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Persistent Augmented Dopamine Release After Acute Cocaine Requires Dopamine Receptor Activation

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PERIS, J. AND N. R. ZAHNISER. *Persistent augmented dopamine release after acute cocaine requires dopamine receptor activation.* PHARMACOL BIOCHEM BEHAV 32(1) 71–76, 1989.—Pretreatment of rats with a single injection of cocaine produces a persistent augmentation of amphetamine-induced [^{3}H]dopamine ([^{3}H]DA) release measured using the in vitro striatal slice preparation. Cocaine has several actions in the nigrostriatal DA system: it blocks DA uptake and thereby indirectly stimulates DA receptors and it also acts as a local anesthetic. We investigated which of these actions is responsible for the augmented amphetamine-stimulated [^{3}H]DA release by determining whether pretreatment with drugs sharing one or more of these actions also augmented release. Release was increased in striatal slices one week after a single injection of either mazindol, a DA uptake blocker and indirect DA receptor agonist, or apomorphine, a direct-acting receptor agonist, whereas the local anesthetic lidocaine had no effect. The prerequisite of DA receptor stimulation was confirmed by pretreatment prior to the cocaine injection with either a nonselective, a D-1 selective or a D-2 selective DA receptor antagonist. Each of these blocked the long-lasting augmentation of release. From these experiments, we conclude that cocaine indirectly activates both D-1 and D-2 DA receptors to produce the persistent augmentation of striatal amphetamine-stimulated [^{3}H]DA release.

Cocaine Dopamine release Amphetamine Striatum Mazindol Apomorphine Fluphenazine SCH-23390 Sulpiride Sensitization

LONG-LASTING sensitization of DA-mediated behaviors occurs after only one injection of cocaine (14). Likewise, amphetamine-induced release of [^{3}H]DA from striatal slices is augmented from one day through two weeks after a single exposure to cocaine but then returns to control levels by one month (22). Since the time courses of these two effects are similar, it is possible that augmented striatal DA release underlies the increase in DA-mediated behaviors, or behavioral sensitization, seen after acute cocaine exposure. Understanding the mechanism by which cocaine administration induces this persistent increase in release may contribute to our understanding of how cocaine can produce behavioral sensitization.

Cocaine has several different pharmacological actions in the central nervous system. Due to its inhibition of DA uptake, it is an indirect-acting DA receptor agonist; additionally it is a local anesthetic. The purpose of the present studies was to determine which of these actions is responsible for the long-lasting increase in amphetamine-stimulated [^{3}H]DA release seen after one exposure to a moderate dose of cocaine. Release was measured either one or seven days after animals received a single dose of various substances sharing one or more of the neuroactive properties of cocaine. Drugs tested were mazindol, a DA uptake inhibitor and indirect-acting DA receptor agonist not shown to have local anesthetic properties (18,31); apomorphine, a nonselective direct-acting DA receptor agonist (3); and lidocaine, a local anesthetic. Additionally, in order to evaluate the contribution of indirect receptor activation by cocaine, the effects produced by a single injection of cocaine were measured after pretreatment with the nonselective DA receptor antagonist fluphenazine [see (6)]. Pretreatment with antagonists specific for the D-1 or D-2 DA receptor subtypes, SCH 23390 and sulpiride, respectively [see (6)], was used to test the importance of the two receptor subtypes in mediating the effect of cocaine.

METHOD

In Vivo Treatment

Groups of male Sprague-Dawley rats (250–300 g; Sasco; Omaha, NE) were injected IP with either 1 ml/kg saline, 10 mg/kg cocaine-HCl (Mallinckrodt, Inc.; St. Louis, MO), 1 or 10 mg/kg mazindol (Sandoz Pharmaceuticals; E. Hanover, NJ), 0.5 or 5.0 mg/kg apomorphine-HCl (Merck, Sharp & Dohme; Rahwey, NJ) or 20 mg/kg lidocaine (Sigma; St.

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Louis, MO). Doses of mazindol (34) and apomorphine (16) were chosen for moderate to maximal stimulation of the DA system. The dose of lidocaine (26) was chosen to produce local anesthetic effects. Other groups of rats received either 5 mg/kg fluphenazine-HCl (E. R. Squibb; Princeton, NJ), 0.5 mg/kg SCH 23390-maleate (Schering Corp.; Bloomfield, NJ) or 100 mg/kg sulpiride (Sigma Chemical Co.; St. Louis, MO) 15 min before an injection of either saline or 10 mg/kg cocaine. Doses of fluphenazine (6), SCH 23390 (15), and sulpiride (15) were chosen from the literature for maximal but selective antagonism of DA receptors. Animals were sacrificed either one day or one week after the drug injection(s).

[^{3}H]DA Release Assay

The methods for measuring tritium release from rat striatal slices preloaded with [^{3}H]DA have been described previously (22). Briefly, 0.4 mm slices of corpus striatum were incubated in Krebs' solution (pH=7.4) saturated with 95% O_2–5% CO_2 for 30 min at 35°C. The composition of the Krebs' buffer was (in mM): NaCl, 118; glucose, 11.1; $NaHCO_3$, 25; KCl, 4.7; NaH_2PO_4, 1.0; $MgCl_2$, 1.2; $CaCl_2$, 1.3; EDTA, 0.004; ascorbate, 0.11. The slices were incubated for an additional 30 min in fresh buffer containing a final concentration of 0.1 μM [^{3}H]DA (dihydroxyphenylethylamine 3,4-ethyl-2-[N-^{3}H]; 31.6 Ci/mmol; New England Nuclear; Boston, MA). Slices were washed, placed into separate glass chambers maintained at 33°C and superfused with oxygenated Krebs' buffer at a rate of 1 ml/min. The superfusate was collected at 5-min intervals beginning 50 min after the start of superfusion. At 70 min, slices were superfused for 2.5 min with either 2, 6 or 20 μM D-amphetamine (Sigma Chemical Co.; St. Louis, MO). At 115 min, slices were exposed to 5 Hz electric pulses (20 mA, 2 msec duration) for 1 min. Radioactivity in both superfusate and solubilized tissue was determined by liquid scintillation counting.

The composition of the tritium collected is known to differ with the two types of stimulation. Because amphetamine also inhibits uptake, it causes primarily [^{3}H]DA overflow (21). In contrast, electrical stimulation in the absence of uptake blockers or monoamine oxidase inhibitors causes primarily [^{3}H]dihydroxyphenylacetic acid ([^{3}H]DOPAC) overflow (20). It has been shown that [^{3}H]DOPAC is a reliable indicator of DA release (8). We henceforth refer to release measured in our system as tritium overflow.

The amount of tritium released in each fraction was expressed as a percentage of total tritium content present in each slice at the time of sample collection. An estimate of spontaneous release was averaged from the two 5-min fractions preceding each stimulus plus the first fraction after each stimulus in which release was either equal to or below prestimulation levels. The evoked tritium release was then calculated by subtracting spontaneous release from the tritium efflux collected in each fraction beginning immediately after the stimulus and continuing until the efflux again equalled spontaneous release (from 5 to 30 min depending on the amphetamine concentration). Each dose of D-amphetamine was tested in duplicate slices from the same animal. Results are expressed as mean values±SEM; N indicates the number of animals. Two-factor ANOVAs were used for statistical analysis in conjunction with Newman-Keuls follow-up comparisons. Each drug treatment was compared to a separate saline-treated group of animals; however since the data did not differ between these saline groups, the data were pooled for graphical representation.

RESULTS

We first determined whether drugs sharing one or more mechanism of action in common with cocaine also produced a persistent augmentation of tritium release from rat striatal slices. The effects of a single injection of cocaine, mazindol, apomorphine, or lidocaine were examined both one day and one week after the drugs were administered (Fig. 1). In agreement with our previous observations (22), in vivo pretreatment with cocaine produced a long-lasting increase in amphetamine-stimulated release (Fig. 1A). Release was augmented from 30–50% by all three concentrations of amphetamine tested one day after injection with cocaine, and this augmentation did not diminish after a one-week withdrawal period. In contrast to the effects on tritium overflow induced by amphetamine, tritium overflow induced by electrical field stimulation (5 Hz, 1 min, 300 pulses) from the same slices was not affected. One injection of mazindol also increased amphetamine-stimulated tritium release by 30–50% after one week, $F(1,5)=65.7$, $p<0.001$, but not after one day (Fig. 1B). In contrast to cocaine, mazindol decreased release by up to 25% one day after treatment, $F(1,5)=6.6$, $p<0.05$. Mazindol had no effect on tritium release evoked by electrical stimulation from the same slices (Fig. 1B). Similar results were observed with a higher dose of mazindol (10 mg/kg) with the exception that electrically-stimulated release was also increased to a significant degree after one day (data not shown). Similar to cocaine and mazindol, a single injection of apomorphine resulted in a 30–50% increase in amphetamine-stimulated tritium release one week later, $F(1,6)=6.0$, $p<0.05$; but unlike cocaine, apomorphine administration did not change release after one day (Fig. 1C). When a higher dose of apomorphine (5 mg/kg IP) was tested, tritium release was augmented to a similar degree after one week but again no change was seen after one day (data not shown). Neither dose of apomorphine affected electrically-stimulated tritium release (Fig. 1C). Pretreatment with a single injection of lidocaine at a dose able to produce local anesthesia affected neither amphetamine- nor electrically-stimulated tritium overflow at either time point (Fig. 1D).

In the next set of experiments, we determined whether the persistent effects of cocaine could be blocked by pretreatment with DA receptor antagonists (Fig. 2). When the nonselective DA receptor antagonist fluphenazine (5 mg/kg) was injected 15 minutes prior to cocaine administration, the cocaine-induced augmentation of tritium overflow was abolished both at one day and one week (Fig. 2A). Pretreatment with either the selective D-1 DA receptor antagonist SCH 23390 (0.5 mg/kg) or the selective D-2 DA receptor antagonist sulpiride (100 mg/kg) was equally effective in blocking the effects of cocaine on amphetamine-stimulated release (Fig. 2B and C). None of the antagonists tested had an effect on tritium overflow when injected alone (Table 1). Since SCH 23390 and sulpiride injected alone had no effect one day after injection, longer times after treatment were not examined. No significant main effects or interactions of the antagonists alone or the antagonists plus cocaine were found using ANOVA when compared with saline treatment. Furthermore, pretreatment with any of the antagonists either alone or in combination with cocaine did not consistently affect tritium overflow evoked by electrical stimulation from these same slices (Table 1 and Fig. 2).

DISCUSSION

The results obtained support the involvement of the indi-

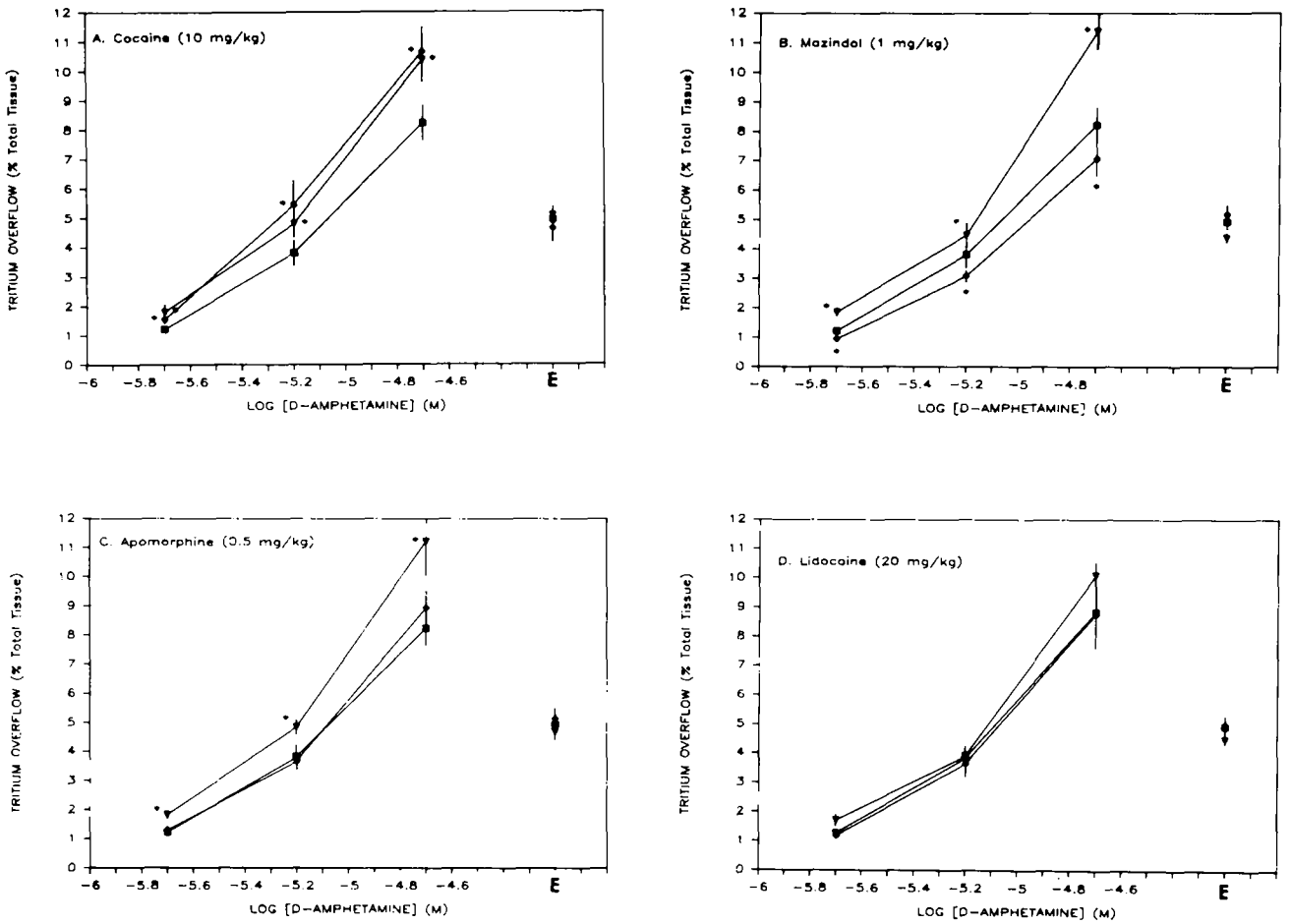

FIG. 1. D-amphetamine-induced [^{3}H]DA release is augmented one week after a single injection of cocaine, mazindol or apomorphine. Rats received one injection of either saline (■) or the drug indicated and were sacrificed one day (◆) or one week (▼) later. Tritium release was measured in response to 2.5 min exposure to 2, 6 or 20 μM amphetamine or 60 sec, 5 Hz electrical stimulation (E). Mean values ±SEM for N=18 (saline) and N=5 (drug treatments) are shown. ANOVA revealed a significant effect of amphetamine dose for all drugs tested and a significant effect of cocaine (panel A), mazindol (panel B) and apomorphine (panel C) treatment but not lidocaine treatment (panel D). Subsequent analyses indicated that cocaine treatment increased release relative to controls at both time points tested, whereas mazindol and apomorphine treatment increased release only one week later. Mazindol decreased release one day after treatment. *Indicates a significant change from control.

rect DA receptor agonist properties of cocaine in the development of enhanced amphetamine-evoked tritium release from striatum. Mazindol and apomorphine, which share the ability to stimulate DA receptors, mimicked the long-lasting effects of cocaine one week, but not one day, after injection. Pretreatment with DA receptor antagonists blocked the effect of cocaine normally observed both one day and one week after injection. These data indicate that DA uptake blockade, which would still occur in the presence of cocaine and a DA receptor antagonist, is not sufficient to cause the long-lasting augmentation of tritium release. It is also unlikely that the local anesthetic effect of cocaine is involved because lidocaine did not augment release.

It was expected that both apomorphine and mazindol would produce the same effects as cocaine at one day, as well as one week, after injection. This, however, was not the case. One difference between cocaine, apomorphine and mazindol is their duration of action in the brain. Cocaine and apomorphine are cleared by 99% from brain within 60 minutes (16, 19, 27), while mazindol has a relatively long half-life in plasma [30 hr; (28)]. Therefore, one day after injection, tissue levels of mazindol may still be high enough to interfere with the uptake pump and the ability of amphetamine to promote release. Consistent with this suggestion, amphetamine-stimulated release was significantly decreased one day after injection of either 1 or 10 mg/kg, and evoked overflow in response to electrical stimulation was increased after the higher dose. Therefore, it is likely that one day after treatment residual mazindol confounded the measurement of stimulation-evoked release.

In contrast with cocaine and mazindol, apomorphine had no effect on amphetamine-stimulated tritium release one day after a single injection. Apomorphine should be absent from the tissue at this time, however other long-lasting effects of apomorphine may obscure augmentation. For example, the higher dose of apomorphine administered in the current

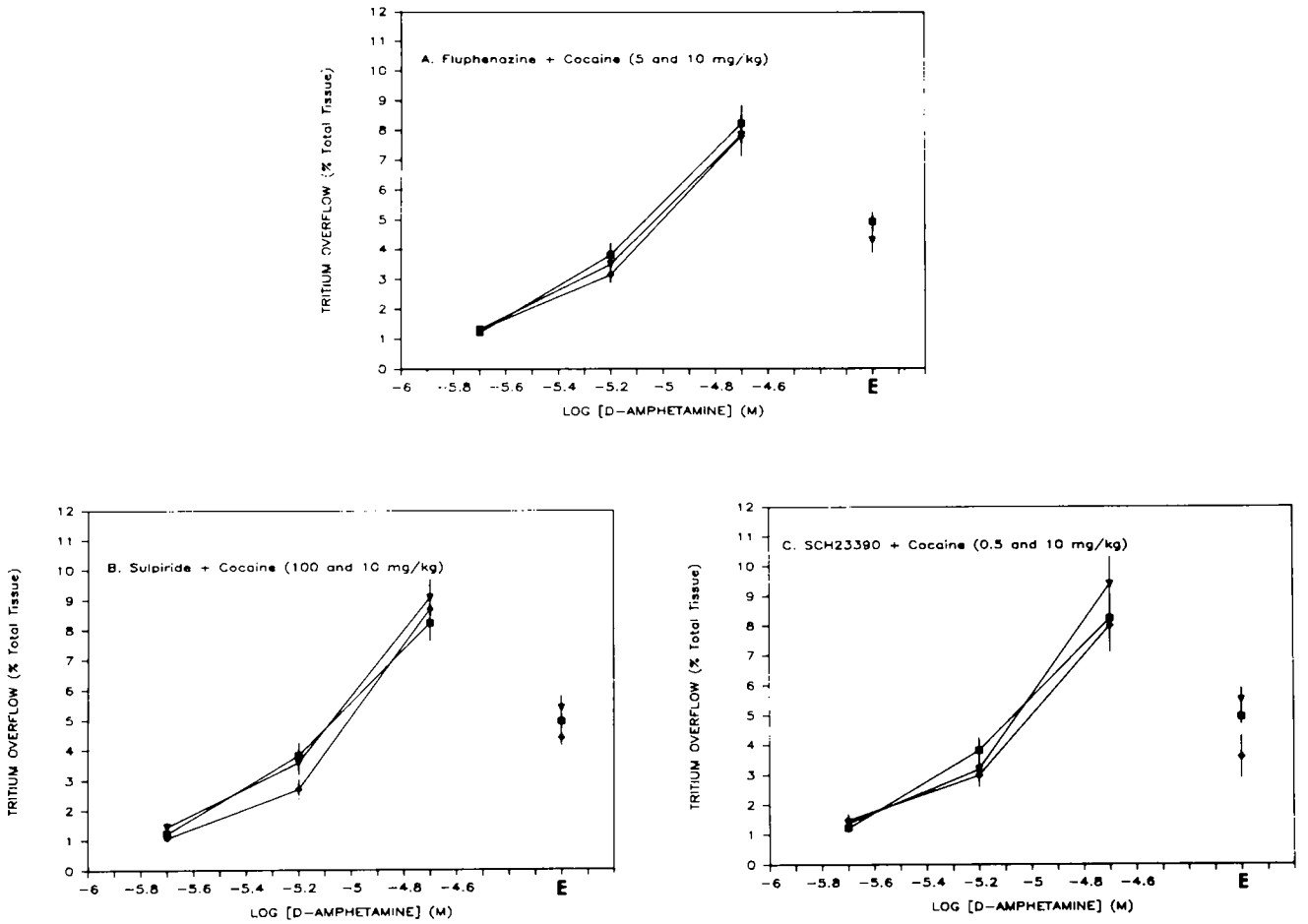

FIG. 2. Cocaine augmentation of D-amphetamine-induced [^{3}H]DA release is blocked by pretreatment with DA receptor antagonists. Rats were pretreated with the antagonists indicated, and then injected 15 min later with cocaine (10 mg/kg). Animals were sacrificed one day (◆) or one week (▼) later, and tritium release was measured as in Fig. 1. Data are compared to saline-treated controls (■). Mean values ±SEM are shown for N=18 (saline), N=5 (fluphenazine + cocaine at one day) and N=6 (all other drug treatments). ANOVA revealed a significant effect of amphetamine dose for all drugs tested but no significant effect of cocaine when proceeded by antagonist treatment. No change was seen in electrically-evoked (E) tritium release after any drug treatment. *Indicates a significant change from control.

TABLE 1

Drug Treatment	Tritium Overflow (% Total Tissue) D-Amphetamine Stimulation 2 μM	6 μM	20 μM	Electrical Stimulation
Saline				
1 day	1.2 ± 0.10	3.2 ± 0.26	8.0 ± 0.63	4.6 ± 0.19
Fluphenazine (5 mg/kg)				
1 day	1.8 ± 0.22	4.4 ± 0.38	9.2 ± 0.95	4.7 ± 0.47
1 week	1.4 ± 0.12	3.7 ± 0.29	8.4 ± 1.0	4.5 ± 0.62
SCH 23390 (0.5 mg/kg)				
1 day	1.1 ± 0.32	3.3 ± 0.83	8.8 ± 1.4	4.9 ± 0.42
Sulpiride (100 mg/kg)				
1 day	1.2 ± 0.18	4.0 ± 0.93	9.6 ± 1.0	4.9 ± 0.36

There was no effect of pretreatment with DA receptor antagonists on amphetamine- or electrically-stimulated tritium release. Shown are mean values ± SEM for N=4.

studies decreases striatal homovanillic acid levels for as long as eight hours following injection, even though apomorphine is not detectable in the brain at that time (16). Alternatively, changes in release caused by cocaine or apomorphine may be correlated with differential appearance of behavioral sensitization to these drugs. A single injection of cocaine increases stereotypic rotational behavior at least as early as one week (14); this observation is consistent with the occurrence of augmented amphetamine-stimulated release in striatum. A single injection of apomorphine causes long-lasting stereotypic behavioral sensitization, but this sensitization only becomes apparent two weeks after the initial injection (30). This observation supports the delayed augmentation of tritium release seen after a single dose of apomorphine although it is also possible that the latent increase in rotational behavior caused by apomorphine may involve more complex associative processes (29). On the other hand, behavioral sensitization involving climbing behavior has been observed as early as two hours after similar doses of apomorphine, and this effect lasts for two weeks (16). These discrepant results may reflect differences in the development of sensitization to apomorphine in the nigrostriatal system, which mediates stereotypic behaviors, and the mesolimbic system, which mediates locomotor activity. Thus, although eventually apomorphine and cocaine have similar effects on both striatal DA release and stereotypic behaviors, the time course of development of these effects appears to differ.

The results from the experiments in which rats were pretreated with DA receptor antagonists indicate that activation of both D-1 and D-2 DA receptors is necessary for cocaine-induced augmentation of release to occur. It has been suggested recently that D-1 receptors play an additive, a permissive or even an obligatory role in D-2 receptor-mediated events [see (7)]. For example, apomorphine activation of locomotor behavior can be blocked by either D-1 or D-2 receptor antagonists (1, 12, 27, 33). Thus, an interaction in the responses mediated by these two receptors may also be important in mediating the effects of cocaine.

Following a single dose of cocaine, the development of augmented amphetamine-stimulated DA release and behavioral sensitization parallel each other. In contrast, no changes have been found in striatal DA uptake, metabolism, synthesis, D-2 release-modulating autoreceptors or D-2 receptor binding after a single injection of cocaine (9, 11, 17, 32, 35). Changes in DA release have also been closely correlated with behavioral sensitization induced by amphetamine administration (24); both are present one day after acute exposure and persist for at least two weeks (13,25). Although amphetamine and cocaine appear to produce their in vivo effects on DA nerve terminals primarily via different mechanisms, i.e., amphetamine via promotion of release and cocaine via inhibition of uptake, the resulting increase in synaptic levels of DA may ultimately result in the same regulatory changes being induced. This, however, remains to be proven. It should be noted that other recent results suggest that cocaine and amphetamine induce behavioral sensitization characterized by different properties (23). Additionally, it has been shown that amphetamine exposure also increases DA release evoked by electrical or potassium stimulation (5); a similar change has not been demonstrated after cocaine exposure (22). The authors suggest that the underlying mechanism of the action of amphetamine is a redistribution of DA into a releasable vesicular pool that could ultimately increase both amphetamine- and electrically-stimulated release (5). Differences between treatment groups were greatest when DA was evoked by electrical stimulation frequencies greater than 5 Hz. Since our experiments employed 5 Hz electrical stimulation, increases in electrically-stimulated [^{3}H]DA release from striatum of cocaine-treated animals may become apparent if higher frequencies of stimulation are tested.

Our data suggest that the presynaptic change in DA release caused by cocaine administration requires activation of both D-1 and D-2 DA receptors rather than simply blockade of the DA uptake site. Previous attempts to block behavioral sensitization to repeated cocaine injections with nonselective DA receptor antagonists has resulted in either complete (2,4) or partial blockade (10) supporting this relationship. Activation of DA receptors, the majority of which are localized postsynaptically, must then affect presynaptic mechanisms determining release of DA from pools susceptible to different types of stimulation. It therefore seems likely that the striatonigral and nigrostriatal pathways are integral in this feedback loop and are necessary for this augmentation to occur.

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