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A Single Preexposure Produces Sensitization to the Locomotor Effects of Cocaine in Mice

HELEN C. JACKSON[1] AND D. J. NUTT

Reckitt & Colman Psychopharmacology Unit, Department of Pharmacology, School of Medical Sciences, University Walk, Bristol, BS8 1TD, UK

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JACKSON, H. C. AND D. J. NUTT. *A single preexposure produces sensitization to the locomotor effects of cocaine in mice.* PHARMACOL BIOCHEM BEHAV **45**(3) 733–735, 1993.—Sensitization to the locomotor effects of cocaine (10 mg/kg, IP) occurred in mice following preexposure to a single high dose (40 mg/kg, IP) of the drug on the previous day. Behavioral sensitization only occurred under certain experimental conditions; that is, in mice which were injected in a novel environment (i.e., the activity boxes) on day 1 and tested in the same environment on day 2. It did not occur in mice that were fully habituated to the test apparatus on both days of the experiment or in mice that were injected in the home cage on day 1. This model is consistent with studies in rats, and offers the opportunity for further characterization of the processes underlying cocaine sensitization.

Cocaine Locomotor activity Sensitization (2-day paradigm) Conditioning Environment-dependent mice

IT is now well established that cocaine increases locomotor activity in animals and that repeated administration of low to moderate doses of cocaine enhances this response. This process is called behavioral sensitization or reverse tolerance, and is thought to reflect the psychomotor stimulant properties of the drug rather than its local anesthetic properties (1).

Recently, it has been shown that sensitization to the behavioral effects of cocaine can develop after preexposure of rats to a single high dose of cocaine (7). In the current study, we have investigated whether this 2-day sensitization paradigm can be extended to another species—mice. These animals have several advantages over rats. They are less expensive and require smaller amounts of drug. Moreover, it is possible to directly administer drugs into the cerebral ventricles of mice without either stereotaxic surgery or cannula implantation. In addition, there are strains of mice available that differ in the neurochemical pathways associated with reward (2,5,6).

Hence, a quick and easy model of cocaine sensitization in mice could be of use in evaluating the mechanisms underlying the development and expression of sensitization to psychomotor stimulants. In addition, it could also be of value in exploring the use of peptides and other compounds with limited availability in the treatment of addiction to cocaine and other drugs of abuse. Since experimental conditions can have an important influence on the development of behavioral sensitization (3,4,7), studies were performed in mice that were unaccustomed to the activity cages, in fully habituated mice, and in animals given their first injection of cocaine in the home cage.

METHOD

Animals

Male mice (TO strain; Bantin & Kingman; 28–35 g) were housed in groups of 30 in white polypropylene cages (57 × 37 × 20 cm high; sawdust bedding) at 23 ± 2°C under a 14L : 10D cycle (lights on at 0500 h) with free access to standard rodent diet and water. Mice were drug-naive at the start of each experiment and had not been previously exposed to the automated activity boxes. At the start of each experiment, mice were removed to a quiet, air-conditioned laboratory, rehoused in groups of 16 (thereafter called the home cage), and acclimatized to these conditions for at least 1 h before use. All procedures were carried out between 0900 h and 1600 h at a temperature of 23 ± 2°C.

Experimental Procedures

Locomotor activity was measured using four automated activity boxes. Each consisted of an open transparent-perspex arena (60 × 60 × 30 cm high; no bedding); that is, the boxes were quite different from the animals' normal housing conditions. Around the arena (at floor level) were located 15 sets of infrared emitters and detectors, which were interfaced to a

[1] Requests for reprints should be addressed to Helen C. Jackson, Pharmaceutical Research Division, Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Malov, Denmark.

computer that recorded continuously the number of beam breaks per unit time. Four identical sets of equipment were used so that the locomotor activity of animals from each of four different treatment groups could be monitored concurrently to control for any variations due to the time of day. Animals were tested individually and two animals from each treatment group were tested in each of the four boxes to account for any variability in either the activity boxes or their environment. Hence, treatment groups contained eight animals.

Four treatment groups were used, in an experimental design similar to that previously reported to show behavioral sensitization in rats (7). Thus, the treatment groups were: animals injected with vehicle on the first day of the experiment and also with vehicle on the second day; animals given vehicle on day 1 and cocaine 10 mg/kg on day 2; animals given cocaine 40 mg/kg on day 1 and cocaine 10 mg/kg on day 2; and finally, a group injected with cocaine 40 mg/kg on day 1 and vehicle on day 2.

Three different experiments were performed. In the first, animals were placed into the activity boxes immediately after drug administration on both day 1 and day 2. The locomotor activity of these animals was measured for 1 h on each day. In the second experiment, mice were given 40 min to habituate to the activity boxes on both day 1 and on day 2 before being injected with either vehicle or cocaine. The locomotor activity of these animals was monitored for 1 h on both days. A 40-min habituation period was used, since this is the time required for mice to fully explore the novel apparatus and for their activity levels to stabilize (I. J. Griffin; unpublished observations). In the third experiment, mice were injected and immediately returned to the home cage on day 1. On the second day, animals were injected, placed in the activity boxes for the first time, and their locomotor activity was monitored for 1 h. Mice were kept in the home cage between day 1 and day 2 in all experiments, and each cage contained four animals from each of the four different treatment groups.

Drugs

Cocaine hydrochloride (Sigma) was dissolved in 0.9% saline and administered IP in an injection volume of 10 ml/kg.

Statistical Analysis

Locomotor activity counts per 60-min period were statistically compared using nonparametric one-way analysis of variance (Kruskal-Wallis; $p < 0.05$; $H > 7.81$) followed by the Mann-Whitney U-test (two-tailed; $p < 0.05$; U values < 13; $n = 8$) for comparisons between two treatment groups.

RESULTS

In the first experiment, cocaine 40 mg/kg produced a large significant increase in locomotor activity in unhabituated TO mice (Table 1). On day 2, treatment with a lower dose of cocaine (10 mg/kg) also significantly increased locomotor activity over control levels in mice given vehicle or cocaine 40 mg/kg on day 1. However, the locomotor activity scores of animals previously exposed to the high dose of cocaine were significantly greater than those of the group treated with vehicle on the first day of the experiment (Table 1), being similar to those produced by cocaine 40 mg/kg on day 1. Interestingly, animals injected with the high dose of cocaine on day 1 but with vehicle on day 2 also had significantly greater levels of locomotor activity than the mice treated with the saline vehicle on both days.

In the second experiment, cocaine 40 mg/kg and cocaine 10 mg/kg significantly increased locomotion in mice that were

TABLE 1

LOCOMOTOR EFFECTS OF COCAINE IN MICE USING THE 2-DAY SENSITIZATION PARADIGM

Day 1		Day 2	
Treatment (mg/kg, IP)	Locomotor Activity (counts per 60 min)	Treatment (mg/kg, IP)	Locomotor Activity (counts per 60 min)
Unhabituated mice			
Vehicle	15510 ± 1340	Vehicle	11760 ± 1630
Vehicle	18250 ± 1840	Cocaine 10	26850 ± 1910*
Cocaine 40	41830 ± 3150*	Cocaine 10	39660 ± 3070*†
Cocaine 40	40470 ± 3270*	Vehicle	19130 ± 1730*
Habituated mice			
Vehicle	10710 ± 1730	Vehicle	7010 ± 1670
Vehicle	8870 ± 1190	Cocaine 10	17160 ± 2110*
Cocaine 40	31940 ± 4800*	Cocaine 10	21570 ± 4266*
Cocaine 40	32230 ± 3620*	Vehicle	9550 ± 2210
Mice injected in the home cage on day 1			
Vehicle	Not tested	Vehicle	18310 ± 1590
Vehicle	Not tested	Cocaine 10	25820 ± 1950*
Cocaine 40	Not tested	Cocaine 10	33440 ± 3040*
Cocaine 40	Not tested	Vehicle	16390 ± 1530

Results, expressed as mean ± SE, are given as a measure of variance. $n = 8$.

*$p < 0.05$ vs. the appropriate control group (given vehicle on day 1 or on both day 1 and day 2) for each experiment.

†$p < 0.05$ vs. the vehicle-cocaine 10 mg/kg group.

fully habituated to the activity boxes (Table 1). However, the activity scores of both the control and cocaine-treated groups tended to be lower than those of the unhabituated animals. Previous exposure to cocaine 40 mg/kg on day 1 did not significantly increase the locomotor response to cocaine 10 mg/kg on day 2 in the prehabituated mice (Table 1). In addition, the activity scores of habituated mice given cocaine 40 mg/kg on day 1 and vehicle on day 2 were not greater than those of the vehicle–vehicle control group.

In the third experiment, cocaine 10 mg/kg significantly increased locomotor activity in animals previously injected in the home cage with either vehicle or cocaine 40 mg/kg. The locomotor scores of these two groups were not significantly different (Table 1). Moreover, the scores of mice treated with the high dose of cocaine (40 mg/kg) in the home cage on day 1 and vehicle on day 2 were similar to those of the group given vehicle on both days.

DISCUSSION

The major finding of this study is that sensitization to the locomotor-activating effects of cocaine in mice develops after exposure to a single high dose. These findings replicate those previously reported in rats using a similar paradigm (7). Such studies are unlikely to be simply explained in terms of pharmacokinetics, since sensitization occurs under some but not all experimental conditions. For instance, the increase in locomotor responses to cocaine appears to be context dependent, since it was not observed in animals that were injected in the home cage on day 1. Similar findings that cocaine induced more activity in rats trained and tested in the same environment than in rats initially exposed to cocaine in the home cage have been reported by others (7). Thus, conditioning to the environment appears to play a role in the development of sensitization to cocaine. Interestingly, in rats cocaine will produce sensitization even when administered in the home cage, but this requires repeated administration (3). It would be relevant to perform similar experiments in mice.

Conditioning to the environment may also account for the increased activity over controls in the unhabituated mice given high-dose cocaine on day 1 and vehicle on day 2. An alternative explanation may be that on the first day cocaine interfered with habituation to the locomotor activity boxes. Increased activity of the cocaine–vehicle group was not observed in the mice that had explored their environment thoroughly before cocaine was administered on the first day. However, these effects, and also the lack of behavioral sensitization to the locomotor effects of cocaine in fully habituated mice, which was observed in this study, may also be explained in terms of classical conditioning. Thus, the association between the effects of cocaine and the activity boxes may have been reduced in the fully habituated animals. Studies of cocaine sensitization in fully habituated rats do not appear to have been performed as yet using the 2-day paradigm [although there is some evidence that it develops in these animals after repeated treatment with low doses of cocaine (4)].

Finally, the activity scores of cocaine (and vehicle)-treated mice were attenuated by habituation, and it may be that a certain level of behavioral activation is required before sensitization is manifest in the 2-day model. Thus, the stimulating effect of a novel environment during the first exposure to cocaine may contribute to the expression of behavioral sensitization.

The current data therefore suggest that two factors are necessary for cocaine sensitization in mice using the 2-day paradigm. The first is that animals are initially exposed to cocaine in an environment that they are unaccustomed to. The second is that animals are tested in the same environment as the initial exposure. In rats, exposure to a novel environment on day 1 (i.e., different from both the home cage and the test arena) is not sufficient to produce sensitization (3), suggesting that both conditions must be satisfied for it to occur. Further studies in rats habituated to the test arena are required to confirm this. In conclusion, this study has demonstrated that cocaine sensitization can be produced by single administration in mice but that it is dependent on certain experimental conditions. These data offer the opportunity for further characterization of the processes underlying cocaine sensitization.

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