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The 5-HT_3 Antagonist Zacopride Attenuates Cocaine-Induced Increases in Extracellular Dopamine in Rat Nucleus Accumbens

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McNEISH, C. S., A. L. SVINGOS, R. HITZEMANN AND R. E. STRECKER. *The 5-HT_3 antagonist Zacopride attenuates cocaine-induced increases in extracellular dopamine in rat nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 45(4) 759–763, 1993.—Pretreatment with the serotonin-3 (5-HT_3) antagonist racemic (±)-Zacopride hydrochloride (ZAC, 0.1 mg/kg, IP) has been previously found to completely abolish the locomotor activity induced by cocaine (10 mg/kg, IP). To determine if this effect was mediated by fluctuations in the extracellular levels of forebrain dopamine (DA), we examined the ability of ZAC to attenuate cocaine-induced increases in extracellular DA levels. Microdialysis samples were collected from the nucleus accumbens region (NAS) of awake, male, Sprague-Dawley rats. ZAC treatment alone (0.1 mg/kg, IP) did not alter DA levels relative to baseline. However, this dose of ZAC given 1 h prior to cocaine challenge (10 mg/kg, IP) caused a 27% reduction in the peak level of extracellular DA produced by cocaine, relative to saline-pretreated control animals. These results suggest that the ability of ZAC to attenuate cocaine-induced increases in extracellular DA levels may contribute to ZAC's ability to suppress cocaine-induced locomotor activity in the rat. However, additional neurochemical mechanisms are likely to be important in mediating the robust behavioral effects previously reported.

Serotonin-3 receptor Zacopride Dopamine release Cocaine Rat Nucleus accumbens Microdialysis

PHARMACOLOGICAL agents that are capable of blocking the effects of drugs of abuse promise to both further illuminate the mechanism of action of abused drugs, and to provide potential clinical therapeutic value. For example, pharmacological agents capable of blocking the reinforcing properties of drugs of abuse, or the cravings associated with abstinence, may have therapeutic value for addicted patients. One approach has been to identify compounds that interact with the mesolimbic dopamine (DA) system, as this neurotransmitter system is thought to play an important role in the brain mechanisms of drug abuse. For example, the ability to increase the extracellular levels of DA in the nucleus accumbens (NAS) has been identified as a common attribute of various drugs of abuse (3,10). More generally, DA changes in the NAS have been proposed to play a critical role in the central mediation of reinforcement and reward (27).

Apparent interactions between the serotonin-3 (5-HT_3) receptor and the DA system have attracted considerable attention. 5-HT_3 receptor antagonists (ICS 205-930 and MDL 72222) have been demonstrated to block the reinforcing properties of morphine and nicotine, as measured by the conditioned place preference test (7). An interaction between 5-HT_3 receptors and DA release in the NAS has been suggested as a possible mechanism of this effect, since the 5-HT_3 antagonist ICS 205-930 has also been reported to dose-dependently reduce the morphine-, nicotine-, and ethanol-evoked increases in extracellular DA concentration in the NAS (6,12,28). In addition, 5-HT_3 receptors are located in the NAS and caudate putamen of rat brain (15), areas richly innervated by the mesolimbic dopamine system. Finally, investigators have reported an increase in extracellular DA levels in the NAS in response to 5-HT_3 agonists such as 2-methylserotonin (13), or phenylbiguanide (8).

Cocaine is a potent psychomotor stimulant drug whose reinforcing and locomotor activity-producing properties are thought to be mediated by changes in DA levels in the NAS [for review see (16)]. Direct evidence links cocaine treatment with elevations of DA in the NAS (4,5,10,20). We and others

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have recently reported that 5-HT_3 antagonists can dose-dependently attenuate the cocaine-induced locomotor activity in mice (21) and rats (25). A dose of 0.1 mg/kg racemic (±)-Zacopride (ZAC) completely prevented the robust locomotor activity normally seen in rats treated with cocaine (10 mg/kg, IP). The interaction of the 5-HT_3 receptor with the DA system provides a plausible mechanism to explain this effect, since the reinforcing and locomotor-stimulating properties of cocaine are thought to involve its ability to increase extracellular DA levels in forebrain areas such as the NAS. Hence, in the present experiment we tested the hypothesis that 0.1 mg/kg of ZAC would reduce the cocaine-induced increase in extracellular DA in the NAS, since this dose of ZAC abolishes the locomotor activity-stimulating properties of cocaine.

METHOD

Microdialysis sample collection was conducted in the NAS region of awake, freely moving rats in order to quantify changes in extracellular concentrations of DA. Twenty-one male, Sprague-Dawley rats (Taconic Farms) weighing 250–350g were maintained on a 12L : 12D cycle (lights on at 7:00 a.m.), and were housed in groups of two with food and water available ad lib. All procedures in this experiment strictly adhered to Federal, State, and University guidelines concerning the use of animals in research. Under general anesthesia (equithesin, 3.3 ml/kg) and using aseptic techniques, stainless steel guide cannulae were stereotaxically implanted above the NAS, at least 24 h prior to the microdialysis experiment. The guide cannulae (22-gauge, thin-wall tubing 10 mm in length) were affixed to the skull with the aid of steel skull screws and dental acrylic cement.

Microdialysis probes were of a concentric design and were constructed in our laboratory according to the procedure of previous investigators (22). Hollow nitrocellulose dialysis fibers (Spectra/Por; Spectrum Medical) were used to produce probes with a dialyzing region 3 mm in length and 250 μm wide, and less than 500 μm wide immediately above the dialysis membrane. In vitro probe recoveries for DA were about 10% when using a perfusion flow rate of 2 μl/min. Approximately 16 h prior to sample collection, rats were briefly anesthetized with ether and the dialysis probe was inserted through the guide cannula into the NAS. Relative to bregma (AP and ML) and skull surface at bregma (DV), and with the incisor bar set at −3.3 mm, the coordinates for the ventral tip of the dialyzing region were: A = +1.0, L = 1.5, D = −8.5. The dorsal part of the dialyzing region (approximately 0.5 mm) was in the ventromedial caudate-putamen, a region that receives its DA input from ventral tegmental area (A10) dopamine neurons, as the NAS does (2). The probe was cemented in place, the rats connected to both a steel spring tether and the inlet perfusion tubing (PE20). The test cage consisted of a glass 10-gallon fishtank with opaque walls (49.2 × 25.4 × 29.5 cm, L × W × H). During the experiment, artificial cerebrospinal fluid (147 mM NaCl, 4 mM KCl, 1.8 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.0 mM NaH_2PO_4, pH 6.0) contained in 2.5-ml gastight Hamilton syringes was continuously perfused through the probes at 2 μl/min by means of a syringe pump (Carnegie Medicin). Samples (40 μl) were collected at 20-min intervals, followed by the addition of 10 μl 0.1 M perchloric acid to each sample to prevent air oxidation of the neurotransmitters. The outlet tubing (fused glass silica) was placed in a microvial that was secured to the spring tether just above the rat's head. Samples were withdrawn from the microvial with 100-μl Hamilton syringes, and refrigerated for up to 12 h prior to assay. At the conclusion of the experiment, rats were sacrificed by overdose with pentobarbital (100 mg/kg, IP). The brains were removed and stored in 10% formalin until sectioning for histological confirmation of probe placement.

Following the collection of about seven baseline microdialysis samples, rats were administered a pretreatment of 0.9% physiological saline (1 ml/kg, IP) or racemic (±)-Zacopride hydrochloride (4-amino-*N*-1-azabicyclo[2.2.2]oct-3-yl-5-chloro-2-methoxy-benzamide hydrochloride hydrate) (0.1 mg/kg, IP). We chose this relatively high dose of ZAC based on the dose–response data obtained in our previous behavioral study [(25); see inset in Fig. 1]. ZAC is a highly potent 5-HT_3 antagonist that generally produces maximal physiological and behavioral effects at doses as low as 0.001 to 0.01 mg/kg [see references cited in (25)]. Lower doses were tested in preliminary studies (see the Discussion section). ZAC was generously supplied by Wyeth-Ayerst (Princeton, NJ). Sixty minutes after the pretreatment, (−)-cocaine (10 mg/kg, IP) was administered (Sigma Chemical Co., St. Louis, MO).

Microdialysis samples were analyzed by high performance liquid chromatography (HPLC) using a dual potentiostat electrochemical detector (BAS 200, W. Lafayette, IN). Samples were injected via a refrigerated autoinjector (CMA 200). The glassy carbon electrodes were set in parallel at applied potentials of 600 mV and 450 mV relative to an Ag/AgCl reference electrode. The mobile phase composition was 50 mM NaH_2PO_4 monobasic, 0.1 mM EDTA, 1 mM SOS, 9.5% methanol, pH 4.0. Mobile phase was delivered at a flow rate of 1.0 ml/min onto a 10 cm × 3.2 mm chromatography column with ODS 3-μm packing (BAS, W. Lafayette, IN). Extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) per 40-μl sample were identified in this assay, and converted to picogram (pg) amounts by comparing the peak heights of these compounds to that of known amounts of standards. Data presented as the percentage of baseline were calculated by comparison to the average of the four baseline samples collected prior to the first injection (defined as 100%). Statistical comparisons were conducted on normalized data using the Mann–Whitney *U*-test for those comparisons identified a priori. Other analyses used one-way and two-way repeated measures analysis of variance (ANOVA) coupled to post hoc means tests (Fisher PLSD).

RESULTS

Administration of ZAC (0.1 mg/kg, IP; $N = 11$) significantly attenuated the increase of extracellular DA levels in the NAS seen following an injection of cocaine (10 mg/kg, IP). Prior to any drug treatment, a two-way ANOVA with repeated measures over time indicated that the groups did not differ, $F(3, 57) = 1.29$, NS, in the amount of DA measured in the 20-min (40 μl) baseline perfusates (combined mean ± SEM = 9.6 ± 1.7 pg). In the group of rats pretreated with saline, the injection of cocaine produced a large increase in the level of extracellular DA that began during the first 20 min postinjection and returned to baseline within 2 h postinjection [Fig. 1; $N = 10$; ANOVA with post hoc comparisons, $F(1, 9) = 23.3$, $p < 0.0001$]. The cocaine-induced increase in DA reached an average of 338 ± 37.2% of baseline DA levels, which corresponded to 25.1 ± 7.8 pg (mean ± SEM) of DA measured in the perfusate sample collected in the first 20 min

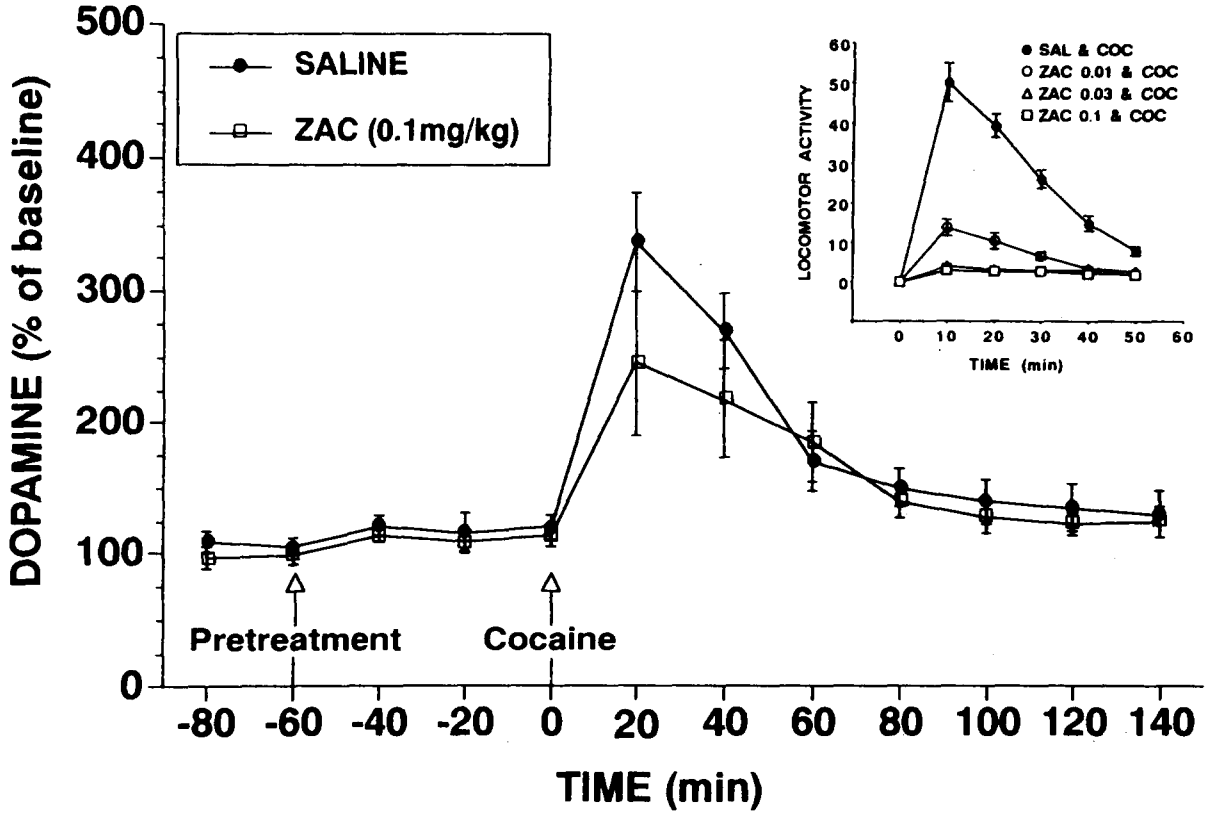

FIG. 1. Cocaine-induced increase in extracellular dopamine in the nucleus accumbens is reduced by Zacopride (ZAC) pretreatment. The difference in the peak increases in DA level between the saline-pretreated group (N = 10) and the ZAC group (N = 11) was significant ($p < 0.05$). Values plotted for DA are group means expressed as the percentage of baseline ± SEM, and represent DA levels collected in 20-min samples that ended at the time points indicated. Inset graph: Data from our previous experiment (25) are presented in the upper right inset. The inset graph illustrates the robust attenuation of locomotor activity in rats receiving 0.1 mg/kg (±)-ZAC IP prior to cocaine challenge. Locomotor activity is expressed as the mean ± SEM number of crossovers that rats made from one quadrant of the observation chamber to another during a 4-min observation period taken every 10 min. N = 12 (saline), N = 6 (0.1 mg/kg ZAC), N = 8 (0.03 mg/kg ZAC), N = 6 (0.01 mg/kg ZAC). In both experiments, the cocaine (coc) dose was always 10 mg/kg, IP.

postinjection of cocaine. On the other hand, in those rats pretreated with ZAC, the peak increase in extracellular DA produced by cocaine was 246 ± 55.2% of baseline (Fig. 1), an increase that was significantly less than that seen in the saline-pretreated rats (Mann-Whitney U-test, $Z = -1.97$, $p < 0.05$). At the second sample collected after cocaine (20 to 40 min postinjection), the difference between the two groups was not quite significant ($p = 0.08$). Note that pretreatment of rats with ZAC alone (0.1 mg/kg, IP) had no effect on basal DA levels during the 60 min prior to cocaine administration (Fig. 1, ANOVA, NS).

The levels of the DA metabolites in the baseline perfusates were: DOPAC = 4901 ± 604 pg, and HVA = 2516 ± 347 pg. Following cocaine treatment, the extracellular levels of these metabolites showed long-lasting decreases. The decrease in DOPAC reached significance at the second postcocaine sample, and leveled off at 15% below baseline for the remaining 2 h sampled [ANOVA with post hoc comparisons: $F(1, 9) = 5.54$, $p < 0.0001$]. Pretreatment with ZAC appeared to block this reduction in DOPAC, but the group × time interaction term in a two-way ANOVA did not reach significance, presumably due to variability in the ZAC group ($p = 0.095$). HVA levels were also slightly decreased by the injection of cocaine (≤8% below baseline), but this decrease did not reach significance (ANOVA, NS). The effect of ZAC pretreatment alone on the DA metabolite levels was to produce small increases (DOPAC increased 12%; HVA increased 21%) that reached significance for both metabolites in the third post-ZAC sample (40 to 60 min postinjection) (ANOVA, $p < 0.05$). The duration of this ZAC effect on the DA metabolites is unknown, as only three samples were collected after ZAC and prior to cocaine. Nonetheless, these data support the idea that 5-HT$_3$ antagonists have similar properties as the DA antagonists drugs (neuroleptics). Thus, both drug classes can antagonize some of the actions of DA, and both drug classes produce increases in extracellular DOPAC and HVA levels, possibly via an increase in intracellular synthesis and metabolism of DA (29). The HPLC assay also allowed measurement of 5-HIAA (a metabolite of serotonin) in the perfusates (mean basal levels ± SEM = 1363 ± 146 pg). Neither ZAC or cocaine treatment produced any significant changes in the extracellular levels of 5-HIAA (ANOVA, NS).

Behavioral observations were also possible since the rats were awake during the drug treatments. However, in our test apparatus, cocaine did not produce reliable increases in locomotor activity in those rats pretreated with saline. Hence, locomotor activity was not further analyzed. A likely explanation for the lack of a reliable cocaine-induced increase in locomotion is the constraints of the present test apparatus, such as the restraint imposed by the tethering system. Most of the rats exhibited stereotyped behaviors (sniffing and head bobbing) following cocaine injection. The treatment groups were not different in their expression of this stereotyped behavior (Mann-Whitney U, $p = 0.62$).

DISCUSSION

The 5-HT_3 antagonist Zacopride has been shown to attenuate cocaine-induced locomotor activity in mice (21) and rats (25). Male rats pretreated with an IP dose of 0.1 mg/kg (±)-ZAC showed virtually no increase in locomotor activity when challenged with cocaine (10 mg/kg, IP) [see inset Fig. 1; data from Svingos and Hitzemann (25)]. The present study found that the neurochemical mechanism by which ZAC pretreatment blocks the cocaine-induced increase in locomotor activity may include ZAC's ability to reduce cocaine-induced increases in extracellular DA level in the NAS. However, the ability of ZAC to completely block cocaine-induced locomotor activity contrasts with ZAC's more modest reduction (27%) of the cocaine-induced increases in extracellular DA in the NAS (see Fig. 1). Therefore, we conclude that an adequate explanation of the attenuation of cocaine-induced locomotor activity by 5-HT_3 antagonists will require the identification of other neurochemical mechanisms, in addition to the effect produced by ZAC on cocaine-evoked increases of extracellular DA in the NAS.

The results of several published studies would lead one to predict a neglible effect of ZAC on cocaine-induced DA levels (1,6,7,18,19). In an electrophysiological model, ZAC failed to alter the cocaine-induced suppression of the discharge activity of A10 DA cells in the VTA, a finding suggesting that ZAC would not influence cocaine's ability to increase extracellular DA levels (1). In other behavioral paradigms, 5-HT_3 antagonists do not block the effects of cocaine. For example, GR38032F, a 5-HT_3 antagonist, does not alter the self-administration of cocaine by rats (19). Similarly, neither ICS 205-930 nor MDL 72222 were found to be capable of preventing the discriminative stimulus properties of cocaine (18). The effects of amphetamine, another psychomotor stimulant, have also been reported to be unaffected by 5-HT_3 antagonists. 5-HT_3 antagonists do not attenuate amphetamine-evoked DA release, nor do they block amphetamine-induced place conditioning when both drugs are administered systemically (6,7). However, another study found that local injection of the 5-HT_3 antagonist GR38032F can inhibit the increase in locomotor activity that occurs after local injection of amphetamine into the NAS (9). Finally, the results presented in the present study are consistent with our preliminary reports of this work in which it was conservatively stated that ZAC did not block the cocaine-induced increases in extracellular DA in the NAS (25,26). These preliminary experiments were conducted using female rats (25,26), and when large effects were not seen we switched to using male rats (data presented here). The experiments with female rats have since been completed (data not shown), and the results support the results obtained with male rats presented herein. Thus, in female rats, pretreatment with a dose of 0.1 mg/kg ZAC produced a 34% reduction in the cocaine-induced peak in extracellular DA levels in the NAS, relative to saline-pretreated controls, $t(9) = -1.98$, $p < 0.05$. Additional female rats pretreated with either 0.01 or 0.03 mg/kg ZAC also did not exhibit a complete block of the cocaine-induced DA changes in NAS.

5-HT_3 antagonists have been shown to block the reinforcing and DA release-inducing properties of morphine, nicotine, and ethanol (6,7,12,28). A plausible mechanism that can parsimoniously interpret most of the available data has been proposed by Carboni and collegues (6). The authors propose that the common factor among the drugs whose reinforcing and DA-releasing properties were diminished by 5-HT_3 antagonists was those drugs' ability to increase the electrical discharge activity of DA cells in the midbrain. Thus, only the effects of those drugs (e.g., nicotine, morphine, and ethanol) that increase extracellular DA levels via their ability to increase the discharge rate of the DA neurons can be antagonized by 5-HT_3 antagonists. The relevant 5-HT_3 receptors could be located either on the midbrain DA cell bodies, or presynaptically on the DA terminals in the forebrain. However, this proposed mechanism cannot readily interpret the effect of 5-HT_3 antagonists on cocaine-induced locomotor activity, since cocaine induces increased extracellular DA via its ability to block reuptake of DA from the synaptic cleft (23), which subsequently results in a suppression of DA cell firing (11). Multiple mechanisms may be required to explain all of the effects of the 5-HT_3 antagonists in animal models of drug abuse.

Thus, the mechanism by which ZAC attenuates cocaine-induced increases in locomotor behavior remains to be elucidated. Our findings suggest that this robust behavioral observation is not solely mediated by the modest reduction of cocaine-evoked increases of extracellular dopamine levels in the NAS produced by ZAC pretreatment. The effect of 5-HT_3 antagonists on cocaine-induced locomotor activity could certainly involve additional neurotransmitters and/or brain structures. In addition to its effects on DA, cocaine is known to block the reuptake of the monoamine neurotransmitters serotonin (24) and norepinephrine (23) [for review see (16)]. Cocaine-induced changes in the extracellular levels of either serotonin or norepinephrine could be involved in the effects of 5-HT_3 antagonists on cocaine-induced locomotor behavior. Finally, in addition to the NAS, other brain areas are undoubtedly part of the central circuitry mediating the reinforcement and locomotor behavior induced by psychomotor stimulants. For example, the hippocampus and amygdala project to the NAS, and are thought to be part of the pathway regulating the locomotor activity caused by psychomotor stimulants (14,17). High densities of 5-HT_3 receptors are located in both the hippocampus and amygdala (15) and, hence, 5-HT_3 antagonists could alter cocaine-induced locomotor activity via these receptors. Further studies are necessary to determine the precise mechanism by which ZAC is able to block cocaine-induced locomotion.

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