the interactions between cocaine and 5-HT have examined the ability of 5-HT systems to modulate the reinforcing, discriminative stimulus, or locomotor stimulatory properties of cocaine, behavioral actions thought to be mediated principally by cocaine's effects on DA neurotransmission. For example, enhancement of 5-HT neurotransmission through the administration of the 5-HT precursor L-tryptophan (28) or the 5-HT uptake inhibitor fluoxetine (8,37) have been reported to decrease indices of cocaine self-administration [but see Porrino et al. (35)]. Conversely, depletion of 5-HT by administration of the selective serotonergic neurotoxin 5,7-DHT increases the apparent reinforcing efficacy of cocaine (24). 5-HT systems have also been shown to influence the discriminative stimulus properties of cocaine. Pretreatment with fluoxetine potentiated the discriminative stimulus effects of cocaine in animals trained to discriminate cocaine

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from saline, although fluoxetine did not substitute for the training drug (9). Finally, 5-HT may interact with the psychomotor stimulant properties of cocaine because pretreatment with the selective 5-HT uptake inhibitor sertraline attenuates cocaine-induced hyperactivity (36). Although the results of these studies suggest functional interactions between cocaine and 5-HT systems, they do not demonstrate serotonergic effects of cocaine because they may be due to the modification of DA neurotransmission produced by serotonergic drugs.

Previous experiments have suggested that cocaine can alter extracellular concentrations of 5-HT. Using in vivo microdialysis, Manley and co-workers reported that administration of cocaine through the dialysis probe increased baseline interstitial concentrations of 5-HT in the caudate nucleus and potentiated the enhancement of 5-HT release produced by stimulation of the medial forebrain bundle (26). However, their method was not sufficiently sensitive to measure basal 5-HT levels without cocaine present in the system. Studies examining the effects of cocaine on central monoamines using in vivo voltammetry in freely moving rats have recently reported that cocaine increases extracellular concentrations of 5-HT in the nucleus accumbens (5,6).

The purpose of the present study was to determine whether cocaine directly enhances 5-HT neurotransmission using both a behavioral measure associated with 5-HT receptor activation and by monitoring extracellular concentrations of 5-HT and DA using in vivo microdialysis. First, the effects of cocaine were examined on the head-shaking response, a behavior that is dependent on the enhancement of 5-HT neurotransmission. The head-shaking response is produced by the stimulation of 5-HT_2 receptors, either by 5-HT_2 receptor agonists or by administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) following the administration of 5-HT uptake inhibitors (2,3,14,16,17,25,27). Second, cocaine's effects on the extracellular concentrations of DA and 5-HT in the nucleus accumbens were examined using in vivo microdialysis in anesthetized animals. The results presented here demonstrate that cocaine increases extracellular 5-HT concentrations which have functional consequences in behaving animals.

METHOD

Animals

Male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighed 250–400 g (behavioral studies) or 275–350 g (microdialysis studies) at the time of the experiments. Animals were housed in groups of three in clear polycarbonate cages. Water and food were freely available in the home cage. The rats were maintained on a 12 L : 12 D cycle (lights on: 0700–1900). All of the experiments were conducted during the light phase of the cycle.

Behavioral Procedure

The animals were observed individually, in clear polycarbonate cages (45 × 24 × 20 cm) with the cage floor covered with fresh bedding. Rats were placed in the test cages 10 min prior to drug administration. Rats were pretreated intraperitoneally (IP) with the test compounds or saline followed 15 min later by 5-HTP (75 mg/kg, IP). GBR 12909 was administered 45 min before 5-HTP because of its relatively slow onset of action (9). For antagonism experiments, ketanserin (1 mg/kg, IP) was administered concomitantly with either fluoxetine or cocaine. This dose was selected because it effectively blocks the head-shake response but not behavioral responses mediated by other 5-HT receptors (25). Ten minutes following the 5-HTP injection, each rat was observed for the occurrence of the head-shake response during alternate 10 min periods for 80 min. The head-shake response was defined as a rapid rhythmic shaking of the head in a radial motion, sometimes accompanied by shaking of the forequarters or body. Animals were tested only once with any combination of uptake inhibitor and 5-HTP, but may have been tested twice with different drug combinations.

Microdialysis Procedure

Each rat was anesthetized (350 mg/kg chloral hydrate, IP) and placed in a stereotaxic frame (nose bar: −3.5 mm below interaural zero; David Kopf Instruments, Tujunga, CA). Anesthesia was maintained by supplemental injections of chloral hydrate (100 mg/kg, IP) at approximately 40-min intervals. A CMA 10 microdialysis probe [Bioanalytical Systems, Inc. (BAS), West Lafayette, IN] was implanted with the tip aimed at the nucleus accumbens [coordinates from bregma: AP: +1.7; ML: +1.5; DV: −8.0; derived from Paxinos and Watson (32)]. The microdialysis probes had a 2 mm dialysis membrane, 640 μm in diameter, with a 20,000 molecular weight cutoff. Artificial cerebrospinal fluid (ACSF (mM): 147.0 NaCl; 1.5 $CaCl_2$; 0.9 $MgCl_2$; 4.0 KCl) was perfused through the probe at a flow rate of 0.78 μl/min for the duration of the experiment. Immediately prior to the experiment, the recovery of each probe was determined by placing it in a standard solution of 13.1 nM DA and 11.4 nM 5-HT and comparing the concentrations of the resulting dialysates to this standard. The probe recoveries were used to estimate the in vivo concentrations of DA and 5-HT in the extracellular space.

Microdialysis samples were collected every 20 min following probe implantation. Three baseline samples were collected from each rat at 120, 140, and 160 min after probe implantation. Previous studies suggested that DA and 5-HT extracellular concentrations stabilized prior to these time points. Cocaine (10 mg/kg IP) was injected 2 min 45 s prior to the beginning of the 180-min sample to account for the dead volume in the outflow tube of the microdialysis probe. The first postcocaine sample was collected 180 min following probe implantation, and subsequent samples were collected every 20 min for a period of 140 min after the cocaine injection (i.e., 300 min after probe implantation). Following the experiments, rats were sacrificed and their brains were removed, sectioned with a refrigerated cryostat, and stained to verify probe placements.

Analytical Procedure

Microdialysis samples were immediately analyzed following collection using an HPLC with an electrochemical detector (BAS, West Lafayette, IN). A 5 μl injection loop was connected in series with a C_{18} microbore column (1 × 100 mm) to provide separation of monoamines in small sample volumes. Dialysate concentrations of DA and 5-HT were determined using an LC-4B detector (BAS) with a glassy carbon working electrode set at a potential of +700 mV vs. an Ag/AgCl reference electrode. Mobile phase (75 mM sodium acetate; 0.67 mM EDTA; 1.5 mM sodium dodecyl sulfate (SDS); 13% v/v acetonitrile; 13% v/v methanol; pH to 5.7 using glacial acetic acid) was perfused through the column at a flow rate of 60 μl/min using a flow splitter. This combination of microbore column and mobile phase allowed for the detection of both DA and 5-HT from the same dialysate without the necessity of including uptake inhibitors to artificially elevate baseline

TABLE 1

THE EFFECT OF TREATMENT WITH 5-HTP, FLUOXETINE, OR COCAINE ALONE ON THE HEAD-SHAKE RESPONSE

Treatment (Dose)	*n*	Head Shakes
Saline + saline	8	0.9 ± 0.3
Saline + 5-HTP (75 mg/kg)	11	2.2 ± 0.6
Fluoxetine (10 mg/kg) + saline	8	0.6 ± 0.3
Cocaine (10 mg/kg) + saline	8	1.6 ± 1.1

Values shown are mean ± SEM of the total number of head shakes in four 10-min observation periods during standard tests. ANOVA indicated no significant differences between groups, $F(3, 31) = 1.32; p > 0.28$.

levels. Elution times for DA and 5-HT were approximately 5 and 10 min, respectively. Detection limits for this analytic procedure were approximately 9.8 fmol for DA and 1.7 fmol for 5-HT (detection limits defined as twice baseline).

Statistical Procedure

One-way analyses of variance (ANOVA) were used to compare the total number of head shakes produced by different treatments or to compare the effects of various doses of fluoxetine and cocaine with saline. Follow-up comparisons between saline controls and the other pretreatment groups were made using Dunnett's *t*-test. The ability of ketanserin to antagonize head shakes produced by pretreatment with either fluoxetine or cocaine was analyzed using Student's *t*-test. Estimates of ED_{50} values for fluoxetine and cocaine were made by log-linear regression.

Estimates of the basal extracellular concentrations of DA and 5-HT were made by comparing corrected peak heights to a gradient of peak heights obtained from standard concentrations of DA and 5-HT and are expressed as fmol/5 μl sample. Peak heights from postcocaine dialysates were transformed into percent of the average baseline peak heights and were analyzed using separate repeated measures ANOVAs for DA and 5-HT levels. Comparisons to baseline values of both neurotransmitters were performed using Dunnett's test.

Chemicals

Cocaine HCl and GBR 12909 HCl were purchased from Research Biochemicals Inc. (Natick, MA); dopamine HCl, serotonin creatinine sulfate, 5-hydroxy-l-tryptophan, and desipramine HCl were purchased from Sigma Chemicals (St. Louis, MO); and sodium dodecyl sulfate was obtained from Eastman Kodak Co. (Rochester, NY). Fluoxetine (Eli Lilly Co., Indianapolis, IN), desipramine, and cocaine were dissolved in deionized water. GBR 12909 was moistened with a few drops of Tween 80, diluted with deionized water, and injected as a suspension. All doses were calculated as the weight of the free base.

RESULTS

Head-Shaking Response

Table 1 compares the baseline incidence of head shakes produced by two saline injections to the number of head

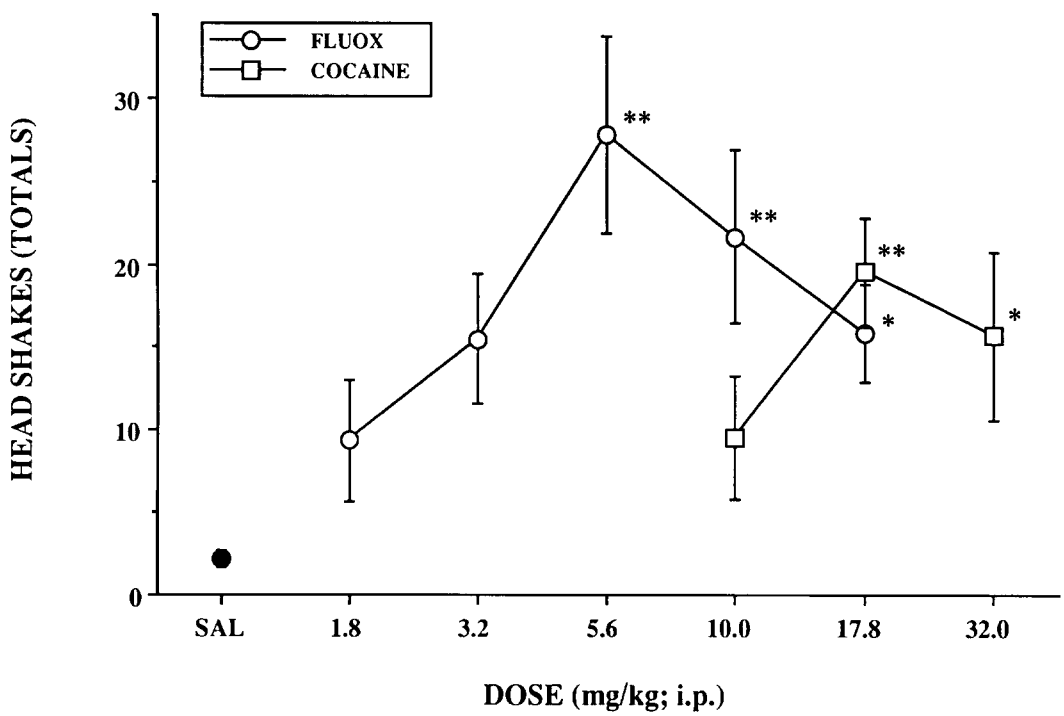

FIG. 1. Potentiation of 5-HTP-induced head shakes by pretreatment with various doses of fluoxetine and cocaine. Values shown are head shakes totals ± SEM for four 10-min observation periods distributed across 80-min test sessions. $N = 11$ rats for the group treated with saline and six rats for the other groups. Asterisks indicate values that were significantly greater than saline-treated controls, according to Dunnett's test: $*p < 0.05$; $**p < 0.01$.

shakes produced by 5-HTP (75 mg/kg) preceded by a saline pretreatment and either fluoxetine or cocaine (10 mg/kg of each drug) followed by saline administration. ANOVA indicated that there were no significant differences between any of these treatments, $F(3, 31) = 1.32, p > 0.28$.

Figure 1 illustrates that the head-shake response was potentiated by pretreatment with various doses of fluoxetine and cocaine given prior to 5-HTP, when compared with the 5-HTP response following saline pretreatment. Fluoxetine was more potent than cocaine, with an estimated ED_{50} of 2.5 mg/kg compared to 10.1 mg/kg for cocaine. Fluoxetine produced a greater maximum number of head shakes than did cocaine, although the difference between these two maxima was not statistically significant.

The elevation in head-shake frequency following fluoxetine and cocaine administration was pharmacologically selective, in that neither desipramine nor GBR 12909 increased the frequency of head shakes (Fig. 2). ANOVA indicated that there were significant differences in the effects of the pretreatment drugs in potentiating the head-shake response, $F(4, 39) = 24.63, p < 0.0001$. Fluoxetine (5.6 mg/kg) and cocaine (17.8 mg/kg) produced a significant increase in the 5-HTP-induced head shakes compared to saline. In contrast, desipramine (10 mg/kg) failed to enhance the head-shake response above saline-treated controls. GBR 12909 (32 mg/kg) was effective in producing psychomotor stimulation (increases in activity, sniffing, and rearing), but did not increase head shakes. Lower doses of GBR 12909 (10 and 16 mg/kg) were also ineffective at producing head shakes (data not shown).

Table 2 shows the effect of pretreatment with the selective 5-HT_2 receptor antagonist ketanserin. Ketanserin (1 mg/kg) significantly attenuated head shakes produced by fluoxetine (5.6 and 10 mg/kg) and cocaine (10 and 17.8 mg/kg) plus 5-HTP.

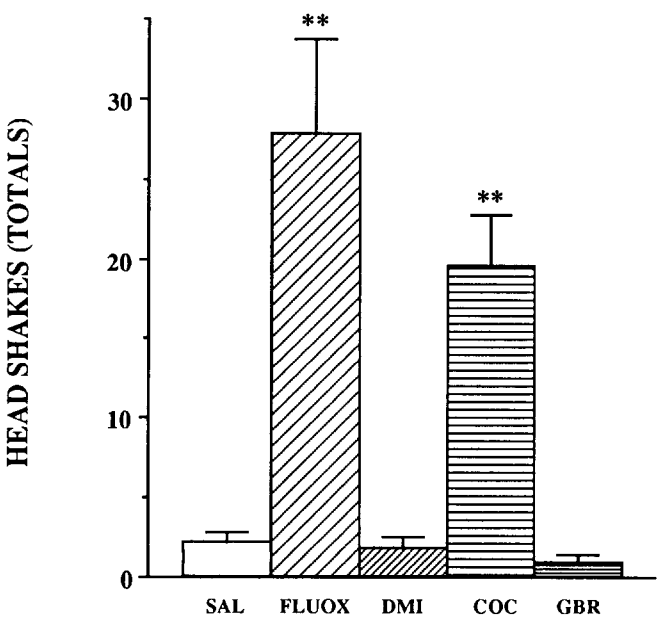

FIG. 2. Head shakes observed following various pretreatments to 5-HTP. SAL: saline (2 ml/kg; $N = 11$); FLUOX: fluoxetine (5.6 mg/kg; $N = 6$); DMI: desipramine (10 mg/kg; $N = 8$); COC: cocaine (17.8 mg/kg; $N = 6$); GBR: GBR 12909 (32 mg/kg; $N = 8$). Values shown are the total number of head shakes observed during the observation period + 1 SEM. Asterisks indicate values that were significantly greater than saline-treated controls, according to Dunnett's test (**$p < 0.01$).

TABLE 2

ANTAGONISM BY THE 5-HT_2 RECEPTOR ANTAGONIST KETANSERIN OF HEAD SHAKES PRODUCED BY FLUOXETINE OR COCAINE WITH 5-HTP

Treatment	n	Head Shakes
Fluoxetine		
Fluoxetine (5.6 mg/kg) + 5-HTP	6	27.8 ± 5.9
+ ketanserin (1.0 mg/kg)	6	0 ± 0*
Fluoxetine (10 mg/kg) + 5-HTP	6	21.7 ± 5.2
+ ketanserin (1.0 mg/kg)	8	0.5 ± 0.4†
Cocaine		
Cocaine (10 mg/kg) + 5-HTP	6	9.5 ± 3.7
+ ketanserin (1.0 mg/kg)	8	0.8 ± 0.4‡
Cocaine (17.8 mg/kg) + 5-HTP	6	19.5 ± 3.3
+ ketanserin (1.0 mg/kg)	6	1.2 ± 0.6†

Values represent total head shakes ± SEM observed over four 10 min observation periods starting 10 min after 5-HTP administration. Ketanserin was administered concomitantly with either fluoxetine or cocaine, followed 15 min later by 5-HTP (75 mg/kg).

Symbols indicate that ketanserin significantly attenuated head shakes compared to those produced by fluoxetine or cocaine plus 5-HTP (Student's unpaired t-test). *$p < 0.001$; †$p < 0.0005$; ‡$p < 0.05$.

Effects of Cocaine on Extracellular Concentrations of DA and 5-HT

Figure 3 shows the effects of 10 mg/kg cocaine on the extracellular concentrations of DA and 5-HT in the nucleus accumbens of anesthetized rats. Basal extracellular concentrations of DA and 5-HT were estimated to be 10.5 ± 1.8 fmol and 1.25 ± 0.1 fmol, respectively. Cocaine administration significantly elevated extracellular concentrations of DA from 60 to 120 min after injection. DA concentrations reached a maximum increase over baseline of 332 ± 71.4% at 80 min following cocaine administration. Cocaine produced a similar effect on extracellular concentrations of 5-HT, which were significantly increased over baseline at 60 min following cocaine administration and remained elevated until the end of the experiment. The maximum increase over the baseline concentration of 5-HT of 307 ± 94.6% occurred at 60 min following cocaine administration.

DISCUSSION

The present experiments demonstrate that systemic administration of cocaine can produce a behavioral response, potentiation of 5-HTP-induced head shakes, that is similar to that produced by the selective 5-HT uptake inhibitor fluoxetine and indicative of the stimulation of 5-HT_2 receptors. Furthermore, cocaine's ability to produce an increase in the extracellular concentrations of 5-HT in the nucleus accumbens, a representative 5-HT terminal region, as shown in the microdialysis experiment, suggests that cocaine's effects in the behavioral experiments were mediated through the blockade of 5-HT uptake.

The 5-HT-mediated head-shake response in rats was se-

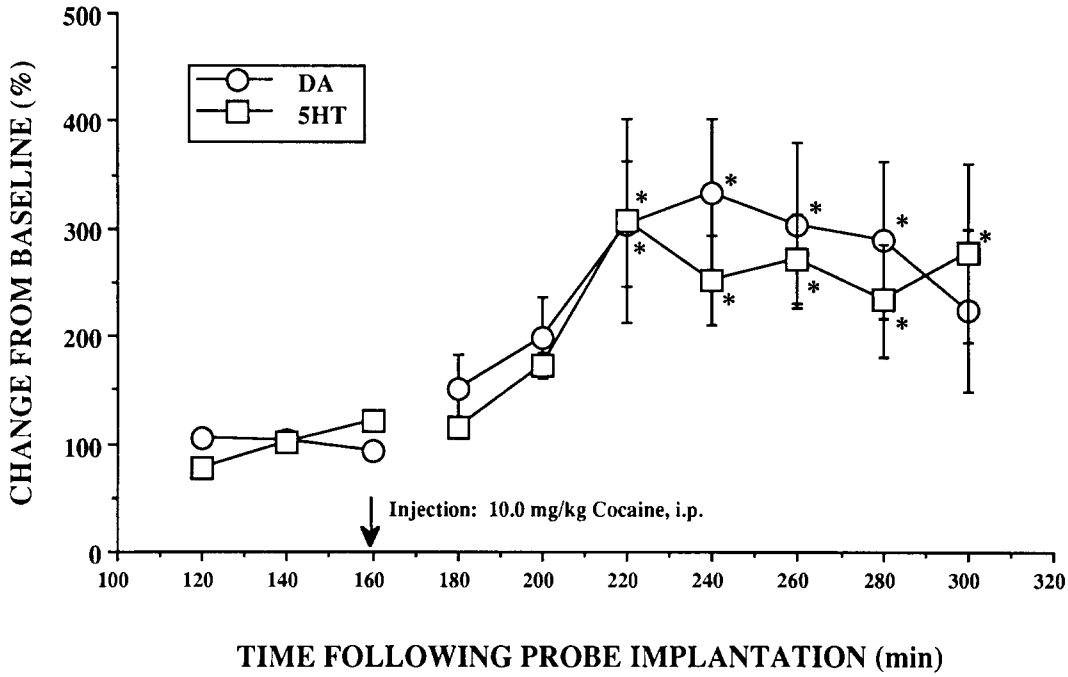

FIG. 3. Effects of cocaine on extracellular concentrations of DA and 5-HT in the nucleus accumbens. Dialysis samples were collected every 20 min following probe implantation. Extracellular concentrations of both DA and 5-HT were estimated concurrently from the same dialysis sample in each rat (n = 5). DA and 5-HT concentrations in the dialysates were expressed as a percentage of baseline levels determined 80–120 min following probe implantation. Asterisks indicate values that differed significantly from baseline, according to Dunnett's test (*$p < 0.05$).

lected for study because it has been well characterized as associated with the activation of 5-HT_2 receptors [for review, see Glennon and Lucki (16)]. Head-shaking behavior is produced by a variety of drugs that commonly activate 5-HT receptors, including 5-HT precursors, 5-HT receptor agonists, and intraventricular administration of 5-HT itself. Furthermore, 5-HT-mediated shaking behavior, but not other forms of head-shaking behavior, is blocked by pretreatment with 5-HT_2 receptor antagonists (2,25,27,30,34) and discriminately altered by lesions of 5-HT neurons (14). The potency of a variety of antagonists for the blockade of head shakes was directly correlated to their affinity at 5-HT_2 receptors, but was unrelated to their potency for dopaminergic, noradrenergic, histaminergic, or cholinergic receptors (30,34). Finally, the time course for the head-shake response following 5-HTP administration is correlated with the elevation in 5-HT levels (3), suggesting that 5-HT_2 receptors are stimulated by the increase in extracellular 5-HT produced by 5-HTP. Studies have suggested that catecholamine systems are not necessary for the production of 5-HT-mediated shaking behavior, because administration of the catecholamine-selective neurotoxin 6-hydroxydopamine did not significantly alter 5-HT-induced head shakes (14), and blockade of DA receptors was not associated with antagonism of the head-shake response (30).

Results from the present experiments are entirely consistent with the hypothesis that cocaine's potentiation of 5-HTP-induced head shakes was due to the stimulation of 5-HT_2 receptors secondary to the blockade of the uptake of 5-HT. The difference in behavioral potency between fluoxetine and cocaine agree with differences in the potency of these drugs to inhibit 5-HT uptake (1). The selective 5-HT_2 receptor antagonist ketanserin was equally effective in antagonizing the head shakes produced by pretreatment of either fluoxetine or cocaine prior to 5-HTP administration, indicating that head shakes were produced through stimulation of 5-HT_2 receptors. Furthermore, neither cocaine nor fluoxetine produced head shakes when administered prior to saline, indicating that neither of these compounds act independently as direct 5-HT_2 receptor agonists. Although cocaine has the ability to inhibit the uptake of DA and NE in addition to 5-HT (3,8,39,40), the inability of the selective NE uptake inhibitor desipramine and the selective DA uptake inhibitor GBR 12909 to facilitate head-shaking behavior supports the necessity of 5-HT uptake blockade in the effects of cocaine on head-shaking behavior. The doses of both desipramine and GBR 12909 used in the present experiments are within a range that is behaviorally active: desipramine (5–20 mg/kg) produces decreases in immobility time in the forced swim test (44), whereas GBR 12909 (32 mg/kg) produced increases in locomotor activity and sniffing in the present experiment, and in other studies (at 20 mg/kg) (43). The present results, therefore, provide strong evidence that cocaine is producing a potentiation of 5-HTP-induced head shakes through serotonergic mechanisms, most likely through the inhibition of the uptake of 5-HT.

In the present study, fluoxetine was slightly, though not significantly, more effective than cocaine in potentiating head shakes. Although the stimulation of catecholamine receptors is not necessary for the production of the head-shaking response in rats (14,30), administration of DA receptor agonists have been reported to attenuate 5-HT-mediated head shakes (2,3). Consistent with this finding, preliminary experiments in this laboratory found that pretreatment with GBR 12909

(32 mg/kg) eliminated head shakes produced by fluoxetine (5.6 mg/kg) and 5-HTP (unpublished results). Other studies in mice reported that cocaine inhibited the head-twitch response produced by the direct 5-HT_2 receptor agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (12,13). Taken together, these results suggest that indirect stimulation of catecholamine receptors by cocaine may serve to modulate head-shaking behavior produced initially through the stimulation of 5-HT_2 receptors.

The present results, indicating that cocaine increases extracellular concentrations of 5-HT, are supported by previous studies examining cocaine's effects on 5-HT systems. These studies have reported that cocaine increases extracellular concentrations of 5-HT both in the caudate-putamen as measured by in vivo microdialysis (26) and nucleus accumbens as measured by in vivo voltammetry following IP or intravenous administration (5,6), although cocaine's effects on DA and 5-HT release may depend on the route of administration (4,5). The profile of 5-HT and DA release after cocaine may be different if studied in combination with 5-HTP administration. The increase in extracellular 5-HT observed following cocaine administration provides a mechanism through which cocaine could potentiate 5-HTP-induced head shakes, and is consistent with the hypothesis that cocaine produces such a potentiation through the inhibition of 5-HT uptake.

Cocaine's ability to produce a behavioral response mediated through an increase in extracellular 5-HT concentrations allows for the possibility that additional behavioral effects of cocaine may be mediated either by the enhancement of 5-HT neurotransmission or by interactions between the serotonergic and dopaminergic properties of cocaine. Although the nucleus accumbens is probably not involved in the head-shake response, it is thought to play a role in several behavioral effects of cocaine, including its ability to produce reinforcing and discriminative stimuli. For instance, the finding that the 5-HT_2 receptor antagonist ritanserin reduces cocaine intake (29) could suggest that the reinforcing stimulus properties of cocaine are influenced by 5-HT receptors. Fluoxetine also potentiates the discriminative stimulus properties of cocaine (9), indicating that 5-HT may be involved in the subjective effects of cocaine. Finally, several amphetamine derivatives have been shown to increase locomotor activity through a 5-HT mechanism (7), suggesting that the hyperlocomotor effects of cocaine may also involve the stimulation of 5-HT receptors. Taken together, these findings, along with the present study, support the role of serotonergic mechanisms in the behavioral actions and the abuse potential for cocaine.

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