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Effects of SCH-23390 and Raclopride on Cocaine Discrimination in Male and Female Wistar Rats

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ANDERSON, K. G. AND F. VAN HAAREN. *Effects of SCH-23390 and raclopride on cocaine discrimination in male and female Wistar rats.* PHARMACOL BIOCHEM BEHAV **65**(4) 671–675, 2000.—Male and female rats were trained to discriminate 10.0 mg/kg cocaine from saline in a two-lever discrimination task. Injection-appropriate responding was reinforced by food pellet presentation on a tandem random-interval 30-s fixed-ratio 10 schedule. Generalization testing was conducted in extinction 10 min following an injection of saline, 1.0, 3.0, 5.6, or 10.0 mg/kg cocaine. No differences in the generalization gradients and ED_{50}s were observed between male and female rats. Following the determination of the cocaine generalization gradient, the dopamine D_1 antagonist SCH-23390 (0.01–0.10 mg/kg) and the dopamine D_2 antagonist raclopride (0.1–1.6 mg/kg) were administered (independently) prior to the injection of the training dose of cocaine (10.0 mg/kg). Cocaine-antagonism tests were conducted in extinction. It was found, for each dopamine antagonist, that as the dose increased, the percentage of cocaine-appropriate responding decreased. No sex differences were observed between these generalization gradients. © 2000 Elsevier Science Inc.

Cocaine discrimination Dopamine antagonist SCH-23390 Raclopride Male and female rats Sex differences

THE subjective effect of a drug may be one of the factors that contribute to its abuse potential. Cocaine's ability to block the reuptake of monoamines, particularly dopamine (DA), is a major determinant of its reinforcing (20) and subjective effect (18). Many nonselective DA agonists have been shown to partially or fully substitute for a cocaine discriminative stimulus in rats (10,18), squirrel monkeys (23), and rhesus monkeys (14). In addition, nonselective DA antagonists, such as *cis*-flupenthixol (23) appear to block the cocaine discriminative cue.

Since the identification of numerous DA receptor subtypes, many studies have been conducted to attempt to characterize the cocaine cue more specifically. Both the D_1 and D_2 receptor subtypes have been implicated in the mediation of cocaine's discriminative cue. For example, D_1 (e.g., SKF 38393) or D_2 (e.g., quinpirole) agonists often only partially substitute for cocaine during a discrimination task (4,7,14,23). Likewise some D_1 (SCH 39166) or D_2 (e.g., spiperone, haloperidol) antagonists only partially attenuate cocaine's discriminative cue (4,18,23). Findings like these have led many to suggest that cocaine's stimulus effects involve both D_1 and D_2 receptors (4,7,14,23). It is also worth noting that recent research has implicated the D_3 receptor subtype in mediating some of cocaine's action (34), including its reinforcing (6) and subjective effect (1).

Differences in cocaine's effects in male and female rats have been observed in schedule-controlled behavior (26, 28,29), locomotor activity (31), and conditioned taste aversions (30). In addition, it has been reported that female rats in estrus, reached higher breaking points on a progressive-ratio schedule when cocaine self-administration was contingent upon lever pressing (21). However, it has also been shown that chronic cocaine administration may disrupt a female rat's estrous cycle (12,13). Further, there is evidence that intact female rats metabolize cocaine differently following repeated cocaine administration than ovariectomized female rats and male rats (32). Although the mechanisms are not fully understood, it is likely that the effects of cocaine administration may vary as a function of gonadal hormones as well as environmental parameters. Gonadal hormones, of course, affect a variety of reproductive and nonreproductive behaviors [for reviews see (5,33)].

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Research with rats (2,3,8) has shown that the cocaine cue does not vary as a function of the presence or absence of gonadal hormones. However, the specific discriminative aspects of a cocaine cue may differ between male and female subjects, as it has been shown that elimination of gonadal hormones via castration (15,35) or ovariectomy (11) results in increased sensitivity or upregulation of DA receptors, specifically striatal D_2 receptors. The overall subjective effect of cocaine has been shown to be mediated in part by the DA system, but the degree to which particular DA receptor subtypes contribute to this effect may differ between male and female subjects. Therefore, the present study was designed to investigate the effects of the selective D_1 and D_2 antagonists, SCH-23390 and raclopride, on a cocaine discrimination (10 mg/kg vs. vehicle) in male and female rats.

METHOD

Subjects

Six male and six female Wistar rats were purchased from Charles River when they were approximately 90 days old. They were allowed to adjust to the laboratory housing conditions for about 10 days before the start of the experiment. All subjects were experimentally naive and housed in groups (three same-sex subjects to a cage) upon arrival in the laboratory. Temperature and humidity conditions were held constant throughout the experiment, and a reversed 12 L:12 D cycle (lights on at 1900 h) was in effect. All experimental sessions were conducted within 2–4 h after the onset of the dark cycle. Water was always available in the home cage. The rats were fed approximately 16 g of Purina Rat Chow immediately following the experimental session. This feeding schedule resulted in each rat being food deprived for approximately 22 h prior to each experimental session. The female rats weighed 338 g (range: 295–385 g) and the male rats weighed 426 g (range: 374–482 g) when cocaine generalization gradients were determined.

Apparatus

Experiments were run in six identical Coulbourn Instruments modular, rodent operant-conditioning chambers that were 25 cm wide, 30 cm long, and 29 cm high. The side walls of the chamber, except for the front panel, were made of translucent Plexiglas. The floor consisted of 16 rods, spaced 2 cm apart (center to center). Two nonretractable rodent levers were located symmetrically on either side of the pellet tray, 7 cm from the floor of the chamber. The levers protruded 2 cm from the front panel, and required a force in excess of 0.20 N to be operated. Three stimulus lights were located directly above each lever. A Sonalert was mounted above each lever, approximately 6 cm from the ceiling of the chamber. A houselight was located 2 cm from the ceiling in the middle of the front panel. A white light could illuminate the pellet tray. Each experimental chamber was contained in a sound-attenuating, ventilated cabinet. The chambers were connected to a PDP 11-23 microcomputer (Digital Equipment Corporation, Maynard, MA) located in the experimental room itself. Experimental contingencies and data acquisition procedures were programmed using SKED-11 (22), obtained from State Systems, Inc. (Kalamazoo, MI).

Procedure

Lever-press acquisition. All subjects were trained to press the levers using a free-operant acquisition procedure (27) in which a food pellet was presented according to a random-time 60-s schedule, and following every lever press [conjoint RT 60-s, fixed-ratio (FR) 1 schedule], whether it was emitted on the left or the right lever (stimulus lights were illuminated above both levers). When a response was made and recorded, an auditory feedback stimulus was provided. All sessions were terminated after 40 pellets had been presented or after 30 min, whichever came first.

After five sessions of this initial training procedure, when the rats reliably obtained the majority of food pellets by lever pressing, five sessions were conducted in which subjects were required to complete a FR 1 schedule of reinforcement that alternated (with the illumination of the stimulus lights) between the two levers after the presentation of every fifth food pellet. During the next three sessions, which were identical with respect to the alternation procedure, subjects completed a random-interval (RI) 15-s schedule. Similarly, completion of a RI 30-s was required during the final two sessions of lever-press acquisition training. Experimental sessions were conducted Monday through Friday of each week.

Discrimination training. Injection of the drug (D) or the vehicle (V) prior to any particular session was determined according to the following schedule: VDVDD DVDVV. Immediately after the intraperitoneal (IP) administration of 10.0 mg/kg cocaine or the vehicle (saline), the subject was placed in the darkened operant chamber. Ten minutes postinjection the houselight and both lever lights were illuminated. Responses on one lever (cocaine- or saline-appropriate) were followed by pellet presentation according to a tandem random-interval 30-s fixed-ratio 10 (TAND RI 30-s FR 10) schedule of reinforcement. Presses on the other lever were never followed by pellet presentation (extinction). A 2-s changeover delay (COD) was initiated following a response on the lever associated with extinction to prevent adventitious reinforcement of switching between levers. The tandem schedule was chosen because it allows for equal reinforcement frequencies in the presence of response rate differences during drug and vehicle sessions and because it allows for more graded responding than a simple FR 10 schedule [cf. (24) for a detailed discussion of these issues].

Generalization testing. Generalization testing began after at least 20 discrimination training sessions and when the subjects made at least 80% injection-appropriate lever presses during five consecutive sessions. Generalization tests were conducted in extinction. Subjects were placed in the darkened experimental chamber immediately after cocaine administration. Ten minutes later the houselight and lever lights were illuminated until the response requirement necessary for pellet presentation established during training sessions (TAND RT 30-s FR 10) had been met (but a pellet was not presented) or for 5 min, whichever came first.

Determination of cocaine generalization gradient. In the first phase of the experiment, various doses of cocaine (1.0, 3.0, 5.6, and 10.0 mg/kg) and its vehicle (saline), were injected (IP) and tested for generalization to the training stimulus (10.0 mg/kg cocaine). Administration of each dose of cocaine occurred in random order. Each dose of cocaine was tested at least twice, intermediate doses (3.0 and 5.6 mg/kg cocaine) were tested more often (range three to six times) to establish a representative dose effect as determined by visual inspection of the data. All observations were included in the determination of the generalization gradient. Testing was conducted on Tuesdays and Fridays of each week if the criterion of 80% correct responding had been met on the preceding day. Each test dose was presented, at least once, following a cocaine training session and a saline training session.

DA antagonists with cocaine. In the second condition of the experiment, different doses of the selective D_1 antagonist, SCH-23390 (0.01, 0.025, 0.05, 0.075, or 0.1 mg/kg), or saline were administered by subcutaneous (SC) injection 30 min prior to the administration of 10.0 mg/kg cocaine. In the third condition of the experiment, different doses of the selective D_2 antagonist, raclopride (0.1, 0.2, 0.4, 0.8, or 1.6 mg/kg), or saline were injected by intraperitoneal injection (IP) 15 min prior to the administration of 10.0 mg/kg cocaine. Administration of each dose of the antagonists occurred in random order, and each dose was tested at least once in each subject. Antagonists test days were not counterbalanced with respect to preceding saline and drug training sessions. Testing occurred on Tuesdays and Fridays of each week if the criterion of 80% correct responding had been met on the preceding training day.

Drugs

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Raleigh, NC). SCH-23390 was obtained from Sigma Chemical Company (St. Louis, MO), and raclopride was generously provided by Astra (Sweden). All drugs were dissolved in physiological saline and drug doses were calculated from the salt.

Estrus Cycle

Vaginal smears were obtained prior to all test sessions on Tuesdays and Fridays to determine the stage of the estrus cycle at the time of generalization testing.

Data Analysis

For all discrimination-training measures, the percentage of correct lever presses was determined by dividing the number of responses emitted on the stimulus-appropriate lever by the total number of responses emitted on both levers prior to the delivery of the first food pellet. Calculations were identical during generalization tests, which were conducted in extinction. The ED_{50}s were calculated by log-linear interpolation of the ascending portion of the dose–effect curve, and includes one point below 20% and one point above 80%. Statistical analyses consisted of two-way, repeated measures ANOVA (sex × dose), with the significance level set at $p < 0.05$ for all analyses.

RESULTS

Two subjects, one male and one female, expired before the completion of the experiment, and their data have been omitted from the analysis. The male subjects required an average of 23.2 training sessions to reach the cocaine cue discrimination criterion; the female subjects reached criterion in an average of 21.2 sessions. This difference was not statistically significant, $t(8) = 0.39$, $p = 0.71$.

The top panel of Fig. 1 shows the percentage of total responses on the cocaine-appropriate lever after saline administration and following administration of the different doses of cocaine (1.0–10.0 mg/kg). Responding in the presence of the training dose of cocaine (10.0 mg/kg) during test sessions was at or above the criterion value of 80%. The generalization gradients obtained for the male and female subjects were not different [gender, $F(1, 8) = 0.01$, n.s.]. As the dose of cocaine decreased, cocaine-appropriate responding also decreased [dose, $F(4, 32) = 143.30$, $p < 0.0001$]. The interaction between gender and dose was also not significant, $F(4, 32) = 0.84$, n.s. The ED_{50}s (95% confidence limits) were 2.99 mg/kg (2.36–3.79 mg/kg) for male rats, and 2.90 mg/kg (1.46–5.76) for female rats, respectively. Visual inspection of the relevant data indicated that there was no obvious correlation between the behavioral effects of cocaine administration and the stage of the estrus cycle in female rats during this and subsequent experimental conditions. This statement should be taken at face value, as our experiment was not designed to test drug effects at each stage of the estrus cycle.

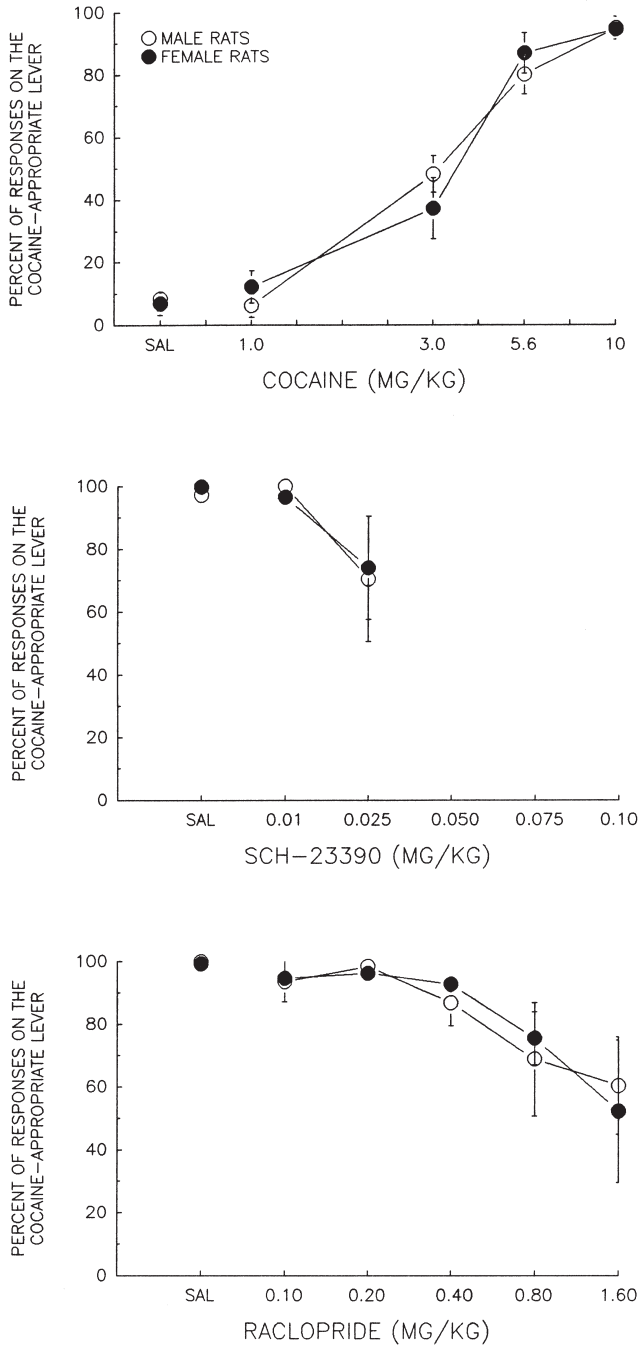

FIG. 1. Percentage of the total responses emitted on the cocaine-appropriate lever, for male and female rats, during the cocaine generalization test (top panel), and during antagonism tests with SCH-23390 (middle panel) and raclopride (bottom panel).

The middle and bottom panels of Fig. 1 show the percentage of total responses on the cocaine-appropriate lever following administration of SCH-23390 (middle panel) and raclopride (bottom panel) for male and female rats, respectively. Both functions show that as the dose of the respective antagonist was increased (administered prior to the 10.0 mg/kg cocaine injection) percent responding on the cocaine-appropriate lever decreased. The SCH-23390 dose–effect curve only shows results obtained after the two smallest doses of this drug, as higher doses significantly depressed or completely eliminated responding during test sessions in male and female subjects alike. Thus, SC administration of SCH-23390, 30 min prior to the administration of the 10 mg/kg cocaine training dose, dose dependently decreased cocaine-appropriate responding in male and female rats at these doses, but there was no difference between male and female rats [gender, $F(1, 8) = 0.01$, n.s.; and dose $F(2, 16) = 4.04$, $p < 0.05$]. The bottom panel of Fig. 1 shows that IP raclopride administration, 15 min prior to the administration of the cocaine training dose decreased responding on the cocaine-appropriate lever [dose, $F(5, 35) = 7.78$, $p < 0.001$] in male and female rats to an equal extent [gender, $F(1, 7) = 0.01$, n.s.]. The interaction between gender and dose was also not significant, $F(5, 35) = 0.77$.

DISCUSSION

The results from the present investigation show that there were no differences in cocaine's generalization gradient and related ED_{50}s between male and female Wistar rats when assessed 10 min following the administration of the 10 mg/kg cocaine training dose. Also, an analysis of the number of sessions to acquire the cocaine discrimination revealed no sex differences. As such, these results confirm those from other experiments (2,8). In addition, there were no sex differences observed in the discrimination of cocaine (10.0 mg/kg) following the administration of the selective D_1 antagonist SCH-23390 or the D_2 antagonist raclopride.

Although many behavioral differences between male and female rats have been noted (5,33), and although cocaine may affect the behavior of male and female rats differently (2,26,28–31), there appears to be no difference in the subjective effects of cocaine administration between male and female rats, as assessed in the context of the present experiment. These observations, however, are preliminary at the very least, as it is well possible that other DA antagonists and/or doses, or different temporal parameters may have resulted in another experimental outcome. In addition, evidence is available to show that the training dose of cocaine may reveal different D_1 and D_2 involvement (25). These are all variables that should be considered in future investigations. However, given the present data and those of another recently published experiment (8), which show similar results with a different training dose (5.6 mg/kg cocaine), reinforcement schedule (FR 10), DA antagonist (fluphenazine), and housing conditions, it is reasonable to suggest that cocaine's subjective effects in male and female rats as measured in a typical drug-discrimination paradigm do not involve differential D_1 and D_2 involvement. Although DA is certainly important for the subjective effects of cocaine, the differences in levels or receptor subtypes alone, may play only a minor role in accounting for any sex differences seen in clinical settings (16,17).

It is also possible that cocaine's effects on other neurochemical systems may be responsible for some of the differences reported between the sexes in other studies. Cocaine's primary effects seem to be in the DA system (blocking reuptake), but the drug also affects other neurotransmitter systems, for example, serotonin (5-HT) and norepinephrine (NE) (9). Repeated cocaine injections have also been shown to affect gamma-aminobutyric acid ($GABA_A$) receptors in male rats (19). Thus, it is possible that any differences seen between the sexes in other studies may be a result of aspects of the cocaine cue other than those mediated by D_1, D_2, or other DA receptor subtypes.

Given that the subjective effects of a drug are likely tied to its abuse potential, and that differences in cocaine's subjective effects have been reported with male and female human volunteers (16,17), it seems worthwhile to further investigate cocaine's discriminative stimulus properties as they differ between male and female subjects. However, in view of the results from this and another recent study involving rats (8), it is plausible that the differences in cocaine's subjective effects, as reported in human volunteers, may be due to factors other than differential DA sensitivity. In trying to account for the differences in cocaine's subjective effects and abuse, perhaps research efforts should be focused on other factors that differ between men and women, for example, body weight, body fat, and drug metabolism (8).

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