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Effects of Cocaine on Locomotor Activity and Schedule-Controlled Behaviors of Inbred Rat Strains

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WITKIN, J. M. AND S. R. GOLDBERG. *Effects of cocaine on locomotor activity and schedule-controlled behaviors of inbred rat strains.* PHARMACOL BIOCHEM BEHAV **37**(2) 339–342, 1990.—Effects of cocaine on several behaviors considered to be reflective of psychomotor stimulation were compared in F344/CR1BR and NBR/NIH inbred rat strains. Effects of cocaine on locomotor activity were compared with effects on either bar-press or nose-poke responses maintained under a multiple fixed-interval 3-min, timeout 1-min schedule of food presentation. In locomotor activity experiments, NBR rats were twice as active as F344 rats under baseline conditions and displayed dose-dependent increases in locomotion (5–20 mg/kg). Maximal increases in locomotor activity of F344 rats were only 200% compared to 1000% in NBR rats. In contrast to locomotor activity, no strain differences in the effects of cocaine were observed under the schedules of food delivery. Bar-pressing under the fixed-interval schedule was increased to a maximum of 150% of control in both rat strains. Nose-poke responding under the fixed-interval schedule was not significantly increased, but timeout rates were increased in both strains. These results suggest that NBR and F344 rats do not differ in general sensitivity to stimulant effects of cocaine but exhibit marked differences in responsivity to cocaine that are dependent upon the behavior studied. Further delineation of the behavioral specificity of strain differences in sensitivity to cocaine should help to identify neurobiological substrates underlying unique biologically determined responses to cocaine.

Cocaine Rat strains Fixed interval schedule Locomotor activity Psychomotor stimulant Bar press Schedule-controlled behaviors Nose poke

THERE is evidence for genetic differences in response to some actions of cocaine. Shuster *et al.* (20) showed that cocaine increased locomotor activity to a greater extent in C57BL/6J mice than in A/J mice. Ruth *et al.* (19) reported that while cocaine produced increases in Y-maze activity, there were significant strain differences in the magnitude of this response, with C3H mice being more responsive than DBA or C57BL. These investigators also found genetic differences in vertically directed activity and heart rate related to cocaine administration; however, these effects of cocaine did not correlate precisely with locomotor stimulation. Similarly, de Fiebre *et al.* (1) reported that Short-Sleep mice were more sensitive than Long-Sleep mice to cocaine-induced hypothermia, whereas LS mice displayed greater effects of cocaine on locomotor activity. These studies suggest that specific behavioral effects of cocaine may be phylogenetically determined traits as has been demonstrated by recombinant genetic analysis of the locomotor stimulatory effects of d-amphetamine [cf. (16)].

Inbred strains which differ substantially in their response to a drug can be important research tools in the analysis of specific aspects of the pharmacology of that compound [e.g., (11)]. In a preliminary report using two genetically divergent rat strains, F344/CR1BR and NBR/NIH (2), cocaine was reported to produce dramatically different effects on locomotor activity [(4), abstract]. One question posed by the observation of larger increases in the locomotor stimulatory effects of cocaine in the NBR strain is whether these differences represent a general enhanced sensitivity to the psychomotor stimulant effects of cocaine in NBR rats. Alternatively, as suggested by the studies cited above, the differential effects of cocaine on one measure of psychomotor stimulation may not occur with other measures. Analysis of a range of behaviors is necessary to isolate specific behaviors that are uniquely affected by cocaine in a given inbred population. Defining the critical features or determinants of a behavior that are differentially affected by cocaine is an important step toward pinpointing underlying neural mechanisms involved in unique biologically determined actions of cocaine [cf. (24)].

The present study was, therefore, designed to determine whether the difference in sensitivity to the effects of cocaine in NBR and F344 rats was a general phenomenon, occurring across a number of different measures of psychomotor stimulation. Effects of cocaine on locomotor activity were determined to

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extend the previous brief report of strain differences and to provide detailed dose-response information. These results were then used for comparison with effects of cocaine on learned operant responding under multiple schedules of food presentation. The multiple schedules consisted of two components, a fixed-interval component and a timeout component, both of which have been shown to be sensitive to the rate-increasing effects of psychomotor stimulant compounds [cf. (7,10)]. The multiple schedule also allowed for direct assessment of the contribution of baseline response rate to the effects of cocaine for comparison with locomotor activity [cf. (23)]. Since the physical nature of a response or response topography can also influence behavioral effects of psychomotor stimulants, two different response topographies were studied, nose-poking and bar-pressing [cf. (5, 6, 8)]. These responses have been shown to generate different rates of responding and to be differentially sensitive to drug administration (5,9). Comparison of a range of behavioral effects of cocaine should also be useful in assessing potential pharmacokinetic differences of NBR and F344 rats with respect to cocaine as has been reported in other strains (21).

METHOD

Experimentally naive male F344/CR1BR and NBR/NIH rats, 14–16 weeks old at the beginning of the study, were used. In the experiments on schedule-controlled behavior, rats were maintained at 350 g and were housed individually with continuous access to water. Rats used in the locomotor activity experiments were housed in groups of 2 to 4 with unlimited access to Purina rat chow and water. All rats were maintained in a temperature-controlled room with a 12-hr light-dark cycle (0700–1900 lights on).

Locomotor Activity

Rats were tested between 0900 and 1300 hr under white fluorescent lighting. Six to eight rats per group were used for control (saline) or cocaine injections. Prior to injection, rats were individually placed in a Digiscan activity monitor (Omnitech Electronics), and allowed to acclimate to the chamber for 20 min prior to testing. Immediately following injection, the rats were again placed in the activity monitor and determinations of horizontal ambulatory activity, as measured by the interruption of photocell light beams, were accumulated electronically for 60 min.

Schedule-Controlled Responding

Four rats of each strain were studied in standard operant conditioning test chambers (BRS/LVE) which contained either a plastic disk or a lever for use as response manipulanda. Chambers were enclosed within sound- and light-attenuating chambers supplied with white noise to further mask extraneous sounds. Experimental events were scheduled and data were collected with a PDP 11/73 computer operating under SKED 11 software (State Systems, Kalamazoo, MI).

After initial training to eat food pellets (45 mg, BioServe, Frenchtown, NJ) delivered to a centrally located receptacle, the rats were trained to either push the disk or depress the lever by presenting food after successive approximations to these responses. When the translucent disk was transilluminated with orange light, pushing on the disk with a minimal force of 0.2 N through 1.5 mm produced food. When white lamps were illuminated above the levers, pressing the lever with a minimal downward force of 0.4 N through 1 mm produced food. All responses produced the audible click of a relay. The schedule under which drug effects were assessed was a multiple fixed-interval 3-min, timeout 60-sec schedule. In the presence of the disk or lever lights, the first response after 3 min produced food. After food delivery, the response lights and overhead houselight were extinguished and a 60-sec timeout period followed. During timeout, responses were recorded but had no scheduled consequences. A 60-sec limited-hold specified that if a response did not occur within 60 sec of the lapse of the 3-min interval, timeout occurred without food delivery. Sessions consisted of 7 cycles of the fixed-interval and lasted approximately 30 min.

Drugs

Cocaine HCl (Mallinckrodt) was dissolved in 0.9% NaCl and injected IP immediately prior to experimental sessions. Doses for the experiments on schedule-controlled responding were given in a range from those without behavioral effects to doses which decreased response rates under the fixed-interval schedule. Doses for the studies of locomotor activity were based on this dose range with the exception that the two lowest doses were not investigated. Effects of each dose were determined in mixed order, and at least twice in each subject in which operant behavior was studied. Baseline rates and patterns of responding generally returned to control values the day following drug administration. Doses are expressed as the salt (operant behavior) or as the base (locomotor activity); mol.wt. = 303.4 for base, 339.8 for HCl. Injections were given in a volume of 1.0 ml/kg for schedule-controlled experiments and 0.3 ml/kg for the locomotor activity studies.

Data Analysis

Effects of cocaine were expressed as a percentage of saline control values for grouped data (locomotor activity) or as a percentage of nondrug values and saline control values in individual subjects (operant behavior). Raw data were analyzed with nonrepeated and repeated measures analysis of variance. Where significant overall F values were obtained, post hoc comparisons were performed using two-tailed *t*-tests; paired *t*-tests were used for the analysis of operant behavior. A maximal acceptable error rate of 0.05 was set for attributing significance to results.

RESULTS

Locomotor Activity

NBR/NIH rats displayed higher saline control levels of locomotion than F344/CR1BR rats (mean ± SEM = 1124 ± 148 vs. 408 ± 87 counts; $p<0.05$). Cocaine produced significant overall dose-related changes in locomotor activity, $F(6,93)=99.57$, $p<0.0001$ (Fig. 1, left panel). A significant strain difference in response to cocaine was also observed, $F(1,93)=347.74$, $p<0.0001$, with NBR rats being substantially more affected overall by cocaine than F344 rats. This strain difference was also evident across cocaine doses, $F(6,93)=85.61$, $p<0.0001$.

For NBR rats, cocaine produced an overall significant effect on locomotor activity, $F(6,46)=108.58$, $p<0.0001$. Increases in activity occurred at 5, 10 and 20 mg/kg cocaine ($p<0.01$). Cocaine (1.25 mg/kg) decreased activity in this strain ($p<0.05$). For F344 rats, an overall significant effect of cocaine on locomotor activity was also observed, $F(6,47)=2.88$, $p<0.02$, although the magnitude of the effect was small relative to the NBR strain. Locomotor activity was significantly greater than saline control values with 20 mg/kg cocaine ($p<0.02$).

Operant Behavior

Visual observation of the animals during response shaping and

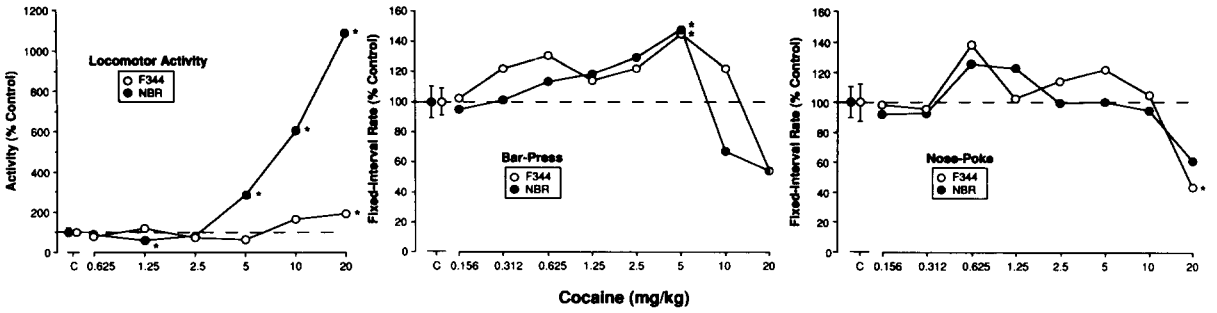

FIG. 1. Left panel: Effects of cocaine on locomotor activity of F344/CR1BR and NBR/NIH rats. Each point represents the mean effect in 6 to 8 rats. Middle panel: Comparison of effects of cocaine on bar-press responding under a fixed-interval schedule of food presentation in F344/CR1BR and NBR/NIH rats. Each point represents the mean of at least duplicate determinations in each of 4 rats. Right panel: Comparison of effects of cocaine on nose-poke responding in F344/CR1BR and NBR/NIH rats. Nose-poke responding was maintained under a multiple fixed-interval 3-min; timeout 1-min schedule. Each point represents the mean of at least duplicate determinations in each of 4 rats. Points above C represent effects of saline (left panel) or results of noninjection control days plus saline injection days (other panels); error bars represent ±S.E.M. Doses of cocaine are expressed as the base for locomotor activity and as the salt for the fixed-interval schedules.

throughout the experiment indicated that rats in chambers with the response disk pressed the disk with their noses and rats in the chambers with the response levers pressed with their paws. Control measures of performance of the NBR and F344 rats in the nose-poke and bar-press experiments are shown in Table 1. Rates of fixed-interval responding were about 10-fold higher than timeout rates. Baseline values were comparable across strains and types of responses except that the rate of bar-pressing under the fixed-interval schedule for NBR rats was higher than for F344 rats.

Cocaine also produced dose-related increases in responding under the fixed-interval bar-press schedule, $F(8,54)=7.19$, $p<0.01$. There were no effects of strain, $F(1,54)=1.66$, $p>0.05$, nor were strain × dose interactions significant, $F(8,54)=0.92$, $p>0.05$. Significant increases in fixed-interval responding were observed in both strains at 5 mg/kg (Fig. 1, middle panel). The large variability in effects of cocaine on the low rates of timeout responding precluded significant differences between strains or strain × dose interactions.

Analysis of group data indicated that cocaine did not significantly increase rates of responding under the fixed-interval schedule of nose-poking in either strain of rat (Fig. 1, right panel). However, peak effects were observed at 0.625 mg/kg where significant increases were observed in 3 of 4 rats in each group.

TABLE 1

BASELINE CONTROL VALUES (MEAN ± SEM) FOR OPERANT RESPONDING IN F344/CR1BR AND NBR/NIH RATS

Group	Fixed-Interval Rate (resp/sec)	Timeout Rate (resp/sec)
Nose-Poke		
F344	0.11 ± 0.01	0.007 ± 0.003
NBR	0.17 ± 0.02	0.011 ± 0.004
Bar-Press		
F344	0.06 ± 0.01	0.004 ± 0.003
NBR	0.13 ± 0.01*	0.004 ± 0.002

*Significantly different than fixed-interval rate of F344 bar-press rats ($p<0.05$).

The highest dose decreased responding in both strains, although this effect failed to reach significance in the NBR strain due to the results of one rat. There were no differences between strains, $F(1,54)=0.75$, $p>0.05$. Strain × dose interactions were also not significant, $F(8,54)=1.49$, $p>0.05$. Effects of cocaine on timeout responding were not significantly affected by strain, $F(1,54)=2.04$, $p>0.05$, or strain × dose interaction, $F(8,54)=0.84$, $p>0.05$. Rates of timeout responding were significantly increased in both rat strains at 10 mg/kg to 400–600% of control value; no differences between strains was observed (data not shown).

DISCUSSION

Differences in effects of cocaine in F344/CR1BR and NBR/NIH rats were observed when locomotor activity was measured. In contrast, F344 and NBR rats were not differentiated on the basis of the effects of cocaine under fixed-interval schedules of food presentation. Similarly, Ruth *et al.* (19) reported differences in various strains of mice that were dependent on the measure of locomotion used to assess psychomotor stimulant effects of cocaine. Whereas pharmacokinetics have been implicated in the strain difference in the effects of cocaine [e.g., (21)], the present data suggest that differences in the locomotor activation between F344/CR1BR and NBR/NIH strains was not due to significant pharmacokinetic variables since comparable differences in the effects of cocaine were not also observed under the fixed-interval schedules. Instead, pharmacodynamic differences are more likely to be related to the differences in the effects of cocaine reported here.

The contrasting effects of cocaine on locomotor activity and fixed-interval responding in the F344/CR1BR and NBR/NIH rat strains suggests that environmental or behavioral variables (e.g., the type or form of behavior, the schedule under which it is studied) can significantly determine the behavioral effects of stimulant drugs and whether strain differences in these effects are observed. For example, Moisset and Welch (15) reported increases in locomotor activity in home cages but not in open-field tests with BALB/cJ mice after d-amphetamine. Thus, strain differences in stimulant effects of d-amphetamine on open-field activity between C57BL/10J and BALB/cJ mice in their study may have been emphasized by environmental factors which mitigated the stimulant effects of the drug in the BALB strain only in the

open-field test (e.g., emotional suppression of activity). Similar variables may help account for the large difference in the locomotor stimulant actions of cocaine in the present study.

The observation of genetic differences in locomotor stimulation but not operant responding induced by cocaine suggests that strain differences in the behavioral effects of cocaine may reflect activation or inhibition of discrete behaviors or behavioral processes rather than effects on a phenomenon as general as psychomotor stimulation per se. Psychomotor stimulation undoubtedly involves a host of discrete behaviors, controlling variables, and neural mechanisms [cf. (24) for a general discussion]. Experiments which further isolate those critical features of behavior which are responsible for the observed differences in locomotor activity between NBR and F344 rats should help to narrow the range of biological variations underlying this strain difference. Such work could also cast further light on the neural substrates underlying stimulant effects of cocaine.

Although stimulation is the predominant effect of cocaine on locomotor activity, decreases in locomotor activity at low doses of cocaine and cocaine analogs have been reported previously (3,17). This locomotor depressant action of cocaine has convincingly been argued to be due to local anesthetic actions of these compounds (17). However, decreases in locomotor activity have also been reported with dopaminergic stimulants devoid of local anesthetic activity such as apomorphine (22). Nonetheless, the possibility that these effects of cocaine occur in only some rodent strains as in the present study is intriguing.

Although the behavioral effects of psychomotor stimulants are, under many conditions, strongly dependent on the nondrug or baseline rate of occurrence of responding (7, 10, 18), the effects of psychomotor stimulants across different strains do not appear to be completely described by rate-dependent actions of these drugs. Wenger (23) reported that the increases in locomotor activity produced by d-amphetamine were greatest in mice with low basal activity levels and that mice with relatively high activity baselines were least affected. However, the opposite relationship was observed in the present study where NBR rats were twice as active in the absence of drug but exhibited much greater locomotor stimulation with cocaine than F344 rats. Divergence from rate-dependent effects of drugs on locomotor activation has been reported previously (13, 14, 19). Likewise, under the fixed-interval schedule, comparable increases in fixed-interval responding occurred for F344 and NBR rats despite a two-fold difference in control rates of bar-pressing.

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