Pharmacology Biochemistry & Behavior, Vol. 39, pp. 923–927. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Sex Differences in Locomotor Activity After Acute and Chronic Cocaine Administration

FRANS VAN HAAREN AND MERLE E. MEYER

University of Florida, Gainesville, FL 32611

Received 16 January 1991

VAN HAAREN, F. AND M. E. MEYER. *Sex differences in locomotor activity after acute and chronic cocaine administration.* PHARMACOL BIOCHEM BEHAV **39**(4) 923–927, 1991.—Adult, intact and gonadectomized male and female Wistar rats (n=9) were exposed to an automated open field to assess the behavioral effects of acute cocaine administration (saline, 1.0 and 10.0 mg/kg subcutaneous). The subjects were exposed to the open field for 10 min, removed to be injected and returned to the open field for another 30 min. Three saline and two drug sessions were run in counterbalanced order. Locomotor activity in intact and castrated male rats and ovariectomized female rats decreased following injection, irrespective of the dose of cocaine. The locomotor activity of intact female rats was higher than that of any other group of subjects. It decreased during the session after saline and 1.0 mg/kg cocaine, but increased towards the end of the 30 min session after 10.0 mg/kg. Rearing measures paralleled the observations on locomotor activity. To determine the effects of chronic, home-cage, cocaine administration, five of the subjects in each group were injected with 10.0 mg/kg cocaine for 9 consecutive days. The remaining four subjects received saline injections. On day 10, all subjects were re-exposed to the open-field for 10 min, removed, injected with 10.0 mg/kg cocaine and returned to the open field for another 30 min. Chronic home cage cocaine administration produced an increase in cocaine's effects on locomotor activity and rearing in intact female rats only. However, behavioral sensitization was also observed in intact female rats who had been treated with saline for 9 consecutive days, suggesting that behavioral sensitization to cocaine in intact female rats may develop very rapidly and independent of environmental context.

Acute cocaine administration Chronic cocaine administration Gonadectomy Sex differences
Locomotor activity Rearing behavior Male and female Wistar rats

PSYCHOMOTOR stimulant drugs can have a variety of behavioral effects. For instance, moderate doses of cocaine increase locomotor activity, while larger doses (in excess of 10.0 mg/kg) produce behavioral stereotypies, seizures and death (3–5, 22). Schedule-controlled behavior of pigeons, rats and monkeys is frequently disrupted by low to moderate doses of cocaine and totally suppressed by higher doses (14,21). Chronic administration of psychomotor stimulants produces sensitization (increased behavioral effects) although evidence of tolerance (decreased behavioral effects) has also been presented (8, 14, 15). The behavioral effects of repeated cocaine administration have been shown to be a function of drug dose and intermittency of administration in addition to being dependent upon the environmental context (7, 9, 10, 20). It has frequently been suggested that the central nervous system (CNS) effects of psychomotor stimulant drugs, including cocaine, are mediated through an inhibition of monoamine uptake, more specifically that of dopamine (DA) (1).

The presence or absence of gonadal hormones may modulate the behavioral effects of manipulations in a number of different environmental variables (17). That gonadal hormones influence the behavioral effects of psychomotor stimulants has extensively been shown after subjects were challenged with d-amphetamine. Schedule-controlled low response rates of female rats were more easily disrupted than those of males after the administration of d-amphetamine (16). In addition, after challenge with psychomotor stimulant drugs, locomotor activity, stereotyped behavior and rotational behavior usually increase more in females than in males (12). The behavioral effects of d-amphetamine also vary as a function of the estrus cycle (12), although different behaviors seem to be affected at different times (6). Not surprisingly, then, evidence has been presented to suggest that the behavioral effects of acute and chronic cocaine administration may differ between male and female rats. For instance, conditioned taste aversions induced by cocaine administration were observed at lower doses in female tnan in male Wistar rats (18), while sensitization to the locomotion enhancing effects of cocaine was observed at lower doses in females than in males (9). Other experiments, in which female rats responded on a progressive ratio schedule to self-administer cocaine, have shown that the reinforcing efficacy of cocaine may vary as a function of the estrus cycle, as breaking points during estrus were much higher than those observed during nonestrus (11).

The present experiment was explicitly designed to investigate whether the presence or absence of gonadal hormones modulates the behavioral effects of acute and chronic subcutaneous (SC) cocaine administration. In spite of the local vasoconstriction induced by cocaine, the absorption of cocaine from the SC injection site has been reported to be relatively rapid (7). Intact and gonadectomized male and female Wistar rats were exposed to an automated activity monitor after acute administration of saline, a low (1.0 mg/kg) and a moderate (10.0 mg/kg) dose of cocaine. The lower dose of cocaine was included to assess the possible inhibitory effects of cocaine on locomotor activity observed in other studies (3,4). Total distance travelled in the activity monitor and rearing behavior were analyzed. Subsequently,

some individuals in each group of subjects were treated with 10.0 mg/kg cocaine for 9 days, while the remaining subjects were treated with the saline solution prior to reexposure to the activity monitor. At that time, all subjects were again injected with 10.0 mg/kg cocaine to assess whether or not chronic exposure to the drug had resulted in behavioral sensitization or tolerance.

METHOD

Subjects

Eighteen male and 18 female Wistar rats were obtained from Charles River (Wilmington, DE) when they were 90 days old. Upon arrival in the laboratory they were housed in same-sex groups of 4 or 5 under a reversed light-dark cycle (lights on 7:00 p.m./lights off 7:00 a.m.). After one week of acclimatization to the laboratory 9 male and 9 female subjects were gonadectomized, while the remaining subjects were sham operated. The experiments started two weeks after surgery at which time the average weights and weight ranges were 298 g (272–338) for intact females, 343 g (321–377) for ovariectomized females, 483 g (429–575) for intact males and 470 g (444–526) for castrated males, respectively. Subjects were housed individually during the experiments with unlimited access to food and water.

Apparatus

Two Digiscan Animal Activity Monitors (Omnitech Electronics, Inc., Columbus, OH) were used. This activity monitor, which has been described in more detail elsewhere (13), consists of a Plexiglas activity monitor cage (40 × 40 × 30.5 cm) surrounded by horizontal and vertical infrared beams to measure a number of different dependent variables associated with the animal's locomotor activity (or the lack thereof). For the purposes of the present experiments the following data were analyzed: 1) distance traveled: a measure of the total distance traveled by the animal in centimeters and 2) number of vertical movements or rearings: a count of each time that the animal goes below the level of the vertical sensor for at least one second before the interruption of the vertical sensor.

Procedure

All subjects were exposed to the activity monitors for five consecutive sessions to determine the effects of acute cocaine administration on distance traveled and rearing behavior. During each 40 min session subjects were allowed to explore the apparatus for 10 min. They were then removed from the apparatus, injected with the drug or saline solution and immediately returned to the apparatus for 30 min. Data on distance travelled and rearing activity were collected separately for the 10 min prior to injection and for the 30 min postinjection (in 10 min intervals). Subjects received one injection each of 1.0 and 10.0 mg/kg/ml cocaine hydrochloride (Sigma, St. Louis, MO) during some sessions, while they received an equal volume of physiological saline during the remaining three sessions. All injections were given subcutaneously (SC) in the nape of the neck. The order of exposure to the saline and drug injections was counterbalanced across subjects.

Six weeks after the completion of this part of the experiment, five subjects in each group received chronic injections of 10.0 mg/kg cocaine in the home cage for 9 consecutive days. The remaining four subjects received saline during that same time period. All subjects were then re-exposed to the activity monitor for 10 min, removed from the monitor and injected with 10.0 mg/kg cocaine before being returned to the activity monitor for another 30 min.

Vaginal smears were obtained from all intact female rats following each session in which drug had been administered.

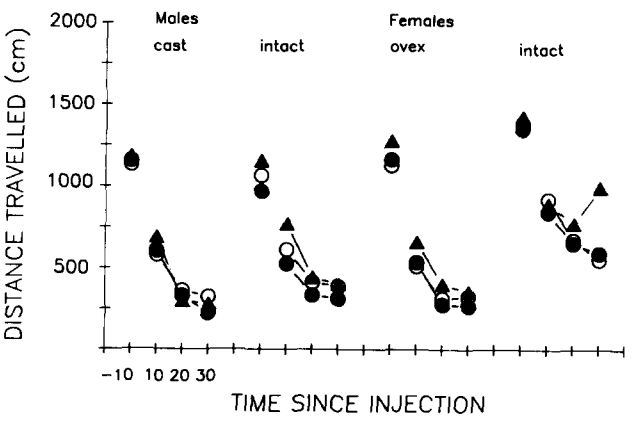

FIG. 1. Total distance traveled (in cm) during the 10 min prior to and the 30 min following drug administration for intact and gonadectomized male and female rats. The open circles represent observations during saline administration, while the filled circles and filled triangles represent observations during the administration of 1.0 and 10.0 mg/kg cocaine, respectively.

RESULTS

Figure 1 shows total distance travelled (in centimeters) during one, 10 min segment preceding the administration of saline or drug and three 10 min segments following drug administration for the different groups of subjects. Saline values represent the average of three sessions.

Analysis of variance (ANOVA) including the factors Gender (male/female, intact/gonadectomized) and Dose of Drug (0.0, 1.0 and 10.0 mg/kg cocaine) did not reveal any differences between groups during the 10 min preceding drug administration [Gender, $F(3,32) = 2.71$, n.s.; Dose, $F(2,64) = 1.49$, n.s.]. After saline and drug administration intact female rats traveled a longer distance than ovariectomized female rats or intact and castrated male rats [Gender, $F(3,32) = 12.60$, $p<0.001$]. The distance traveled decreased for all groups of subjects with prolonged exposure to the activity monitor after the administration of saline, 1.0 and 10.0 mg/kg of cocaine [Time since Injection, $F(2,64) = 131.57$, $p<0.001$]. The distance traveled by intact females, however, increased during the latter part of the session after the administration of 10.0 mg/kg cocaine, as can be seen in Fig. 1 and is confirmed by a significant interaction between gender, dose and time since injection, $F(12,128) = 4.00$, $p<0.001$.

Figure 2 shows total travel distance during one 10 min segment preceding, and three 10 min segments following the administration of 10.0 mg/kg cocaine after different groups of subjects had been treated with 10.0 mg/kg cocaine (closed triangles) or saline solution (open triangles) for 9 consecutive days.

Intact female rats traveled a longer distance than any of the other groups of subjects during the 10 min prior to the administration of 10.0 mg/kg cocaine after chronic saline or drug administration [Gender, $F(3,28) = 4.84$, $p<0.01$]. After drug administration in the final experimental session following chronic, home cage drug administration, intact females who had been chronically treated with saline as well as those females who had been chronically treated with 10.0 mg/kg cocaine traveled sig-

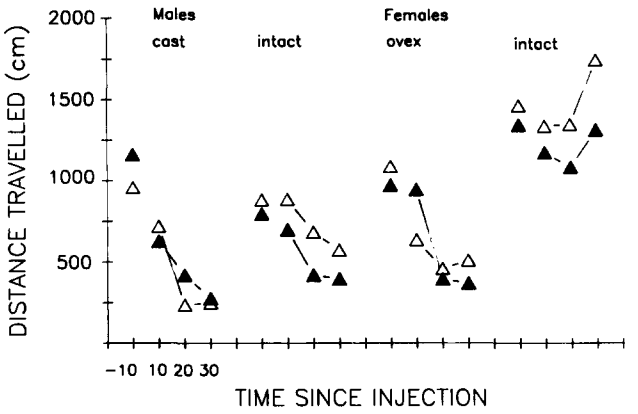

FIG. 2. Total distance traveled (in cm) during the 10 min prior to and the 30 min following the administration of 10.0 mg/kg cocaine for intact and gonadectomized male and female rats chronically treated with 10.0 mg/kg cocaine (filled triangles) or saline (open triangles).

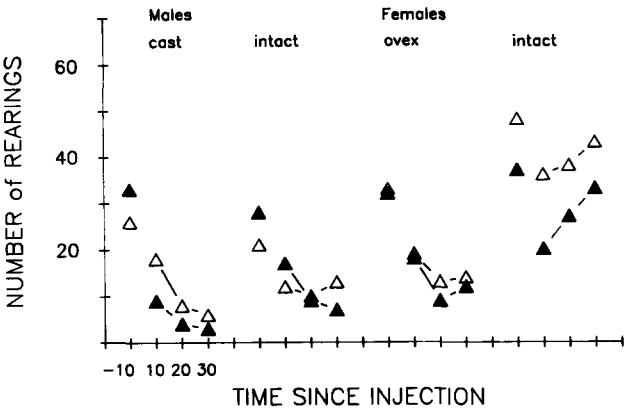

FIG. 4. Total number of rearings during the 10 min prior to and the 30 min following the administration of 10.0 mg/kg cocaine for intact and gonadectomized male and female rats chronically treated with 10.0 mg/kg cocaine (filled triangles) or saline (open triangles).

nificantly farther than ovariectomized females or intact and castrated males [Gender, $F(3,28)=22.53$, $p<0.001$]. Figure 2 also shows that total distance traveled increased during the session for intact female rats, while it decreased for all other groups of subjects [Gender × Time since Injection, $F(6,56)=12.50$, $p<0.001$]. Saline-treated intact females traveled a longer distance than cocaine-treated intact females [Gender × Treatment × Time, $F(6,56)=3.05$, $p<0.01$].

Figures 3 and 4 show rearing behavior after acute drug administration (Fig. 3) and after drug administration following chronic administration of saline or 10.0 mg/kg cocaine hydrochloride (Fig. 4). Rearing behavior was tabulated 10 min prior and 30 min following drug administration.

Prior to drug administration intact males engaged in less rearing behavior than any of the other groups of subjects [Gender, $F(3,32)=5.74$, $p<0.01$]. All groups of subjects reared less frequently after drug administration than after the administration of saline [Dose, $F(2,64)=6.64$, $p<0.01$]. Intact female rats engaged in more rearing behavior than any of the other groups of subjects after saline or drug administration [Gender, $F(3,32)=14.23$, $p<0.001$]. Rearing decreased during the session, except when intact females had been treated with 10.0 mg/kg cocaine. An increase in rearing activity was observed toward the end of the session in these subjects [Gender × Time × Dose, $F(12,128)=3.28$, $p<0.001$].

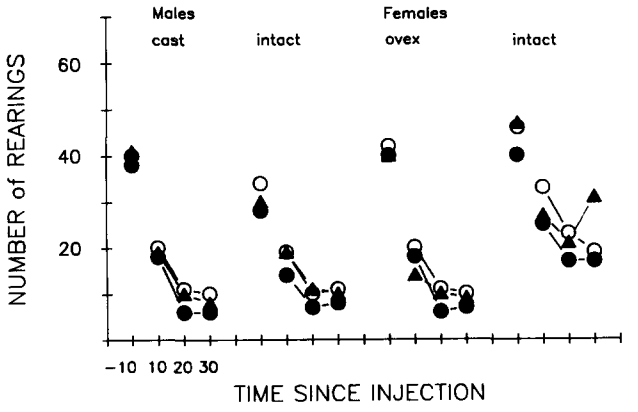

FIG. 3. Total number of rearings during the 10 min prior to and the 30 min following drug administration for intact and gonadectomized male and female rats. The open circles represent observations during saline administration, while the filled circles and filled triangles represent observations during the administration of 1.0 and 10.0 mg/kg cocaine, respectively.

As can be seen in Fig. 4, intact females more readily engaged in rearing behavior than any of the other groups of subjects after chronic drug administration but prior to drug administration in the test session [Gender, $F(3,28)=4.34$, $p<0.05$]. Ten mg/kg cocaine after chronic drug administration produced higher levels of rearing activity in females than in any of the other groups of subjects [Gender, $F(3,28)=22.76$, $p<0.001$], while subjects chronically treated with saline reared more than cocaine-treated subjects [Treatment, $F(1,28)=4.23$, $p<0.05$]. Rearing activity decreased during the session [Time since Injection, $F(2,56)=5.25$, $p<0.01$], except for intact females whose rearing activity increased over the course of the 30 min session irrespective of chronic treatment [Gender × Time, $F(6,56)=5.73$, $p<0.001$].

The analysis of vaginal smears did not suggest any obvious relationship between the behavioral effects of drug administration and the stage of tl.e estrus cycle (estrus vs. nonestrus) at the time of testing.

DISCUSSION

The results of the present experiment are interesting for a number of reasons. First of all, they show that acute cocaine administration differentially affects the behavior of male and female rats as locomotor activity and rearing behavior of intact female rats exceeded that of ovariectomized female rats and intact and castrated male rats. The data also show that ovarian hormones need to be present at the time of testing to functionally alter the behavioral effects of acute cocaine administration. However, differential behavioral effects were only observed after the administration of 10.0 mg/kg cocaine and not after 1.0 mg/kg, suggesting that neurochemical stimulation needs to exceed threshold values in intact male and female rats for behavioral differences to be observed. In addition it needs to be pointed out that the effects of cocaine administration on locomotor behavior and rearing activity were only assessed during 30 min after drug administration. Although such time period usually is sufficient to

be able to assess the behavioral effects of cocaine in other experimental preparations, such time period may not have been sufficient to allow cocaine's behavioral effects to appear in intact and castrated males and ovariectomized females.

In the second part of the present experiment some subjects received saline injections while others received 10.0 mg/kg cocaine for 9 consecutive days. On day 10, both treatments resulted in sensitization to the behavioral effects of another dose of 10.0 mg/kg cocaine in intact female subjects only. Although this part of the experiment was conducted with relatively small groups of subjects these data confirm observations by others (9) and raise interesting questions to be explored in future experiments. The absence of sensitization to the behavioral effects of cocaine in intact and castrated males and ovariectomized females confirms data from previous experiments, in which sensitization (or tolerance for that matter) was only observed when subjects received chronic drug administration in the experimental environment itself and not when subjects were treated in an environment totally distinct from the testing environment, as in the present experiment. The lack of sensitization to the behavioral effects of cocaine administration may also have been due to the fact that a relatively low dose of cocaine was chronically administered. Frequently doses well in excess of 10.0 mg/kg are used. In addition, the behavioral effects of cocaine were again only assessed for 30 min after drug administration.

Sensitization to the behavioral effects of cocaine was observed in intact female rats who had also been treated in the home cages, both after chronic treatment with saline and after treatment with 10.0 mg/kg cocaine. This observation could imply that behavioral sensitization after chronic drug administration may be observed even when subjects have been treated in an environment totally distinct from the testing environment, like the home cage environment in the present experiment. However, the fact that behavioral sensitization was also observed in females who had been chronically treated with saline in the home cage suggests that behavioral sensitization to cocaine administration may have occured in females even after only one administration of the higher dose of cocaine (during the first part of the experiment).

Drugs of abuse, including cocaine, amphetamine and alcohol enhance catecholaminergic, especially dopaminergic (DA) transmission in the brain. Previous research has shown that synaptic DA concentrations in terminal DA areas, the nucleus accumbens (terminal area of the mesolimbic DA system) and the dorsal caudate nucleus (projection area of the nigrostriatal DA system) are enhanced after administration of these drugs (2). Other experiments, of course, have shown that gonadal hormones, in particular, modulate striatal and hypothalamic DA-release in a sexually dimorphic manner (19). Numerous experiments have shown that the behavioral effects of acute and chronic amphetamine administration are very much modulated by the presence or absence of testicular and ovarian secretions (12). Even though very little research has been aimed at investigating the way in which endogenous gonadal hormones modify the behavioral effects of acute and chronic cocaine administration through neurochemical mechanisms, it seems likely that the central dopaminergic system is intrinsically involved.

ACKNOWLEDGEMENTS

The research reported in this manuscript was supported by a grant from the National Institute on Drug Abuse (U.S. Public Health Service, RO1 DA-06463) and a Research Career Development Award from the University of Florida to Frans van Haaren. The authors thank Bonnie McLaurin for expert technical assistance.

REFERENCES

1. Dackis, C. A.; Gold, M. S. New concepts in cocaine addiction: The dopamine depletion hypothesis. Neurosci. Biobehav. Rev. 9:469–477; 1985.
2. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85:5274–5278; 1988.
3. George, F. R. Cocaine produces low dose locomotor depressant effects in mice. Psychopharmacology (Berlin) 99:147–150; 1989.
4. George, F. R.; Ritz, M. C. Cocaine produces locomotor stimulation in SS but not LS mice: relationship to dopaminergic function. Psychopharmacology (Berlin) 101:18–22; 1990.
5. George, F. R.; Porrino, L. J.; Goldberg, S. R. Differences in locomotor activation and lethality in response to acute administration of cocaine across several rat genotypes. Behav. Genet. 17:622; 1987.
6. Joyce, J. N.; Van Hartesveldt, C. Behaviors induced by intrastriatal dopamine vary independently across the estrus cycle. Pharmacol. Biochem. Behav. 20:551–557; 1984.
7. Misra, A. L. Disposition and biotransformation of cocaine. In: Mule, S. J., ed. Cocaine: chemical biological, clinical, social and treatment aspects. Cleveland: CRC Press; 1976.
8. Post, R. M. Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. Life Sci. 26:1275–1282; 1980.
9. Post, R. M.; Contel, N. R. Human and animal studies of cocaine: implications for development of behavioral pathology. In: Creese, I., ed. Stimulants: neurochemical, behavioral and clinical perspectives. New York: Raven Press; 1983.
10. Post, R. M.; Lockfeld, A.; Squillace, K. M.; Contel, N. R. Drug-environment interaction: context-dependency of cocaine-induced behavioral sensitization. Life Sci. 28:755–760; 1981.
11. Roberts, D. C. S.; Bennett, S. A. L.; Vickers, G. J. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology (Berlin) 98:408–411; 1989.
12. Robinson, T. E. Stimulant drugs and stress: factors influencing individual differences in the susceptability to sensitization. In: Kalivas, P. W.; Barnes, C., eds. Sensitization of the nervous system. Caldwell, NJ: Telford Press; 1988:145–173.
13. Sanberg, P. R.; Zoloty, S. A.; Willis, R.; Ticarich, C. D.; Rhoads, K.; Nagy, R. P.; Mitchell, S. G.; Laforest, A. R.; Jenks, J. A.; Harkabus, L. J.; Gurson, D. B.; Finnefrock, J. A.; Bednarik, E. J. Digiscan activity: Automated measurement of thigmotactic and stereotypic behavior in rats. Pharmacol. Biochem. Behav. 27:569–572; 1987.
14. Schama, K. F.; Branch, M. N. Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter. Pharmacol. Biochem. Behav. 32:267–274; 1989.
15. Shuster, L.; Yu, G.; Bates, A. Sensitization to cocaine stimulation in mice. Psychopharmacology (Berlin) 52:185–190; 1977.
16. van Haaren, F.; Heinsbroek, R. P. W.; Louwerse, A.; van de Poll, N. E. d-Amphetamine differentially affects low, but not high response rates of male and female Wistar rats. Psychopharmacology (Berlin) 89:73–76; 1986.
17. van Haaren, F.; van Hest, A.; Heinsbroek, R. P. W. Behavioral differences between male and female rats: Effects of gonadal hormones on learning and memory. Neurosci. Biobehav. Rev. 14:23–33; 1990.
18. van Haaren, F.; Hughes, C. E. Cocaine-induced conditioned taste aversions in male and female Wistar rats. Pharmacol. Biochem. Behav. 37:693–696; 1990.
19. van Hartesveldt, C.; Joyce, J. N. Effects of estrogen on the basal ganglia. Neurosci. Biobehav. Rev. 10:1–14; 1986.

20. Weiss, S. R. B.; Post, R. M., Pert, A.; Woodward, R.; Murman, D. Context-dependent cocaine sensitization: Differential effects of haloperidol on development versus expression. Pharmacol. Biochem. Behav. 34:655–661; 1989.
21. Woolverton, W. L.; Balster, R. L. Effects of local anesthetics on fixed-interval responding in rhesus monkeys. Pharmacol. Biochem. Behav. 18:383–387; 1983.
22. Zubrycki, E. M.; Giordano, M.; Sanberg, P. R. The effects of cocaine on multivariate locomotor behavior and defecation. Behav. Brain. Res. 36:155–159; 1990.