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BRIEF COMMUNICATION

Sensitization of Rotational Behavior Produced by a Single Exposure to Cocaine

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LIN-CHU, G., T. E. ROBINSON AND J. B. BECKER. *Sensitization of rotational behavior produced by a single exposure to cocaine.* PHARMACOL BIOCHEM BEHAV 22(5) 901–903, 1985.—In rats with a unilateral 6-OHDA lesion of the substantia nigra a single exposure to cocaine significantly enhanced the ipsiversive rotational behavior produced by a second injection given one week later. It is concluded that it is not necessary to repeatedly administer psychomotor stimulant drugs to produce long-lasting changes in brain and behavior.

Cocaine Rotational behavior Sensitization Reverse tolerance 6-Hydroxydopamine

THE repeated administration of psychomotor stimulant drugs produces a long-lasting facilitation in the behavioral responsiveness to subsequent injections. For example, the locomotion, stereotypy or rotational behavior produced by amphetamine (AMPH) appears more rapidly, is more intense and/or is more persistent if animals have been previously exposed to AMPH ([4, 8, 10, 18], see [19] for review). This phenomenon of "reverse tolerance," or behavioral sensitization, is thought to provide an animal analogue of stimulant-induced psychosis in humans [12,19]. In many studies relatively high doses of dopamine-mimetic drugs are administered daily for long periods of time to produce behavioral sensitization. However, aggressive drug regimens may not be necessary to produce behavioral sensitization. For example, previous studies have shown that a single injection of AMPH enhances both rotational behavior and AMPH-stimulated striatal dopamine release [13,16]. The experiment reported here was conducted to determine if a single injection of another stimulant, cocaine, could also produce a long-lasting sensitization of rotational behavior.

METHOD

Female Holtzman rats weighing 200–300 g received an injection of 6-hydroxydopamine hydrobromide (8 μg/4 μl) into the right rostral zona compacta of the substantia nigra 30 min following pretreatment with desipramine [2]. After at least 5 weeks of recovery from surgery the rats received an IP injection of either 0.9% saline (n=16), 10 mg/kg of cocaine hydrochloride (n=8) or 40 mg/kg of cocaine (n=10), then were placed in automated spherical rotometers and rotational behavior recorded for 1 hr (see [16]). One week after this initial experience all animals received a second injection of cocaine, and rotational behavior was recorded again. During this second test session half the saline-pretreated rats received 10 mg/kg and half 40 mg/kg of cocaine, and the cocaine-pretreated rats received the same dose of cocaine they were pretreated with. These doses of cocaine were chosen because: (1) Stripling and Ellinwood [20] reported that 40 mg/kg of cocaine produced more reliable sensitization of stereotyped behavior than 20 mg/kg; and (2) Heikkila *et al.* [6] found that 20 mg/kg of cocaine resulted in levels of rotational behavior comparable to that produced by 1.0 mg/kg of AMPH. Therefore, these doses appeared to span the range necessary to produce both rotational behavior and sensitization. At least one week after the last test session all animals were decapitated, the striatum removed, and assayed for dopamine using high performance liquid chromatography with electrochemical detection (see [16]).

RESULTS

Only rats that had at least an 85% depletion of right striatal dopamine and turned ipsiversive when given cocaine were included in the following analysis (mean dopamine depletion ±S.E.M. = 96.9±1.14%). This was done to reduce variation in rotation rate due to variation in (1) the size of the lesion, and (2) the side of the lesion, relative to the "dominant" hemisphere for rotational behavior [14]. Unfortunately, the rats could not be screened to determine the "dominant" hemisphere prior to the 6-OHDA lesion, as suggested by Robinson and Becker [14], because this would "presensitize" them. Approximately 15% of the animals

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TABLE 1

MEAN (±S.E.M.) NUMBER OF NET ROTATIONS DURING THE FIRST AND SECOND TEST SESSIONS

First Test Session		Second Test Session	
Pretreatment	Rotations	Challenge	Rotations
Saline	17.1 ± 3.4	Cocaine (10 mg/kg)	55.0 ± 15.3
Saline	21.9 ± 8.7	Cocaine (40 mg/kg)	239.6 ± 36.2
Cocaine (10 mg/kg)	61.6 ± 24.6	Cocaine (10 mg/kg)	120.0 ± 21.2*
Cocaine (40 mg/kg	325.6 ± 75.2	Cocaine (40 mg/kg)	419.5 ± 95.9†

Differs from saline-pretreated, $*t=2.53$, $p=0.011$; $\dagger t=1.51$, $p=0.075$ (One-tailed tests because increased rotation predicted [13,16]).

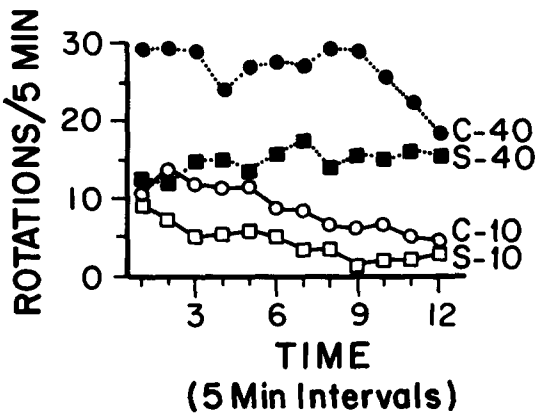

FIG. 1. Number of rotations (360° turns) made during each of 12 five min intervals following an injection with either 10 or 40 mg/kg of cocaine. C-10, C-40: Pretreated one week earlier with 10 or 40 mg/kg of cocaine, respectively, and then tested with the same dose of cocaine. S-10, S-40: Pretreated one week earlier with saline and then tested with 10 or 40 mg/kg of cocaine, respectively. Note: Cocaine-pretreated animals made significantly more rotations than did saline-pretreated animals (see text).

tested were excluded because they did not meet these criteria.

Figure 1 shows the number of rotations (one rotation equals 4 consecutive 90° turns in the same direction) made in each of 12 five min intervals during the second test session, following either 10 or 40 mg/kg of cocaine in both saline and cocaine-pretreated animals. Table 1 shows the total number of net rotations during the entire test session following saline or cocaine pretreatment, and the cocaine challenge. An injection of 10 mg/kg of cocaine caused a very rapid onset of rotational behavior that peaked in 5–10 min. Animals that were exposed to 10 mg/kg of cocaine one week earlier made significantly more rotations than those pretreated with saline (C-10 vs. S-10 in Fig. 1; $F(1,15)=4.45$, $p<0.049$; also see Table 1). The injection of 40 mg/kg of cocaine also produced very rapid onset rotational behavior, that was more vigorous and longer-lasting than that produced by 10 mg/kg (Fig. 1). When treated with 40 mg/kg of cocaine in the second test session saline-pretreated rats made significantly fewer rotations than did cocaine-pretreated rats during the first half of the test session, $F(1,15)=4.8$, $p<0.042$. These latter two groups did not quite differ statistically when compared over the entire hour because of considerable individual variation in the rate of offset of rotation at this dose, $F(1,15)=3.51$, $p<0.078$; cf. Table 1.

DISCUSSION

These results show that a single injection of cocaine can produce a long-lasting (at least one week) facilitation of rotational behavior, and supports the contention that it is not necessary to repeatedly administer psychomotor stimulant drugs for them to have enduring effects on brain and behavior [13,16]. In fact, the intermittent exposure to stimulants may produce more robust and enduring changes in brain and behavior than injections closely spaced in time [1, 7, 11].

The cause of this long-lasting enhancement in the behavioral responsiveness to infrequently administered AMPH or cocaine is not known. Previous studies have established that the behavioral sensitization produced by intermittent injections of AMPH is probably not due to metabolic or peripheral effects [3, 9, 17]. Both AMPH and cocaine-induced behavior can be conditioned following repeated administration in a unique test environment, suggesting that conditioning may contribute to sensitization (e.g., [12]). However, Robinson [13] recently showed that the long-lasting sensitization of rotational behavior produced by infrequent injections of AMPH is *not* due to drug-environment conditioning effects (also see [17]), and therefore it is unlikely that conditioning could account for the enduring effects of a single injection reported here. Exposure to AMPH can produce a long-lasting (>1 month) enhancement in the AMPH-stimulated release of endogenous dopamine from striatal tissue in vitro, suggesting a change in the presynaptic sensitivity of dopaminergic neurons [15,16]. Since cocaine and AMPH have fairly similar effects on dopaminergic neurons [5] a comparable change may be involved in the phenomenon reported here.

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