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5-HT_3 Receptor Antagonists Do Not Modify Cocaine Place Conditioning or the Rise in Extracellular Dopamine in the Nucleus Accumbens of Rats

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CERVO, L., L. POZZI AND R. SAMANIN. *5-HT_3 receptor antagonists do not modify cocaine place conditioning or the rise in extracellular dopamine in the nucleus accumbens of rats.* PHARMACOL BIOCHEM BEHAV **55**(1) 33–37, 1996.—Three 5-HT_3 receptor antagonists, MDL 72222, tropisetron, and ondansetron were studied for their ability to modify the conditioned place preference (CPP) induced by 10 mg/kg IP cocaine in rats. MDL 72222 (0.03–3 mg/kg SC) and tropisetron (0.01–0.1 mg/kg SC) administered, respectively, 30 min and 1 h before each conditioning session, did not affect the acquisition of cocaine CPP. Ondansetron (0.01–0.1 mg/kg SC) administered 30 min before each conditioning session or just before testing likewise had no effect. At 0.1 mg/kg SC ondansetron did not modify the increase of extracellular dopamine caused by 10 mg/kg cocaine in the nucleus accumbens. The results suggest that 5-HT_3 receptor antagonists have no effect on the rewarding properties of cocaine or on the behaviour elicited by the stimuli previously associated with the drug's action.

Cocaine Conditioned place preference 5-HT_3 receptor antagonists MDL 72222 Tropisetron Ondansetron Rat

VARIOUS drugs of abuse preferentially increase the extracellular concentrations of dopamine (DA) in the nucleus accumbens (11) and this effect is believed to mediate their reinforcing properties (11,15,26).

Carboni et al. (5–7) found that 5-HT_3 receptor antagonists blocked morphine- and nicotine-induced increases of extracellular DA in the nucleus accumbens and their ability to induce conditioned place preference (CPP), a model commonly used for studying the reinforcing properties of drugs (2,8,24). These antagonists, however, did not influence the effects of *d*-amphetamine on DA and CPP (5,6). These findings suggest that 5-HT_3 receptor antagonists may be useful in the pharmacotherapy of opiate and nicotine but not amphetamine abuse.

Although cocaine closely resembles amphetamine in the mechanism by which it increases extracellular DA in the nucleus accumbens and reduces the firing rate of DA cells in the ventral tegmental area (1,25), Suzuki et al. (23) recently reported that two 5-HT_3 receptor antagonists, MDL 72222 and tropisetron, blocked cocaine-induced CPP; even methamphetamine-induced CPP was blocked by a higher dose of the 5-HT_3 receptor antagonists.

These results are surprising in view of the fact that 5-HT_3 receptor antagonists do not affect self-administration (17,21) or the discriminative stimulus properties (18,19) of cocaine in rats.

In view of the clinical implications of Suzuki's findings, we decided to reassess the interaction between 5-HT_3 receptors and cocaine by studying the effects of three 5-HT_3 receptor antagonists on the acquisition of cocaine-induced CPP by an unbiased design currently used in our laboratory. Because we found recently (9) that different mechanisms are involved in the acquisition and expression of cocaine CPP, in one experiment we examined the effect of ondansetron, a potent and selective 5-HT_3 receptor antagonist (3), on the expression of cocaine CPP. In another experiment we investigated whether ondansetron affected the increase of extracellular DA caused by cocaine in the nucleus accumbens.

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METHOD

Animals

Male Sprague–Dawley CD-COBS rats (Charles River, Italy), weighing 150–175 g, were housed two per cage at constant room temperature (21 ± 1°C) and relative humidity (60%) under a regular light/dark schedule (lights on 0730–1930 h) with food and water available at lib. Animals were allowed to adapt to laboratory conditions for at least 1 week and were handled for 5 min a day during this adaptation period. Testing and training were done between 0900 and 1400 h.

Apparatus

The apparatus consisted of four rectangular boxes (80 × 40 × 30 cm) with three sides made of wood, one long observation wall of Plexiglas, and a wooden lid.

For the conditioning phase (phase II), each box was divided into two equal-sized compartments by a sliding wall. One compartment was gray and the other was black, with vertical white stripes 3 cm wide; the lids were painted to match the compartment below. The two compartments were equipped with distinctive metal floors, one a loose mesh and the other much closer mesh.

For preconditioning (phase I) and test sessions (phase III), the partition between the two compartments was raised 12 cm off the floor and a 5 × 3 cm smooth aluminium platform was inserted along the line between the compartments. Two infrared sensors (one for each compartment), set to detect any heat change due to a moving body (Murata, Milan, Italy), were inserted on the partition between the two compartments. These sensors signalled the animals in a central zone when they were on the platform or stayed very close to it. The sensors were operated by a Paul Fray computer (Cambridge, UK) with Spider software recording the time each animal spent in the different compartments.

The testing room was closed and ventilated, with dim indirect lighting provided by four dark-room incandescent red bulbs hung about 50 cm above the boxes. A loudspeaker about 1 m above the boxes delivered white noise.

Place Conditioning Procedure

Each rat was used once and was always exposed to the same box. The procedure consisted of three phases. On the first day, before any drug treatment (preconditioning period), each rat was allowed to explore the two compartments of the box for 15 min (phase I). The time each animal spent in the two compartments was recorded. Because no difference was found in the unconditioned preference for gray and black/white compartments [mean time (s) spent in the gray and in the black/white sides for all the animals was 404 ± 15 and 412 ± 13, respectively, with mean times spent in the gray and black/white compartments, respectively, in individual experiments ranging from 392 ± 9 to 417 ± 12 and from 396 ± 15 to 422 ± 9, $p > 0.05$, Wilcoxon's test], rats were randomly assigned to treatment groups and conditioning compartments. Care was taken to ensure that all treatments were matched as closely as possible between compartments.

The schedule during the conditioning phase (phase II) consisted of eight injections of drug or vehicle on alternate days. The interval between conditioning days was no less than 24 h and no more than 48 h. On conditioning days 1, 3, 5, and 7 rats were injected with cocaine immediately before being confined to the randomly designated drug side for 30 min. On the inbetween days, each rat was injected with vehicle and confined to the opposite side for 30 min. The daily order of exposure to drug and vehicle was matched for the rats in each experimental group. Control animals received saline in both compartments.

On the test day (phase III) neither cocaine nor saline was injected. Each rat was placed in the center of the smooth aluminium platform separating the two compartments, with free access to both sides of the box, and the time spent in each compartment was recorded over a 15-min period. The difference in the time spent in the drug-paired compartment and in the vehicle-associated side in the final test session is taken as a measure of place conditioning.

Drug Treatments

In all experiments 10 mg/kg cocaine hydrochloride (Macfarlan-Smith Ltd., Edinburgh, UK) or saline was injected IP immediately before exposure to the designated drug-associated side. The dose of cocaine was selected on the basis of preliminary experiments in which lower doses gave highly variable results.

First, we investigated the effects of tropisetron and MDL 72222 on the acquisition of cocaine-induced CPP. Separate groups of eight rats underwent the experimental procedure of place conditioning but received tropisetron and MDL 72222, or their vehicles, before each of the eight conditioning sessions.

Second, we investigated the effects of ondansetron on the acquisition and expression of cocaine-induced CPP. To determine the effects on acquisition separate groups of 10 rats received the 5-HT_3 receptor antagonist, or its vehicle, before each of the eight conditioning sessions.

For the effects on the expression of cocaine CPP, separate groups of 10 rats underwent the experimental procedure of place conditioning and received ondansetron, or its vehicle, in the absence of cocaine, only before testing.

The 5-HT_3 receptor antagonists were given both before the cocaine pairing and saline pairing sessions. By pairing the 5-HT_3 receptor antagonist with both compartments, nonspecific effects would be conditioned to each compartment. This, therefore, enabled us to examine changes in the motivational properties of cocaine that are not confounded by effects resulting from potential motivational properties of the 5-HT_3 receptor antagonists.

Drugs

Tropisetron (R.B.I., Wayland, USA) 0.01–0.1 mg/kg, dissolved in 0.9% NaCl, or vehicle was injected SC, 1 h before each conditioning session.

MDL 72222 (R.B.I., Wayland, USA) 0.03–3.0 mg/kg, initially dissolved in a minimal amount of 0.1 N HCl and brought to the final volume with 0.9% NaCl (the final pH was adjusted to 5–6 with 1 N NaOH), or vehicle, was injected SC 30 min before each conditioning session.

Ondansetron (Glaxo, Greenford, Middlesex, UK), 0.01–0.1 mg/kg, dissolved in 0.9% NaCl, or vehicle was injected SC 30 min before each conditioning session or only before testing.

Dialysis Procedure

The effects of ondansetron, 0.1 mg/kg SC 30 min pretreatment, or vehicle on the increase in DA extracellular concentrations induced by cocaine 10 mg/kg IP in the nucleus accumbens was studied in rats (n = 3–5).

The rats were anesthetized with 3 ml/kg Equithesin and placed on a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). A hole was drilled in the parietal bone and a small incision was made in the dura with a bent needle tip. A probe, perfused with artificial cerebrospinal fluid (aCSF: composition in mM: NaCl, 145; KCl, 3; $CaCl_2$ $2H_2O$, 1.26; $MgCl_2$ $6H_2O$, 1 in distilled water; pH 7.4 with 2 mM sodium phosphate buffer), was lowered slowly into the nucleus accumbens and fixed to the skull using two anchorage screws and acrylic cement. Stereotaxic coordinates were as follows: AP = 10.7; H = 2.0 and L = 1.6 from the interaural line with the incisor bar set at −3.3 mm, according to the Paxinos and Watson atlas (20).

The dialysis probe for the nucleus accumbens was of the concentric type and was prepared essentially as described by Robinson and Wishaw (22), except that the dialysis membrane was made of cuprophan (Sorin Biomedica, Italy; 200 μm inner diameter with 3000 molecular weight cutoff), with the glue-free zone 2 mm long.

After surgery, rats were allowed to recover from anesthesia, one per cage, with food and water ad lib.

About 24 h after probe implanting each rat was placed in a Plexiglas cage where the inlet cannula was connected by polythene tubing (Portex Ltd., UK) to a 2.5 ml syringe mounted on a CMA/100 microinjection pump (CMA Microdialysis, Stockholm, Sweden) containing aCSF. The probe was perfused at a constant flow rate of 2 μl/min. After a 30-min washout period, consecutive 20-min samples (40 μl) of perfusate were collected in minivials and DA was directly assayed by HPLC coupled with electrochemical detection as previously described (14). The detection limit for DA was 10 fmol/20 μl (s/n = 2).

Histology

At the end of the microdialysis perfusion (3 h after the last drug treatment) rats were deeply anesthetized with chloral hydrate and killed by decapitation; their brains were removed, frozen and sliced (40 μm sections) for examination of the probe tracks. Only rats with correct probe placement were considered in the results.

Animal Care

Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with the national (D.L. n. 116, G.U., suppl. 40, 18 Febbraio 1992) and international laws and policies (EEC Council Directive 86/609, OJL 358, 1, Dec. 12, 1987; NIH Guide for the Care and Use of Laboratory Animals, NIH Publication No. 85-23, 1985).

Statistical Analysis

To exclude any spontaneous place preference, the time spent by control rats in black/white and gray compartments was compared using Wilcoxon's matched pairs test. The same test, comparing time spent in the drug-associated and vehicle-associated sides, was used to establish whether cocaine produced significant place conditioning. To detect any differences between cocaine-treated groups, the conditioning scores (the time spent in the drug-associated side minus the time spent in the vehicle-associated side, expressed as mean ± SEM) as well as the time spent in the central zone under different treatments were analysed by one-way ANOVA followed by Dunnett's test.

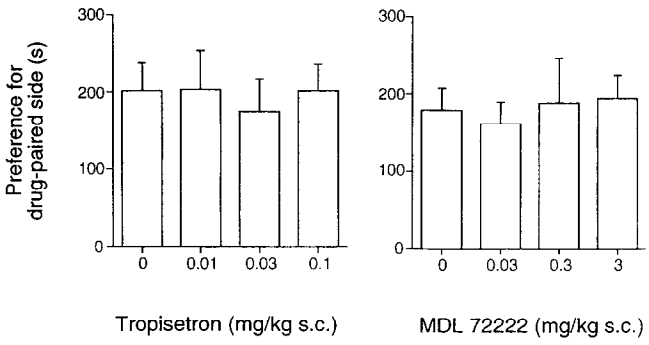

FIG. 1. Effects of tropisetron and MDL 72222 on the acquisition of cocaine-induced CPP when given before conditioning sessions. Histograms represent the mean conditioning score ± SEM of eight rats. See the Method section for details.

Basal values of DA are the mean of at least three consecutive 20-min samples of stable output (no more than 10% difference between samples) before drug treatment. To evaluate the effects of ondansetron on basal DA, data from samples collected 15 and 30 min after its administration were compared to basal values by two-way ANOVA for repeated measures with treatment as between-subjects factor and time as within-subjects factor. Post hoc comparison were made with Tukey's test.

To determine the effects of ondansetron pretreatment on cocaine-induced increase of extracellular DA, data from samples collected from 20 to 220 min after cocaine were analyzed by a three-factor ANOVA (two between, one within subjects). The first between-subjects factor was ondansetron (two levels), the second, two levels of cocaine. There were 10 levels of within-subjects factor time (i.e., DA at baseline and in nine samples at intervals after cocaine). Significant interactions between time, ondansetron, and cocaine were further analyzed by comparing cocaine and ondansetron-treated and non-treated rats at each level separately by a two-way ANOVA for repeated measures (treatment × day) followed by Tukey's test.

RESULTS

No significant differences were found after conditioning in the time the control animals spent in the black/white and gray compartments in the various experiments (mean times (s) were 401 ± 10 in the black/white side and 386 ± 8 in the gray side, with mean time spent in individual experiments ranging from 375 ± 17 to 425 ± 24 and from 363 ± 22 to 406 ± 10 for the black/white and gray compartments respectively, $p > 0.05$ Wilcoxon's test).

In all the experiments cocaine, 10 mg/kg IP, induced a clear CPP in saline-treated rats [mean time (s) spent in individual experiments ranging from 495 ± 32.1 to 504.1 ± 26.7 and from 290.2 ± 22.7 to 321.1 ± 17.4 for cocaine- and saline-paired compartments respectively, $p < 0.01$ Wilcoxon's test).

Figure 1 shows the effects of tropisetron 0.01–0.1 mg/kg SC and MDL 72222 0.03–3.0 mg/kg SC on the acquisition of cocaine-induced CPP. Neither tropisetron, $F(3,28) = 0.1$, $p > 0.05$, one-way ANOVA, nor MDL 72222, $F(3, 28) = 0.1$, $p > 0.05$, one-way ANOVA, affected the acquisition of cocaine-induced CPP.

Figure 2 shows the effects of ondansetron 0.01 and 0.1 mg/kg SC on the acquisition (left panel) and expression (right

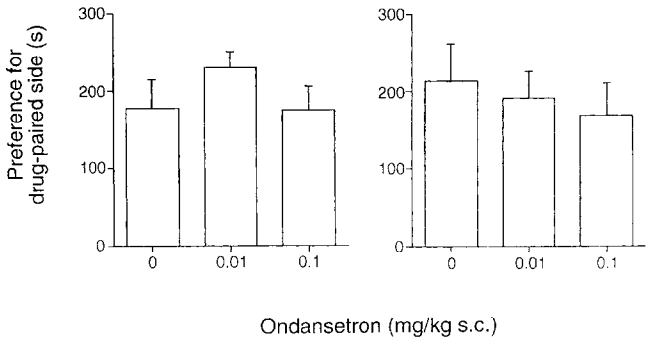

FIG. 2. Effects of ondansetron on the acquisition (left) and expression (right) of cocaine-induced CPP when given before conditioning sessions or only before the test session. Histograms represent the mean conditioning score ± SEM of 10 rats. See the Method section for details.

panel) of cocaine-induced CPP. Analysis of variance of the mean conditioning score showed that ondansetron did not influence either its acquisition, $F(2, 27) = 0.6$, $p > 0.05$, or the expression, $F(2, 27) = 0.3$, $p > 0.05$.

In all the experiments the animals spent from 94.7 ± 13.6 to 125.3 ± 21.3 s on the central zone (platform). This measure was similar for the various experimental groups ($p > 0.05$, one-way ANOVA). Thus, the preference for the drug-paired side of rats treated with the various 5-HT_3 receptor antagonists was not significantly influenced by changes in time spent in the central zone.

Figure 3 shows the effect of ondansetron 0.1 mg/kg SC on DA extracellular concentrations in the nucleus accumbens of rats treated with cocaine 10 mg/kg IP.

In the 30 min before cocaine administration, ondansetron did not alter basal levels of DA, $F(2, 32) = 0.15$, $p > 0.05$, two-way ANOVA.

Three-way ANOVA on DA values after cocaine showed

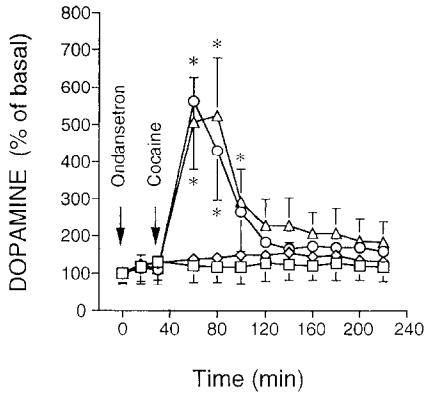

FIG. 3. Extracellular DA concentrations in the nucleus accumbens of the following experimental groups: saline + saline (squares), ondansetron 0.1 mg/kg SC + saline (diamonds), saline + cocaine 10 mg/kg IP (circles), ondansetron 0.1 mg/kg SC + cocaine 10 mg/kg IP (triangles). An arrow indicates the time of injection of ondansetron and cocaine. Basal DA extracellular concentrations (fmol/40 µl) were as follows: 29.7 ± 8.0 (squares), 22.4 ± 2.7 (diamonds), 28.9 ± 9.0 (circles) and 28.1 ± 6.7 (triangles). See the Method section for details. *$p < 0.05$ vs. basal values, Tukey's test.

a nonsignificant interaction time × ondansetron × cocaine, $F(9, 126) = 0.3$, $p > 0.05$. However, there was a significant effect of time, $F(9, 126) = 15.1$, $p < 0.01$, and a significant interaction time × cocaine, $F(9, 126) = 14.3$, $p < 0.01$, suggesting that independently of the pretreatment (saline or ondansetron), cocaine raised the levels of extracellular DA. Post hoc comparisons showed that cocaine increased DA extracellular levels at 20, 40, and 60 min ($p < 0.01$, Tukey's test).

DISCUSSION

None of the three 5-HT_3 receptor antagonists administered before cocaine during the training phase modified the establishment of place conditioning. This contrasts with the findings of Suzuki et al. (23) who blocked cocaine-induced CPP using doses of tropisetron and MDL 72222 in the same range as those used in the present study and previously reported to block CPP induced by morphine and nicotine (6,7). The doses of ondansetron we used were also in the range of those reported to block central 5-HT_3 receptor dependent effects on motor behaviour (10,12).

There is no obvious explanation for the different results, although differences in the training enviroment may contribute. Using a black or white conditioning compartment, as in Suzuki's experiments, Higgins et al. (13) found that ondansetron only antagonized morphine CPP when conditioning was carried out under the white but not the black compartment. They attributed this difference to the fact that animals treated with ondansetron alone and paired with the white chamber tended to avoid this compartment. A drug action on sensory processing was considered a reasonable explanation. If 5-HT_3 receptor antagonists in general make the animals more responsive to sensory stimuli, it is possible that visual and/or tactile stimuli in the white chamber become aversive to animals treated with these antagonists during conditioning. The environmentally dependent place conditioning may have been limited in our experiments because we used a black/white or gray compartment and the animals showed no particular preference for either compartment.

Another factor that could potentially contribute to the different results is the dose used in the two studies. We chose 10 mg/kg cocaine on the basis of preliminary experiments in which doses lower than 10 mg/kg gave very variable results. A ceiling effect of this dose can also be excluded by the fact that 10 and 40 mg/kg cocaine have been reported to cause a dose-dependent increase of extracellular dopamine in the nucleus accumbens (16). Although we consider it unlikely that the different results are fully explained by the different doses, we cannot exclude with certainty that it contributed.

Whatever the factors responsible for the differences, the present results suggest that blockade of 5-HT_3 receptors does not modify the rewarding properties of cocaine as assessed by the establishment of cocaine CPP. This is in line with findings that 5-HT_3 receptor antagonists do not affect self-administration of cocaine in rats (17,18,21).

At doses of 0.01 and 0.1 mg/kg ondansetron did not modify the expression of cocaine CPP, confirming that the proposed interaction between 5-HT_3 receptor antagonists and cocaine effects related to drug abuse (4,23) is not robust.

At the dose used for inducing CPP, cocaine significantly raised extracellular concentrations of DA in the nucleus accumbens, and ondansetron did not prevent this. Since, at the dose used (0.1 mg/kg), ondansetron blocked the hyperactivity induced by stimulation of central 5-HT_3 receptors (10), the failure cannot be attributed to its inability to block central 5-

HT_3 receptors. In previous studies 5-HT_3 receptor antagonists have also failed to block amphetamine's effect on extracellular DA in the nucleus accumbens (5). It seems that only drugs of abuse such as morphine and nicotine, that increase the firing of DA cells in the mesolimbic system, are unable to raise extracellular DA in the nucleus accumbens in the presence of 5-HT_3 receptor antagonists (5).

In conclusion, the present study shows that 5-HT_3 receptor antagonists do not modify the establishment and expression of cocaine CPP, suggesting that these drugs have no significant effects on the rewarding properties and on the behaviour elicited by the stimuli previously associated with the drug's action.

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