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The 5-HT_3 antagonist Y-25130 blocks cocaine-induced lowering of ICSS reward thresholds in the rat

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Abstract

Serotonin-3 (5-HT_3) receptor antagonists have been shown to attenuate drug-induced increases in mesolimbic dopamine (DA), locomotor activation, and drug self-administration. In the present study, we tested whether the selective 5-HT_3 antagonist Y-25130 would attenuate cocaine-induced lowering of intracranial self-stimulation (ICSS) reward thresholds. Rats ($n=6$) were surgically prepared with bipolar stimulation electrodes and trained to self-administer electrical stimulation delivered to the medial forebrain bundle-lateral hypothalamus (MFB-LH). A discrete-trial, rate-free threshold determination procedure was used to detect pharmacologically induced changes from baseline reward thresholds. Four doses of Y-25130 (0.0, 0.03, 0.3, and 3.0 mg/kg ip) were given alone and in combination with cocaine (4.0 mg/kg ip). Y-25130 did not significantly alter reward thresholds or response latencies when given alone as compared to baseline measures. While there were no significant effects at lower doses, the middle and highest doses of Y-25130 (0.3 and 3.0 mg/kg) did attenuate the threshold-lowering effect of cocaine. These findings suggest that the rewarding effects of cocaine are mediated through 5-HT_3 receptor activity.

Keywords: 5-HT_3 receptors; Cocaine; Y-25130; Brain-stimulation reward

1. Introduction

The rewarding effects of cocaine are mediated in part by elevated dopamine (DA) levels in the mesolimbic system. Activation of serotonin-3 (5-HT_3) receptors has been demonstrated to potentiate DA release in striatal slices via Ca^{2+} dependent mechanisms (Blandina et al., 1988, 1989). 5-HT_3 agonists such as 1-phenylbiguanide have also been shown to increase DA levels in the nucleus accumbens (NACC) in vitro, with the presynaptic DA terminals being the likely candidate for site of action (Chen et al., 1991). Various behavioral studies have also demonstrated that administration of 5-HT_3 agonists increase open-field locomotion, a behavior with putative DA mechanisms (Costall et al., 1987; Gillies et al., 1996).

Blockade of 5-HT_3 receptors attenuates DA levels in the NACC raised by ethanol, morphine, amphetamine, and cocaine (Carboni et al., 1989; Kankaanpää et al., 1996; McNeish et al., 1993) without altering basal mesolimbic DA levels (Imperato and Angelucci, 1989). Additionally, 5-HT_3 antagonists such as ondansetron and tropisetron have been shown to attenuate increases in open-field locomotor activity induced by psychostimulants in both rats (Costall et al., 1987) and mice (Reith, 1990) without producing significant changes in basal locomotor activity. Locomotor activity produced by direct infusions of DA into the NACC is also attenuated by the administration of 5-HT_3 antagonists (Costall et al., 1987). There is also evidence that 5-HT_3 receptors modulate the rewarding effects of cocaine. For instance, 5-HT_3 antagonists block cocaine-induced conditioned place preference (Kankaanpää et al., 2002; Suzuki et al., 1992) and sensitization (King et al., 1997), which suggests that the DA-related rewarding effects of cocaine are at least partly modulated by 5-HT_3 receptors. However, other evidence indicates that 5-HT_3 antagonists do not alter the ICSS threshold-lowering

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effects of cocaine (Montgomery et al., 1993) or cocaine self-administration (Depoortere et al. 1993). Thus, the involvement of 5-HT_3 receptors in the rewarding effects of cocaine remain unclear.

The present study was designed to further characterize the involvement of 5-HT_3 receptor activity in the rewarding effects of cocaine. To accomplish this goal, we examined the effects of a highly selective 5-HT_3 receptor antagonist, Y-25130 (Ohno and Watanabe 1997; Sato et al., 1992), on cocaine-induced reductions in reward thresholds using an intracranial self-stimulation (ICSS) paradigm (Esposito et al., 1978; Maldonado-Irizarry et al., 1994; Ranaldi et al., 1997). Given the high affinity binding of Y-25130 for 5-HT_3 receptors (Sakamori et al., 1992) and the ability of 5-HT_3 antagonists in general to attenuate elevated DA release, we predicted that Y-25130 would diminish cocaine reward. Additionally, it was necessary to ascertain whether Y-25130 would alter reward thresholds when administered alone. Since 5-HT_3 antagonists do not alter basal mesolimbic DA release or locomotor behavior (Costall et al., 1987; Imperato and Angelucci, 1989), we predicted that administration of Y-25130 alone would have no significant effect upon baseline reward thresholds. A rate-free ICSS procedure was used to separate changes in reward from diminished response rate induced by motor impairments that can be caused by some pharmacological agents (for a review, see Kornetsky and Bain 1992).

2. Method

2.1. Subjects

Male Long–Evans rats ($n=6$), purchased at approximately 250 g at the start of the experiment (Charles River Laboratories, Wilmington, MA) were used as subjects. The rats were housed individually in plastic cages with food (Teklad, Harlan, Indianapolis, IN) and water available ad libitum. The illumination in the vivarium was maintained on a 12-h light/dark cycle (lights on at 0700 h) and temperature maintained at 22 °C. All behavioral testing was conducted between 0800 and 1200 h. All animal procedures were approved by the Institutional Animal Care and Use Committee and conducted according to the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 1996).

2.2. Surgery

The rats were anaesthetized with pentobarbital (60 mg/kg) and polyimide insulated stainless steel bipolar electrodes (Plastics One, Roanoke, VA, bare diameter = 0.25 mm) were bilaterally implanted into the medial forebrain bundle-lateral hypothalamus (MFB-LH). The electrodes were anchored permanently to the skull via four stainless steel screws and cranioplastic cement (Plastics One). Bilateral implantation was deemed necessary in order to increase the probability of correct electrode placement. Atropine (0.4 mg/kg ip) was administered 10 min before surgery to minimize bronchial secretions. The following flat-skull stereotaxic coordinates from bregma were used for the electrode placement: AP −2.3, L ±2.6, and V −8.7 from the skull surface at −5°. Following surgery, all rats were given buprenorphine (0.2 mg/kg sc) for postoperative pain management. All rats were allowed at least a 1-week recovery period before behavioral testing began.

2.3. Apparatus

All behavioral testing was conducted in standard operant chambers (31 L × 32 H × 24 W cm). Response wheels were mounted on the walls of the operant chambers. The operant chambers were connected to a laboratory interface (Med Associates, St Albans, VT) controlled by a microcomputer (Gateway 2000, North Sioux City, SD). A constant current stimulator (MED Associates) was responsible for the delivery of biphasic symmetrical square-wave pulses (pulse width = 0.2 ms, frequency = 160 Hz, train duration = 500 ms).

2.4. Procedure

The rats initially received electrical stimulation of the MFB-LH by emitting one-quarter turn of the response wheel. The initial electrode used during the screening procedure was randomly chosen. If the rat was not responsive to the stimulation, or if stimulation-induced side effects appeared (e.g., gross head movements to one side, circling in the operant chamber), the shaping procedure resumed using the contralateral electrode. Once robust wheel-turning behavior was established, the ICSS threshold-determination procedure began.

ICSS thresholds were calculated using a modified psychophysical method of limits paradigm (Esposito et al., 1979; Kornetsky and Esposito, 1981; Kushner et al., 1997; Markou and Koob, 1991). At the start of each trial, a noncontingent stimulation (S_1) was delivered to the rat. The rat then had 7.5 s to turn the response wheel to receive an identical contingent stimulation (S_2). There was a randomized amount of time (between 7.5 and 22.5 s) separating the delivery of the S_2 and a next S_1 (start of next trial), so the rat could not "predict" the next S_1 delivery. To ensure stimulus control, the intertrial interval was reset if the rat responded during this time. A "step" consisted of three trials at a fixed current intensity (microamperes). Two or more responses at a particular current intensity was scored as a "+," whereas one or fewer responses was scored as a "−." The current intensity at the beginning of an ICSS session was set at level above the rat's individual estimated threshold from initial train-

ing. If the rat scored a "+" for the first step, then the current intensity was set 5 μA lower for the next step. The current intensity decreased until the rat scored "−" for two consecutive steps. The current intensity then ascended 5 μA until a "+" was scored for two consecutive steps, then began descending 5 μA again. Each of the four descending and ascending series of current intensities was called a "column." In each column, the midpoint between each "+" and "−" was defined as the "current threshold." Each rat had two ICSS sessions per day, a "warm-up," and a "test" session. Data from the first ICSS test session (warm up session) was discarded, as they were sometimes unreliable. Drug testing was not initiated for an individual rat until the baseline test sessions had a standard deviation of 5 μA or less for a minimum of 5 consecutive days.

2.5. Drugs and drug treatment

Y-25130 (Tocris-Cookson, Avonmouth, Bristol, UK) was dissolved in 0.9% NaCl and stored frozen in 1.0-ml aliquots. Cocaine hydrochloride (Sigma, St. Louis, MO) was dissolved in 0.9% NaCl and made up each week of testing. Following a stable baseline, the four doses of Y-25130 (0.0, 0.03, 0.3, and 3.0 mg/kg ip) were administered in randomized order in combination with either of two doses of cocaine (0.0 or 4.0 mg/kg). All rats received all Y-25130–cocaine combinations. Drug administration took place twice a week (Tuesday and Friday) with three nondrug days interspersed (Monday, Wednesday, and Thursday) and 2 days off (Saturday and Sunday). During days in which drug administration took place, two injections were given between the warm-up and test sessions. The first injection (Y-25130) was given immediately following the warm-up session. The rats were then given an additional injection (cocaine) after a 30-min postinjection interval following the Y-25130 administration. After an additional 5-min postinjection interval, the rats were placed in the operant chambers and the test session began.

2.6. Dependent measures and data analyses

The dependent measures for each rat consisted of mean session current thresholds calculated from all four columns during the ICSS test session. ICSS response latencies at current threshold were used to measure any changes in motor behavior. Baseline current thresholds ranged from 42 to 61 μA. Both current thresholds and response latencies were transformed to z scores based on the mean and standard deviation of five post warm-up baseline sessions that occurred prior to the commencement of drug testing. This was done to control for between subject threshold variability and to control for within subject variability across individual baseline days, thus making possible for more accurate baseline-drug comparisons than simply measuring percent change from baseline. A z score of ±1.96 defined the individual 95% confidence limits for each rat. A two-way repeated measures analysis of variance (ANOVA) was conducted on current thresholds and response latencies with cocaine dose (0.0 and 4.0 mg/kg) and Y-25130 dose (0.0, 0.03, 0.3, and 3.0 mg/kg) both as repeated factors. Student–Newman–Keuls t tests were used for all post hoc analyses.

2.7. Histology

At the conclusion of behavioral testing, all rats were deeply anesthetized with pentobarbital (200 mg/kg ip) and perfused transcardially with 60 ml of 0.9% NaCl followed by 300 ml of 10% formalin solution. The brains were removed from the skull and placed into 30% sucrose/10% formalin solution for at least 1 week. Brains were then sliced at 40 μm on a cryostat microtome. Every other brain slice throughout the electrode placement area was collected for cresyl violet staining. Sections were examined using light microscopy in order to determine electrode placements. Electrode placements for all rats were in the MFB-LH (Fig. 1).

2.8. Results

The three doses of Y-25130 (0.0, 0.03, 0.3, and 3.0 mg/kg ip) administered alone did not significantly alter ICSS reward thresholds as compared to the baseline control thresholds [$F(3,15)=2.3$, $P>.05$] (Fig. 2). Although there appeared to be a trend toward increasing reward thresholds at the highest Y-25130 dose (3.0 mg/kg), planned post hoc comparisons found no statistically significant difference. Cocaine (0.0 and 4.0 mg/kg)

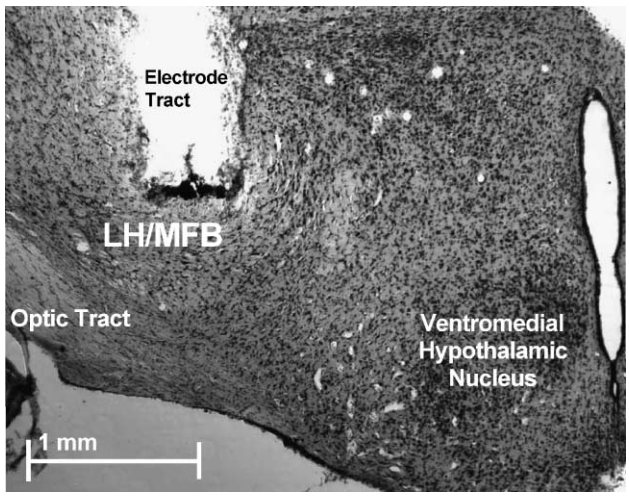

Fig. 1. Representative coronal rat brain section showing electrode placement within the MFB-LH.

produced a significant main effect on ICSS reward thresholds [$F(1,5) = 10.967$, $P < .05$]. There was no significant statistical interaction between cocaine and Y-25130 [$F(3,15) = 1.43$, $P < .05$]. A Student–Newman–Keuls post hoc analysis showed a significant overall difference between 4.0 and 0.0 mg/kg of cocaine irrespective of Y-25130 dose. Additional planned pairwise comparisons showed that cocaine (4.0 mg/kg) was significantly different from baseline ($z = 0.0$) at the lowest Y-25130 dose (0.0 mg/kg) (Fig. 2). Cocaine (4.0 mg/kg) thresholds at the saline Y-25130 dose (0.0 mg/kg) were also significantly lower than thresholds at same cocaine dose combined with the two highest Y-25130 doses (0.3 and 3.0 mg/kg) (Fig. 2). Thus, it appears that higher doses of Y-25130 block the threshold lowering effects of cocaine.

There was also no significant effect of Y-25130 dosage on response latency [$F(3,15) = 0.87$, $P > .05$], indicating that the 5-HT_3 antagonist had no disruptive effects on motor behavior in this paradigm (Fig. 3). The two-way ANOVA showed that cocaine was a significant factor [$F(1,5) = 7.72$, $P < .05$]. However, it is important to note that both saline and cocaine response latencies were well below the 95% confidence limits (±1.96) and subsequent post hoc analysis showed no difference with baseline response latencies. There was no interaction between cocaine and Y-25130 dosage on response latency [$F(3,15) = 1.48$, $P > .05$].

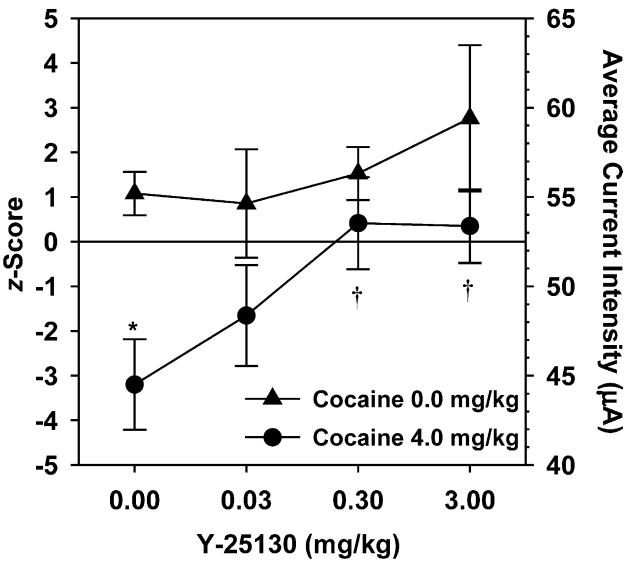

Fig. 2. Effects of cocaine (0.0 and 4.0 mg/kg) on ICSS reward thresholds plotted as a function of Y-25130 dosage. Y-25130 in combination with cocaine (0.0 mg/kg) produced no significant change in ICSS thresholds expressed as mean ± S.E.M. z scores (left y axis) or current intensity (right y axis) compared to baseline ($z = 0.0$; current intensity = 52.6 μA). * Indicates significantly different from baseline at the 0.0 dose of Y-25130, $P < .05$ (Student–Newman–Keuls post hoc analysis). †Indicates significantly different from cocaine (4 mg/kg) combined with Y-25130 (0.0 mg/kg), $P < .05$ (Student–Newman–Keuls post hoc analysis).

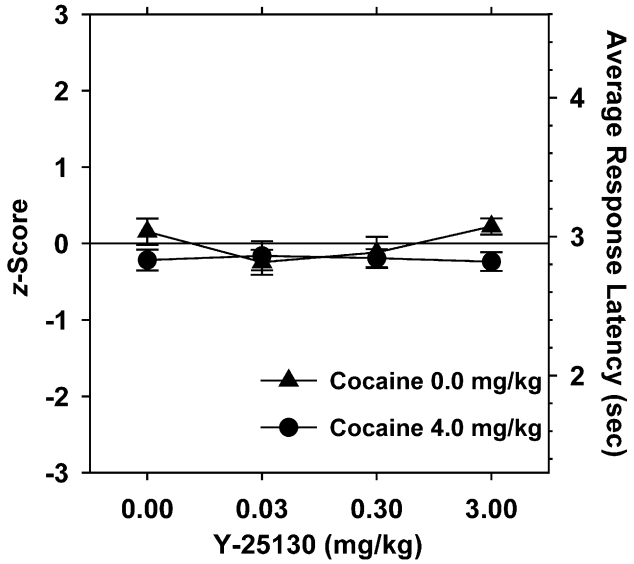

Fig. 3. No significant change in ICSS response latencies expressed as mean ± S.E.M. z scores (left y axis) or current intensity (right y axis) compared to baseline ($z = 0.0$; latency = 2.9 s).

3. Discussion

The initial results demonstrated that the three doses of the 5-HT_3 antagonist Y-25130 (0.03, 0.3, and 3.0 mg/kg) did not significantly elevate reward thresholds when administered alone, as compared to baseline control thresholds. These results indicate that there are no overt aversive effects of Y-25130 administration, although there appeared to be a trend toward increased reward thresholds at the highest dose of Y-25130. Y-25130 also appeared not to disrupt motor performance, based upon the absence of any significant changes in ICSS response latency.

As predicted, 4 mg/kg of cocaine significantly lowered reward thresholds, elevating the "euphoria" induced by baseline electrical stimulation of the MFB-LH. While having no effect at the lowest dose (0.03 mg/kg), Y-25130 significantly attenuated the threshold-lowering effect of cocaine at 0.3 and 3.0 mg/kg. Y-25130 therefore seems to block the rewarding effects of cocaine, possibly by disrupting the DA-releasing actions of presynaptic 5-HT_3 receptor activation in the NACC (Costall et al., 1987; Wozniak et al., 1990).

Previous investigators have examined the effects of other 5-HT_3 antagonists in various brain self-stimulation paradigms (Ivanová and Greenshaw 1997; Montgomery et al., 1993; Rompré et al., 1995). Some of these studies have focused exclusively upon response rate measures rather than on reward thresholds (Borisenko et al., 1996; Herberg et al., 1992; Montgomery et al., 1993). Due to the difficulty in disassociating changes in reward from changes

in performance when looking at ICSS response rates exclusively (Liebman, 1983) it is unclear whether the other 5-HT_3 compounds used in these studies altered "reward" or produced changes in motor performance. Of the studies that did examine the effects of 5-HT_3 antagonists on reward thresholds, granisetron was able to attenuate the threshold-lowering effect of morphine at 0.3 mg/kg, while having no significant effect upon reward thresholds when administered alone (Rompré et al., 1995). Using a rate/frequency analysis to measure reward threshold, ondansetron had no significant effects upon basal ICSS thresholds or the threshold-lowering effect of nicotine (Ivanová and Greenshaw, 1997). Lastly, both granisetron and ondansetron where shown to have no significant effect upon baseline reward thresholds in a rate/frequency curve-shift paradigm. Nor did the 5-HT_3 antagonists attenuate the threshold-lowering effects of cocaine (20 and 10 mg/kg ip) (Hatcher et al., 1995).

The results we obtained with Y-25130 appear to be similar with the effects of granisetron on baseline reward thresholds (Rompré et al., 1995). The absence of a significant effect of Y-25130 upon baseline reward thresholds observed in this study also seems consistent with the results of ondansetron reported in previous studies (Ivanová and Greenshaw, 1997). The dissimilarity between the effects of Y-25130 observed in this study and the effects of ondansetron and granisetron on cocaine-induced lowering of reward thresholds in previous observations may be due to (1) the difference in cocaine doses used (20 mg/kg in previous studies vs. 4 mg/kg in the present study), (2) the different ICSS methodologies used to estimate reward threshold (i.e., rate/frequency curve-shift method vs. the discrete-trial method of limits employed in this study), or (3) different binding affinities between granisetron, ondansetron, and Y-25130, whereby Y-25130 has been demonstrated to have a higher binding affinity to 5-HT_3 receptors than ondansetron, although less affinity than granisetron (Sakamori et al., 1992).

The effects 5-HT_3 antagonists on drug self-administration are varied. 5-HT_3 antagonists such as ondansetron appear to be particularly effective in reducing ethanol and morphine self-administration (Hodge et al., 1993; Hui et al., 1993; Silvestre et al., 1998; Tomkins et al., 1995). However, the effects of 5-HT_3 antagonists on psychostimulant self-administration appear inconsistent with the attenuating effects of these compounds upon psychostimulant-induced locomotion. The vast majority of studies show that 5-HT_3 antagonists fail to significantly alter cocaine self-administration (Depoortere et al., 1993; Lacosta and Roberts, 1993; Peltier and Schenk, 1991). This lack of effect on psychostimulant self-administration, however, is in contrast to some conditioned place preference studies, which have shown disruptive effects of 5-HT_3 antagonists upon acquisition of cocaine place preference (Kankaanpää et al., 2002; Suzuki et al., 1992). The divergence in the results of the conditioned place preference study and the present ICSS results from self-administration studies may be due to a number of factors including (1) the difference in acute dosing versus cumulative dosing that occurs in self-administration studies, (2) difference in the pharmacological time course following the various cocaine administration methods, or (3) the difference in 5-HT_3 antagonist binding specificity, with Y-25130 having a higher receptor binding affinity than ondansetron (Sakamori et al., 1992). It is plausible that ondansetron, which was used in the majority of the cocaine self-administration studies, was ineffective in reducing self-administration due to its binding properties and the comparatively high cocaine doses induced by the cumulative self-dosing procedure. In contrast with cocaine effects, ondansetron has been demonstrated to attenuate robust euphoric effects of acute amphetamine administration in human volunteers (Grady et al., 1996). It is possible that a 5-HT_3 antagonist with higher specificity than ondansetron, such as Y-25130, evenly administered via an osmotic minipump over the course of a session, will attenuate cocaine self-administration.

In conclusion, these results have demonstrated that the 5-HT_3 antagonist Y-25130 may effectively attenuate the ICSS threshold-lowering effect of cocaine. These effects were achieved without any disruptive effects on motor behavior or any significant elevations in reward thresholds when Y-25130 was administered alone, indicating that Y-25130 is potentially nonaversive. Future studies may encompass the effects of Y-25130 on amphetamine-induced changes in MFB-LH ICSS or the effects of Y-25130 on cocaine, amphetamine, or opiate self-administration. Furthermore, this study reopens the question as to the role 5-HT_3 receptors play in psychostimulant reward and reinforcement. It is possible that selective 5-HT_3 antagonists such as Y-25130 could be potential pharmacotherapeutic targets for psychostimulant addiction.

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