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Effects of the serotonin 5-HT_2 antagonist, ritanserin, and the serotonin 5-HT_{1A} antagonist, WAY 100635, on cocaine-seeking in rats

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Abstract

Manipulations of serotonergic systems have been shown to modify many of the behavioral effects of cocaine. It was recently demonstrated that serotonin (5-HT) depletions produced by inhibition of tryptophan hydroxylase reduced cocaine-seeking in an animal model. The present study was designed to determine whether pretreatment with specific 5-HT antagonists might also decrease cocaine-seeking. The effect of pretreatment with the 5-HT_2 antagonist, ritanserin (0.0, 1.0, or 10.0 mg/kg), or the 5-HT_{1A} antagonist, WAY 100635 (0.0, 0.1, 0.3, or 1.0 mg/kg), on cocaine (5.0, 10.0, or 20.0 mg/kg)-produced reinstatement of extinguished drug-taking behavior was measured. Although ritanserin was ineffective, WAY 100635 attenuated cocaine-produced reinstatement in a dose-dependent manner. These effects of WAY 100635 appeared to be specific since responding maintained by saccharin self-administration remained high following pretreatment with 0.3 or 1.0 mg/kg WAY 100635. These data suggest a role of 5-HT_{1A}, but not 5-HT_2, receptors in cocaine-seeking.

Keywords: Cocaine-seeking; Relapse; Serotonin

Recidivism to cocaine abuse occurs in a high percentage of abusers [56] and both preclinical and clinical efforts have been devoted to developing treatments to decrease the high incidence of relapse. Animal models have been developed to establish factors that may precipitate relapse and to assess the effectiveness of potential pharmacotherapies. The reinstatement model, first developed by De Wit and Stewart [12], examines the ability of exposure to drug or non-drug stimuli to reinstate extinguished drug-taking behavior and provides a model of factors that may influence drug-seeking following a period of extinction. Studies have made use of this paradigm in an attempt to determine the mechanisms underlying drug-seeking.

Reinstatement of extinguished cocaine-taking behavior was produced by a number of experimenter-administered drug injections including the indirect dopaminergic agonist, amphetamine [47], the dopamine uptake inhibitors, methylphenidate [46] and GBR 12909 [48], and the cocaine analogs, WIN 35428 and RTI-55 [48]. Caffeine was also effective in reinstating extinguished cocaine-taking behavior [46,49,50,58] which could be mediated through disinhibition of dopamine D_2 receptors produced by caffeine-induced antagonism of adenosine receptors [16,17].

Cocaine-seeking was blocked by D_2 antagonists [54], suggesting a dopaminergic mechanism for drug-produced drug-seeking. Nicotine, morphine, and $^{\Delta}$9-THC, however, failed to reinstate extinguished cocaine-taking behavior [46] even though these drugs increase synaptic dopamine [13,24] through somatodendritic interactions with cholinergic [9], opioid [25], and cannabinoid [20] receptors, respectively. Thus, a drug-produced increase in synaptic levels of dopamine is not always sufficient for the initiation of drug-seeking behavior. Further, these findings raised the possibility that cocaine-seeking may be due, at least in part, to non-dopaminergic mechanisms.

In addition to its ability to block the reuptake of dopamine, cocaine blocks the reuptake of the monoamines, serotonin (5-HT), and norepinephrine [26,42]. There are currently seven 5-HT receptors and 14 structurally and pharmacologically distinct receptor subtypes [2]. The 5-HT_2 receptor is localized in many forebrain regions postsynaptic to serotonergic neurons [28,36]. The 5-HT_{1A}

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receptor is an impulse-regulating autoreceptor located on serotonergic cell bodies in the raphe [53] as well as a post-synaptic receptor located in limbic systems including the hippocampus and amygdala [7].

The effects of pharmacological manipulations of 5-HT_{1A} receptors on cocaine-produced behaviors have been mixed. For example, in one study, cocaine-produced locomotor activation was decreased by prior administration of the 5-HT_{1A} agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT) [40]. In a more recent study [11], however, the effect of this agonist on cocaine-produced motor activation appeared to be dependent on the specific measure. Thus, peripheral activity was increased by pretreatment with 8-OHDPAT, whereas measures of cocaine-produced increases in central and vertical activity were decreased. The discriminative stimulus properties of cocaine, however, were not altered by systemic or intracranial pretreatment with 8-OHDPAT [4,10]. In contrast, self-administration of low doses of cocaine was attenuated by pretreatment with 8-OHDPAT [38].

It was recently demonstrated that depletion of 5-HT via administration of the tryptophan hydroxylase inhibitor, pCPA, decreased cocaine-seeking [55], suggesting that cocaine's ability to enhance synaptic levels of 5-HT may play a role in cocaine-seeking. The specific receptor(s) that may be involved in this effect, however, has not yet been elucidated. The present study sought to determine whether pharmacological antagonism of the 5-HT_2 or 5-HT_{1A} receptors would modulate cocaine-seeking produced by an experimenter-administered injection of cocaine.

1. Method

1.1. Subjects

A total of 57 male Sprague–Dawley rats (Harlan, TX) weighing 325–350 g were used. They were housed individually in hanging polycarbonate cages. The humidity and temperature were controlled and food and water were freely available except during testing. The colony was maintained on a 12:12 h light schedule (lights on at 0800 h) in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care. All experiments were conducted in accordance with the guidelines of the University Laboratory Animal Care Committee of Texas A&M University. Tests were conducted during the light portion and began between 0900 and 1000 h daily.

1.2. Surgery

Rats were implanted with a Silastic catheter in the right jugular vein. Following deep anesthesia produced by separate injections of ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg), the external jugular vein was isolated, the catheter was inserted, and the distal end (22-gauge stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were infused with 0.1 ml of sterile saline solution containing heparin (1.25 U/ml), penicillin G potassium (250,000 U/ml), and streptokinase (8000 U/ml) to prevent infection and the formation of clots and fibroids. The rats were allowed 5 days post-surgery for recovery.

1.3. Apparatus

Self-administration testing was carried out in standard operant chambers (Med Associates, ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in a 0.l-ml intravenous infusion of cocaine HCl dissolved in sterile physiological saline and heparin (3 U/ml). Infusions were of 12.0 s duration. Depression of the other lever (the inactive lever) was without programmed consequence.

Rats were maintained in the animal colony except during testing. Immediately prior to each daily test, the catheter lines were infused with 0.1 ml of the heparin–penicillin–streptokinase solution and the portion of the catheter comprised of stainless steel tubing was connected to a length of microbore tubing that was connected to the syringe. At the end of each test, the lines were again infused with 0.1 ml of the heparin–penicillin–streptokinase solution, the stainless steel tubing was plugged, and the animal was returned to its home cage. Drug delivery and data acquisition were controlled by the OPN software package [52]. Cocaine deliveries were made via mechanical pumps (Razel, Model A with 1 rpm motor equipped with 20.0 ml syringes).

1.4. Training

Acquisition of cocaine self-administration was monitored during daily 2-h sessions. Each session began with an experimenter-delivered infusion of cocaine (0.5 mg kg^{-1} $infusion^{-1}$). Thereafter, depression of the active lever produced automated cocaine infusions according to an FR-1 schedule of reinforcement. The concentration of cocaine was adjusted daily according to body weight for each rat to yield an infusion of 0.5 mg kg^{-1} $infusion^{-1}$. The criterion for acquisition of cocaine self-administration consisted of at least 30 reinforced responses (15.0 mg/kg) during the 2-h session and a ratio of active:inactive lever responses of at least 2:1. Self-administration was considered to be acquired when these criteria were met for 3 consecutive days. Following acquisition, the response requirements were increased to FR-5. Daily 2-h sessions were conducted until there was less than 20% variation in responding on 3 consecutive days. During training, the cocaine infusion was always paired with the illumination of a stimulus light located directly above the active lever.

1.5. Test

Once responding on the FR-5 schedule was stable, the influence of experimenter-administered drug primes upon drug-seeking was measured. During initial tests, the subjects were randomly distributed into each of the 18 treatment groups so that each group was comprised of three to four subjects. Some rats received a second ($n=29$) and third ($n=6$) test to produce final sample sizes for the individual groups of four to six (see Table 1). Interspersed between each test was a minimum of five daily 2-h self-administration sessions during which responding was reinforced according to an FR-5 schedule (0.5 mg kg^{-1} $infusion^{-1}$ cocaine). These five sessions were usually sufficient to reestablish stable responding, as defined by the criteria above.

The reinstatement test was conducted in a single day and consisted of three phases. During all three phases, the light stimulus continued to illuminate according to an FR-5 schedule. The first phase was comprised of a 1-h period of cocaine self-administration (0.5 mg kg^{-1} $infusion^{-1}$, FR-5 schedule of reinforcement) in which the light stimulus was paired with cocaine infusions. After the 1-h self-administration period, the cocaine solution was replaced with saline. During a 3-h extinction phase (phase 2), the light stimulus that had been paired with cocaine was presented with the saline infusion according to an FR-5 schedule.

At the start of the third phase, in which again saline (and the light stimulus) but not cocaine was available, separate groups of animals ($n=4–6$ per group) were pretreated with ritanserin (0.0, 1.0, or 10.0 mg/kg, ip) or WAY 100635 (0.0, 0.1, 0.3. or 1.0 mg/kg, sc) prior to an injection of cocaine HCl (5.0, 10.0, or 20.0 mg/kg, ip). Higher doses of cocaine were not administered since we previously found that an experimenter-administered injection of 40.0 mg/kg was lethal in a high percentage of subjects tested in this paradigm [48]. Ritanserin was administered 20 min prior to cocaine and WAY 100635 was administered 30 min prior to cocaine. The ability of cocaine to elicit drug-seeking, defined as the number of responses made on the lever which previously resulted in the delivery of cocaine, was determined. Responding was monitored for 3 h following the cocaine injection.

1.6. Saccharin self-administration

Since cocaine-produced reinstatement of extinguished cocaine-taking behavior was decreased by pretreatment with WAY 100635 (see Section 2), tests were conducted to determine whether the decrease in responding was specific or represented a generalized inability to perform the lever press operant. For these tests, eight small animal test chambers, identical to those described for the cocaine self-administration tests, were used. Responses on the active lever resulted in a 3-s access to a 0.1-ml dipper located in the center of the front panel 11 cm above the grid floor and recessed into the wall.

When the dipper was activated by a criterion lever response, a light located within the dipper mechanism was illuminated for the 3-s period during which the animal had access to the dipper cup. The saccharin solution was located in a reservoir that was part of the dipper mechanism, and when the dipper was inactivated, the cup lowered into the reservoir and was refilled.

On arrival, rats were acclimated to the laboratory for a minimum of 5 days prior to testing. Initial training sessions for saccharin self-administration were conducted while rats were on a 23-h water deprivation regimen. Test sessions, conducted during several hours of the dark cycle, made use of an autoshaping procedure with each active lever depression reinforced by access to a dipper containing 0.800% (w/v) saccharin solution. When more than 100 responses were produced according to this schedule, rats were placed on ad libitum water in the home cage and responding for saccharin was measured during additional daily tests, as above.

Following the shaping procedure, test sessions were conducted during the light cycle and were restricted to 60-min sessions. Saccharin deliveries were initially made according to an FR-1 schedule of reinforcement. After several days of training, the schedule was increased to FR-5. Training continued until responding on the FR-5 schedule met the following criteria for stability: (1) a minimum of 2 consecutive days with less than 30% daily fluctuation in responding and (2) a minimum of 2:1 active:inactive lever responses.

Once behavior on the FR-5 was stable, the effects of pretreatment with WAY 100635 on responding maintained by 0.800% saccharin (w/v) were determined in separate groups of rats ($n=4$ each). WAY 100635 (0.0, 0.3, or 1.0 mg/kg, sc) was administered in the home cage 30 min prior to the 60-min saccharin self-administration session.

1.7. Drugs

Cocaine HCl (National Institute of Drug Abuse) was dissolved in physiological saline. Ritanserin (RBI-Sigma, St. Louis, MO) was suspended in a 1% methylcellulose solution and WAY 100635 (RBI-Sigma) was dissolved in 0.9% saline. Intravenous infusions were in a volume of 100 μl and intraperitoneal or subcutaneous injections were in a volume of 1.0 ml/kg. All drug weights refer to the salt.

Table 1
Sample sizes

	Dose Ritanserin			Dose WAY 100635		
Dose Cocaine	0	1	10	0.1	0.3	1
5	5	4	4	6	4	6
10	5	5	6	5	5	6
20	5	4	6	6	5	5

1.8. Data analysis

For the reinstatement tests, responses on the lever that had previously resulted in a cocaine infusion were obtained during the 3-h period that comprised Phase 3. The data obtained during each hour following the injection of cocaine were analyzed with a two-way analysis of variance (Dose Ritanserin or WAY 100635 × Dose Cocaine). Main effects and interactions were further analyzed by post-hoc Tukey's tests for multiple comparisons. For the saccharin self-administration tests, a one-way ANOVA (Dose WAY 100635) was conducted on the number of saccharin-reinforced responses during the 60-min self-administration session. All data are expressed as the average number of responses + S.E.M..

2. Results

Fig. 1 shows the effect of pretreatment with the 5-HT_2 antagonist, ritanserin (top panel), and the 5-HT_{1A} antagonist, WAY 100635 (bottom panel), on the reinstatement of extinguished cocaine-taking behavior produced by experimenter-administered cocaine. As we have previously reported [46–48,58], cocaine-produced reinstatement was restricted to the first hour following the injection at the start of Phase 3. Lever responses on the previously inactive lever

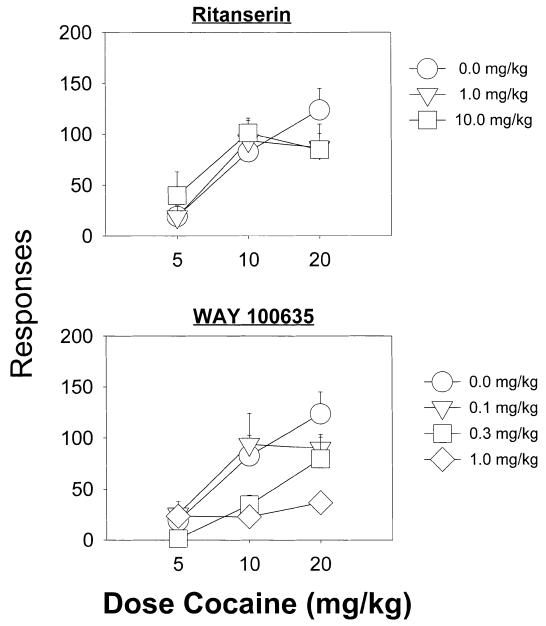

Fig. 1. Effect of pretreatment with ritanserin (top panel) or WAY 100635 (bottom panel) on the number of responses produced following an injection of cocaine at the start of phase 3. Data represent the mean number of responses during hour 1 (+S.E.M.) following extinction of cocaine self-administration in Phase 2. Cocaine produced a dose-dependent reinstatement of extinguished cocaine-taking behavior. Ritanserin failed to alter this effect of cocaine, but pretreatment with WAY 100635 produced a dose-dependent reduction in cocaine-produced cocaine-seeking.

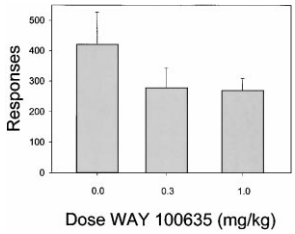

Fig. 2. Effect of pretreatment with WAY 100635 on saccharin self-administration (0.8%, w/v). Pretreatment failed to significantly attenuate responding maintained by saccharin and more than 200 responses were produced during the 1-h session when saccharin served as the reinforcer.

remained low during this test (data not shown). Therefore, only the number of responses on the previously cocaine-associated lever during the first hour of the reinstatement phase is shown.

Cocaine produced a dose-dependent reinstatement of extinguished self-administration behavior in vehicle-pretreated rats ($f(2,12) = 10.858$, $P = .002$). The difference between the effect of 5.0 and 10.0 mg/kg approached significance ($p = .06$) and the difference between 5.0 and 20.0 mg/kg was significant ($P < .01$). Pretreatment with ritanserin failed to attenuate this cocaine-produced effect, but pretreatment with WAY 100635 resulted in a dose-dependent decrease in cocaine-produced reinstatement.

A two-way ANOVA (Dose Cocaine × Dose WAY 100635) revealed a significant main effect of WAY 100635 Dose ($f(3,52) = 6.118$, $P = .001$), Cocaine Dose ($f(2,52) = 13.080$, $P < .001$), and an interaction ($f(6,52) = 2.455$), $P = .036$). Tukey's post-hoc comparisons revealed a significant decrease in the effect of 10.0 mg/kg cocaine produced by 0.3 and 1.0 mg/kg WAY 100635 ($P < .05$) and a significant decrease in the effect of 20.0 mg/kg cocaine produced by 1.0 mg/kg WAY 100635 ($P < .05$).

Fig. 2 shows the effect of WAY 100635 on oral self-administration of saccharin (0.8% w/v). There is a decrease in responding maintained by saccharin, although this decrease was not statistically significant ($f(2,9) = 1.266$, $P = .328$). The average number of responses produced following pretreatment with either dose of WAY 100635 remained high and was greater than the mean number of responses produced during phase 3 of the reinstatement test following extinction of cocaine self-administration (see Fig. 1).

3. Discussion

Cocaine reinstated extinguished cocaine-taking behavior in a dose-dependent manner and this effect was attenuated by pretreatment with the 5-HT_{1A} receptor antagonist, WAY 100635, but not with the 5-HT_2 antagonist, ritanserin. The failure of ritanserin to attenuate cocaine-seeking is not likely due to inadequate dosing since we have previously deter-

mined that a dose of 10.0 mg/kg decreased cocaine-produced locomotor activation [37]. In contrast to the effects of ritanserin, WAY 100635 produced a dose-dependent reduction in cocaine-seeking.

The decrease in cocaine-seeking produced by the lower dose of WAY 100635 (0.3 mg/kg) was surmountable, suggesting that the effect on drug-seeking produced by the 10.0 mg/kg dose of cocaine was not due to a general inability to perform the operant. This was confirmed when the effect of WAY 100635 on responding maintained by saccharin was measured. Although this low dose (0.3 mg/kg) decreased saccharin self-administration, the number of responses produced during the 1-h session was still greater than the number of responses produced during the reinstatement tests. Pretreatment with the higher dose of WAY 100635 (1.0 mg/kg) decreased cocaine-seeking produced by both 10.0 and 20.0 mg/kg cocaine. Higher cocaine doses were not run since we had previously found that they were lethal in a high percentage of rats tested in this paradigm [48]. It was, therefore, not possible to determine whether these effects were surmountable or represented a generalized suppression of lever pressing behavior. This latter possibility is unlikely since saccharin-maintained responding remained high following pretreatment with 1.0 mg/kg WAY 100635.

Interactions between 5-HT and the behavioral effects of cocaine are complex and may be, at least partially, dependent on the behavioral paradigm. Some studies have reported that the influence of 5-HT is inhibitory, whereas others have reported that it is excitatory. For example, pretreatment with the uptake inhibitor, fluoxetine, was reported to decrease cocaine self-administration [5,38], the discriminative stimulus properties of cocaine [51], and cocaine-produced hyperactivity [23]. Pretreatment with compounds specific for 5-HT receptors have, however, indicated that 5-HT_2 [29,34,37,39,45], 5-HT_3 [40,41,54], and 5-HT_4 [31] antagonists also decrease the locomotor-activating effects of cocaine. Antagonists are generally ineffective when tested against the discriminative stimulus properties of cocaine [1,4,30,37] although there have been reports of effects of 5-HT_2 antagonists administered to squirrel monkeys (e.g. see Ref. [44]). One recent study suggested that pretreatment with 5-HT_{1B} receptor agonists enhanced the reinforcing properties of cocaine [35], but another suggested that these compounds attenuated the reinforcing effects of electrical brain stimulation [22].

In the present study, pretreatment with WAY 100635, a potent and selective 5-HT_{1A} receptor antagonist [18,19], decreased cocaine-seeking. The antagonistic effects of WAY 100635 on drug-seeking contrast with the effects of serotonergic manipulations on the maintenance of self-administration. For example, it was shown that increases in synaptic 5-HT via pretreatment with either fluoxetine [5,38] or dietary l-tryptophan loading [6] decreased responding maintained by cocaine. A decrease in cocaine self-administration was also produced by pretreatment with the 5-HT_{1A} receptor agonist, 8-OHDPAT [38]. These findings, coupled with the increase in self-administration produced by neurotoxic lesion of central serotonergic systems [27], suggested that the effects of serotonergic manipulations of the primary reinforcing effects of cocaine were inhibitory. In contrast, the ability of 5-HT depletion [55] or pretreatment with WAY 100635 (present results) to attenuate cocaine-seeking suggests that cocaine-produced increases in 5-HT may produce drug-seeking via activation of 5-HT_{1A} receptor mechanisms.

Of interest, a high density of 5-HT_{1A} receptors is localized in limbic regions, including the amygdala and hippocampus [6]. Both of these structures have been identified as relevant to the expression of learned stimulus/reward associations [3,14,15,43] and the amygdala, in particular, has been implicated in drug-seeking [3,32,33,57]. In abstinent cocaine abusers, presentation of cocaine-associated cues produced reports of cocaine-craving that were correlated with increased regional cerebral blood flow in the amygdala [8,21]. It is, therefore, tempting to speculate that the attenuation of cocaine-seeking produced by pretreatment with WAY 100635 may be due to a blockade of 5-HT_{1A} receptors in this region.

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