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Mixed D_2/5-HT_{2A} Antagonism of Cocaine-Induced Facilitation of Brain Stimulation Reward

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TSIBULSKY, V. L., S. GROCKI, B. A. DASHEVSKY, J. H. KEHNE, C. J. SCHMIDT, S. M. SORENSEN AND R. A. FRANK. *Mixed D_2 /5-HT_{2A} antagonism of cocaine-induced facilitation of brain stimulation reward.* PHARMACOL BIOCHEM BEHAV **59**(2)275–280, 1998.—Previous behavioral, neurochemical and neurophysiological experiments have shown that selective 5-HT_{2A} and mixed D_2/5-HT_{2A} antagonists can attenuate some, but not all, responses to amphetamine. The generality of these findings were determined in the present experiment by assessing the effect of mixed D_2/5-HT_{2A} antagonists on cocaine-induced facilitation of ventral tegmental area self-stimulation in rats. Although amphetamine and cocaine influence activity in monoaminergic neurons through different mechanisms, our previous research has shown that selective D_2 and 5-HT_{2A} antagonists have similar effects on behavioral responses to these psychostimulants. Therefore, we expected a similar pattern of results using mixed D_2/5-HT_{2A} antagonists. As shown previously, cocaine decreased self-stimulation threshold in a dose-dependent manner. Haloperidol and the mixed D_2/5-HT_{2A} antagonists risperidone and MDL 28, 133A antagonized cocaine-induced facilitation of self-stimulation, but only at doses that increased baseline self-stimulation threshold. There was a significant correlation ($r = 0.87$, $p < 0.001$) between antagonist-induced change in baseline threshold and attenuation of cocaine's effect on threshold. Taken together, the results of this and previous experiments support the importance of D_2 receptors in the mechanisms of brain stimulation reward. 5-HT_{2A} receptors appear not to be involved in mediation of both brain stimulation reward and amphetamine- and cocaine-induced facilitation of brain stimulation reward. © 1998 Elsevier Science Inc.

Dopamine Serotonin D_2 receptor 5-HT_{2A} receptor Self-stimulation Ventral tegmental area Amphetamine Cocaine Haloperidol Risperidone MDL 28,133A Rat

ATYPICAL neuroleptics such as clozapine and risperidone exhibit significant antipsychotic activity and a reduced capacity for extrapyramidal side effects (19,25). This profile has been attributed to the ability of these compounds to antagonize both dopamine (DA) and serotonin (5-HT) receptors, and has lead to interest in the ability of serotonin to modulate dopamine function [e.g., (29,46)]. Our previous neurochemical, electrophysiological, and behavioral studies have shown that 5-HT_2 receptor antagonists reverse the effects of psychostimulants on dopamine release and on some of the dopamine-mediated responses like locomotion and the slowing of A_{10} dopaminergic neuron firing, but not others (self-stimulation of the VTA, for example) (26,29). It also appears that 5-HT_{2A} antagonism reverses behavioral effects induced by some psychostimulants, but not others (10). For example, Feldman et al. (1997) found that the mixed D_2/5-HT_2 antagonist MDL 28,133A substantially reduced apomorphine stereotypy, but had no effect on stereotypy produced by amphetamine. Results like these motivated our interest in comparing the effects of mixed antagonists on cocaine and amphetamine because we have recently completed a set of experiments using mixed D_2/5-HT_2 antagonists to reverse the effects of am-

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phetamine (11). In terms of experimental design, the present study with cocaine is the replication of that study with amphetamine.

It is now well established that cocaine administration results in inhibition of dopamine and serotonin reuptake (38,46). Cocaine was 3.3-fold more potent in inhibiting the firing rate of 5-HT neurons compared to DA neurons (9). In anesthetized rats, IP or IV injections of cocaine resulted in a 400% increase of extracellular DA levels in nucleus accumbens and a 200% increase of striatal 5-HT (3). Cocaine-induced DA release in the forebrain correlated with DA-dependent behavior and 5-HT release correlated with 5-HT-dependent behavior (4,5). Repeated cocaine administration resulted in an augmented response to cocaine challenge of both extracellular DA and 5-HT in nucleus accumbens as well as 5-HT in the VTA and dorsal raphe nucleus (30).

The enhancement of dopaminergic neurotransmission has been implicated as a substrate for cocaine's abuse potential. A large body of evidence supports the view that dopaminergic systems play a crucial role in the mechanism of drug reward (16,41,45). The D_2 subtype of DA receptors is involved in rewarding mechanisms in general (2,24) and particularly in psychostimulants' effects on intracranial self-stimulation (4,12).

Few studies have demonstrated a role for serotonergic mechanisms in the rewarding effects of cocaine. Pharmacological manipulations with serotonergic systems have demonstrated that cocaine self-administration is influenced by manipulations of 5-HT neurotransmission. Thus, cocaine self-administration was reduced by dietary L-tryptophan (7,21) or by fluoxetine, a 5-HT reuptake blocker (8,31,37), and facilitated by depletion of forebrain serotonin (20). There is one study that did not find an effect of fluoxetine on cocaine self-administration (33). However, it remains unknown which of more than 10 subtypes of 5-HT receptor are involved in modulation of cocaine's rewarding effects. Although not the topic of the present study, this question remains to be answered even if there is an opinion that the effects of global serotonergic manipulations are not specific in regard to drugs' rewarding effects but are general for any motivated behavior (1,15).

Previous studies have found no evidence that 5-HT_2 receptors are involved in reinforcement mechanisms. The nonselective antihistaminic and 5-HT_2 receptor antagonist cyproheptadine had no effect on self-stimulation (34). The specific 5-HT_{2A} antagonist MDL 100,907 did not affect self-stimulation (11). Two other 5-HT_2 antagonists, ritanserin and ketanserin, did not produce place conditioning (28, 39). Although blockade of 5-HT_2 receptors does not directly influence reward mechanisms, it is possible that 5-HT_2 receptors may be involved in an interaction between DA and 5-HT, especially when the DA system is activated (25,29,46).

The effects of two mixed D_2/5-HT_{2A} antagonists, risperidone (19) and MDL 28, 133A (14) on cocaine-induced facilitation of brain stimulation reward were assessed in the present experiment, and the effects of the mixed antagonists were compared to two compounds with predominantly D_2 antagonist profiles, eticlopride and haloperidol. A comparison of the mixed antagonists and dopaminergic compounds allowed us to evaluate the contribution of 5-HT_{2A} antagonism to the anti-stimulant actions of the mixed antagonists. Although amphetamine and cocaine influence activity in monoaminergic neurons through different mechanisms, our previous research has shown that selective D_2 and 5-HT_{2A} antagonists have similar effects on amphetamine and cocaine-induced facilitation of self-stimulation. Therefore, we expected a similar pattern of results using mixed D_2/5-HT_{2A} antagonists. This would allow us to conclude that the effects of the mixed antagonists on cocaine were related to their D_2, rather than 5-HT_{2A}, activity.

METHOD

Subjects and Surgery

Male Sprague–Dawley rats (Zivic–Miller Labs, Pittsburgh, PA) weighing 450 ± 50 g at the time of surgery were housed individually in stainless steel wire hanging cages. They were maintained on 12-h light–dark cycle (0600–1800, lights on), at 21°C. Food and water were available at all times, except during testing. After 2 weeks of acclimatization, each rat was implanted with bipolar stainless steel electrode (diam. = 0.25 mm, Plastics One, Inc., Roanoke, VA) under sodium pentobarbital anesthesia (65 mg/kg, IP). Electrodes were aimed at the ventral tegmental area (AP = 4.4 from bregma, L = 1.4 from the midline, V = 8.5 mm from skull surface, with the skull flat between bregma and lambda).

Apparatus

Rats were trained and tested in twelve metal and acrylic chambers with an aluminum rod floor. One wall of the chamber had a round hole opening into a small dark chamber containing an infrared, motion detector [see (11) for details]. The computer controlled the train duration of bipolar square pulses (100 HZ, 0.5 ms) delivered to the rats' brains by Grass SD9 simulators. Constant current was maintained using a high-impedance stimulation circuit. Stimulating currents were selected such that train-duration response functions were centered around 40–80 ms (see below).

Drugs

(−)-Cocaine HCl was provided courtesy of National Institute on Drug Abuse and Research Triangle Institute, NC. Risperidone was provided by Janssen Pharmaceutica, Beerse, Belgium, and MDL 28,133A (1-(4-fluorophenyl)-2-[4[(4-methanesulfon-amido-phenyl)carbonyl]-1-piperidinyl]-ethanone hydrochloride) was provided by Marion Merrell Dow, Inc., Cincinnati, OH Haloperidol lactate was obtained from McNeil Pharmaceutical, Spring House, PA. The doses of each drug are shown in Table 1. The cocaine doses were selected to include the lowest doses that consistently produced facilitation of brain stimulation reward, and the highest dose that did not induce stereotypies that interfere with operant responses. Antagonist doses were selected so that they produced a minimal effect on self-stimulation response rates and thresholds when administered alone. All drugs were dissolved in saline.

TABLE 1
DRUGS AND DOSAGE LEVELS

Compound	Doses (mg/kg)	*n*
Cocaine	7.5, 15.0, 30.0	
Haloperidol		
Experiment A	0.075, 0.1, 0.133	12
Experiment B	0.0125, 0.025, 0.0375	22
MDL 28, 133A	5.0, 7.5	10
Risperidone	0.1, 0.2, 0.3	10

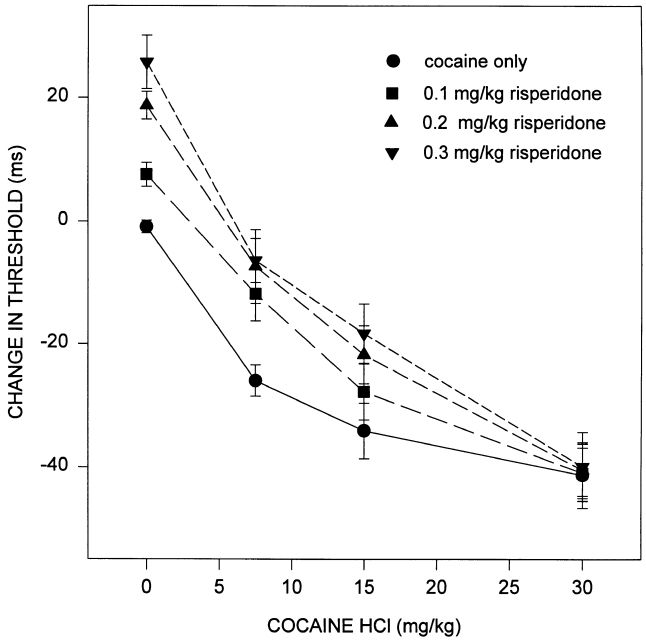

FIG. 1. The effect of risperidone on cocaine-induced decreases in self-stimulation thresholds. Data are shown as mean ± SEM.

Procedure

Subjects were screened for self-stimulation behavior following at least a 10-day, postoperative recovery period [see (11)]. Self-stimulation sessions consisted of 45 trials, with each trial composed of a 15-s warm-up and a 30-s test period followed by 15-s interatrial period. The computers were programmed to randomly vary the stimulation train duration from 0 to 140 ms, resulting in 15 different train durations. Current levels were adjusted so that the train duration that supported 50% of the maximal self-stimulation response rate fell between 40 and 80 ms.

Each experiment started with all animals receiving the three cocaine doses across 3 consecutive days of testing, with the order of doses counterbalanced across animals. Next, randomized combinations of the stimulants and antagonists were evaluated during 3-day blocks of testing separated by 2-day blocks of saline, baseline testing. The cocaine-only injections were repeated once all combinations of cocaine and the antagonist had been administered. Two experiments with haloperidol were performed to increase the range of doses that were tested (Table 1).

Statistical Analysis

To make the results comparable between amphetamine and cocaine, the method of calculation of self-stimulation threshold and drugs effects was exactly like in our previous experiment [see (11)]. Briefly, the average of self-stimulation rates was calculated across the three blocks for each session. Thresholds was defined as the train duration that supported 50% of the mean maximal self-stimulation rate observed for the session. Regression lines plotted for no-drug threshold data of each subject across the course of each experiment were used (a) to determine the variability and the drift of the baseline, (b) to eliminate the influence of the drift on drug effect assessment. Drug effect was defined as the difference between the threshold on the drug-day and the regression line.

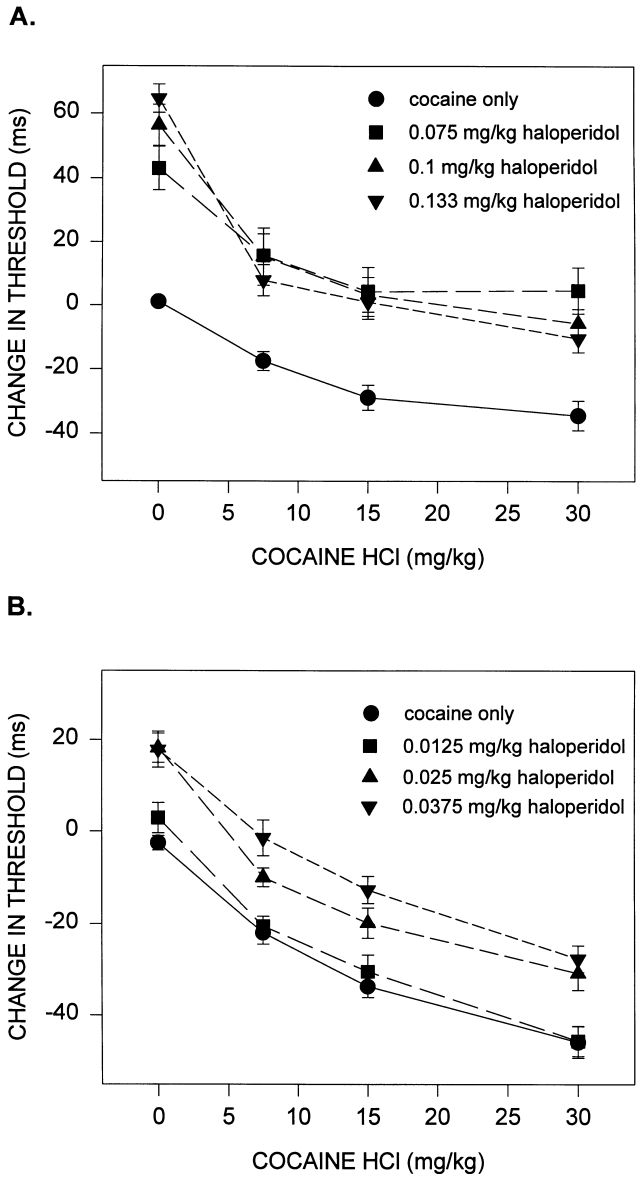

FIG. 2. The effect of haloperidol on cocaine-induced decreases in self-stimulation thresholds. In Experiment A, there was no difference between the effects of three doses of haloperidol collapsed across cocaine doses, $F(2, 136) = 0.029$, $p > 0.9$; ceiling effect. Therefore, doses of haloperidol were decreased in Experiment B. Data are shown as mean ± SEM.

Consistent with our previous experiment there was no evidence for either sensitization or tolerance to cocaine's facilitation effect on self-stimulation threshold (11,43).

Histology

The rats were sacrificed with injection of 130 mg/kg pentobarbital and intracardially perfused with 10% formalin solution. Brains were removed, further fixed, and then frozen and sectioned. Slices (80 μm) were treated as photographic negatives. The location of the electrode tip placements were determined using a stereotaxic atlas (Konig and Klippel, 1963). All

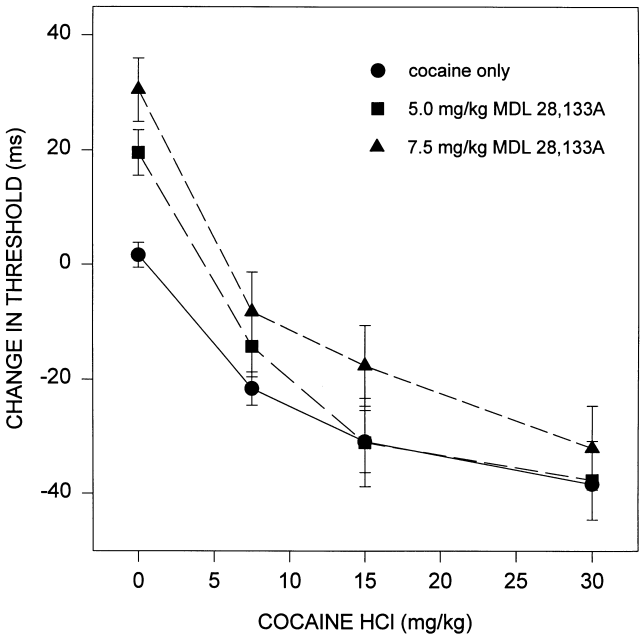

FIG. 3. The effect of MDL 28, 133A on cocaine-induced decreases in self-stimulation thresholds. Data are shown as mean ± SEM.

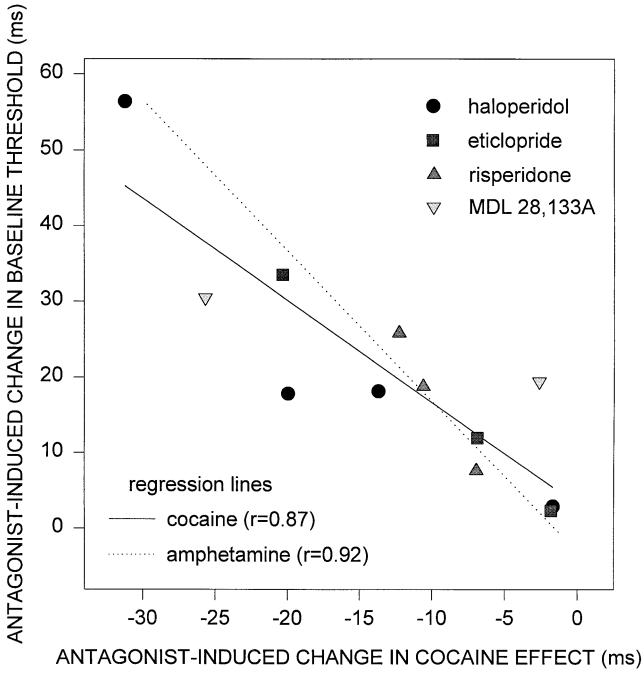

FIG. 4. The relationship between antagonist-induced changes in psychostimulant's effects on self-stimulation threshold and threshold changes induced by administration of the antagonist alone. The data points are for each dose of antagonist collapsed across three doses of cocaine. Dotted line represents the regression line for the antagonism of amphetamine's facilitating effects on self-stimulation threshold [data are taken for comparison from the previous experiment (11)].

placements were found to be along the course of the medial forebrain bundle from the level of the ventral tegmental area to the posterior hypothalamus.

RESULTS

The effects of risperidone, haloperidol and MDL 28,133A on cocaine-induced facilitation of self-stimulation are shown in Fig. 1–3. Analysis of variance (ANOVA) was used to evaluate the drug interactions in each of the experiments. The main effect *F*-ratios for both cocaine and antagonist treatment were significant in all cases (all $p < 0.01$), but no significant interactions between cocaine and the antagonists were observed (all $p > 0.05$).

Parallelism of dose–response curves on Fig. 1–3 suggests that the ability of each antagonist to attenuate cocaine effects is related to its ability to increase the self-stimulation threshold when injected alone. As in the case of amphetamine and for comparison between two psychostimulants, the linear regression analysis was conducted to determine the relationship between the effect produced by each dose of antagonist on the baseline threshold and the attenuation of cocaine-induced facilitation effect (collapsed across doses of cocaine). Data from our recent experiment (43) that examined the same doses of cocaine combined with the specific D_2 antagonist eticlopride (0.01, 0.033, and 0.66 mg/kg, IP) and from experiments with the same antagonists and amphetamine (11) have also been included (Fig. 4). As shown in Fig. 4, the ability of a particular dose of antagonist to attenuate cocaine's effects correlates well with the threshold-increasing effect of that dose. The effects of three highest doses of haloperidol were collapsed because they did not differ (see Fig. 2A). Insufficient number and narrow dose ranges did not allow to compare the slopes of the individual antagonist. However, a single linear function provides an excellent fit to the data for both the D_2 and mixed D_2/5-HT_{2A} antagonists with regression coefficient $r = 0.87$ ($p < 0.05$).

DISCUSSION

Recently, we have shown that the 5-HT_{2A} antagonist MDL 100,907 neither elevated self-stimulation thresholds when administered alone, nor enhanced the ability of the specific D_2 antagonist eticlopride to attenuate amphetamine- or cocaine-induced facilitation of brain stimulation reward (26,43). These findings are consistent with the results obtained in the present experiment. Haloperidol, MDL 28,133A and risperidone produced an equivalent attenuation of the facilitating effect of cocaine on self-stimulation threshold. There was no evidence that the ability of these antagonists to reverse cocaine's effects increased with increasing affinity for the 5-HT_2 receptor. A similar conclusion was also reached in a recently published article that assessed amphetamine-induced facilitation of brain stimulation reward (11).

Several experiments have demonstrated that 5-HT_2 antagonism does not alter the effects of cocaine. Pretreatment with the 5-$HT_{2A/2C}$ antagonist ritanserin or with 5-$HT_{1/2}$ antagonist methysergide did not prevent cocaine-induced locomotor activation (23,36). Ritanserin did not change the stimulus properties of cocaine (23,32) or cocaine-induced decrease in milk consumption (35). The rewarding properties of cocaine do not appear to depend on 5-HT_2 receptor availability. Thus, ritanserin, ketanserin, and cinanserin had no effect on cocaine self-administered intravenously (17,27,31,32,33). Another finding consistent with the idea that 5-HT_2 receptors are not involved in chronic cocaine effects is that the affinity and the number of 5-HT_2 receptors were not changed after chronic cocaine administration in the rat brain (13) and in the brain of chronic cocaine abusers (44). However, there are several ex-

amples of 5-HT_2 antagonism of cocaine effects. Ritanserin virtually eliminated cocaine-induced elevation of plasma ACTH and corticosterone in rats (18) although corticotropin releasing hormone secretion was not affected (6). Another 5-$HT_{2A/2C}$ antagonist cinanserin increased latency to tonic–clonic seizures but did not affect the frequency of cocaine-induced seizures. In addition, it completely eliminated the incidence of status epilepticus and lowered lethality in cocaine-treated rats (40). In contrast to results with intravenous cocaine self-administration, it was shown that ritanserin and another 5-HT_{2A} antagonist amperozide significantly reduced drinking of a cocaine solution without changing total fluid intake (22,23). Taken together, these findings lead to the hypothesis that 5-HT_2 antagonism can affect some peripheral effects of cocaine through the blockade of cocaine-induced activation of the pituitary–adrenal axis.

It is noteworthy that the extrapyramidal and dysphoric side effects of classical neuroleptics are diminished in atypical neurolepitcs that have high affinity for 5-HT receptors. 5-HT_{2a} antagonists have been proposed as a new class of atypical neuroleptics that do not produce the side-effect profile associated with antagonism of the extrapyramidal dopamine system (14,29,42). The failure of 5-HT_{2a} antagonists to reverse the effects of cocaine and amphetamine on brain reward systems suggests that these agents do not affect the regulation of positive affect. If this is true, it would represent another advantage of 5-HT_{2a} antagonists over classical neuroleptic medications.

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