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RAPID COMMUNICATION

Effect of Chronic Cocaine Treatment on D_2 Receptors Regulating the Release of Dopamine and Acetylcholine in the Nucleus Accumbens and Striatum

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GIFFORD, A. N. AND K. M. JOHNSON *Effect of chronic cocaine treatment on D_2 receptors regulating the release of dopamine and acetylcholine in the nucleus accumbens and striatum.* PHARMACOL BIOCHEM BEHAV **41**(4) 841–846, 1992.—The inhibition of electrically stimulated [^{3}H]DA and [^{14}C]ACh release by a submaximal concentration of quinpirole was measured 1 week after pretreating rats for 9 days with cocaine (15 mg/kg IP, twice per day). Although this pretreatment significantly enhanced behavioral response to a challenge injection of cocaine when compared with rats pretreated with saline only, no significant differences were apparent in the degree of inhibition of electrically evoked [^{3}H]DA or [^{14}C]ACh release by quinpirole in either the nucleus accumbens or striatum. In addition, the potentiation of electrically evoked [^{3}H]DA release and corresponding inhibition of [^{14}C]ACh release by 10 μM cocaine, measured in striatal slices only, was not significantly different between the two treatment groups. These results suggest that the enhanced behavioral response resulting from chronic cocaine treatment (behavioral sensitization) is not caused by a subsensitivity of D_2 terminal autoreceptors or by a supersensitivity of postsynaptic D_2 receptors on cholinergic neurons.

Behavioral sensitization Dopamine Acetylcholine Cocaine Autoreceptor D_2 receptor

IT is well known that cocaine prevents the reuptake of dopamine (DA), noradrenaline, and serotonin (32), thus resulting in increased extracellular levels of these transmitters (4,17). When administered to rodents, cocaine increases locomotor activity and, at higher doses, produces characteristic stereotyped movements (35). Repetitive daily administration of cocaine to rats results in a progressive enhancement in its motor-stimulating and stereotypy-inducing effects (20,21). Thus, after several daily injections of cocaine, a dose that initially produced relatively little motor stimulation on the first day of injection will produce a much stronger motor stimulation effect and/or induce stereotyped behaviors. This phenomenon, termed "behavioral sensitization," is also seen with repetitive administration of other dopaminergic agents, such as apomorphine (29,30) and amphetamine (27). Behavioral sensitization is of interest since it may provide a model for the development of psychoses associated with chronic cocaine or amphetamine use in humans, and may also give clues as to the mechanisms underlying schizophrenia.

Despite much research, the neurochemical changes leading to behavioral sensitization are still unclear. One possibility is that behavioral sensitization is a consequence of subsensitivity of release-regulating DA autoreceptors (36). This possibility is consistent with the reports that cocaine- or amphetamine-induced elevations in extracellular DA, as measured by in vivo microdialysis in the nucleus accumbens, are greater in sensitized animals (14,18,28). Previous in vitro studies by Dwoskin et al. (9) and Fitzgerald and Reid (11), in which the ability of the D_2 agonist, pergolide, to inhibit electrically evoked DA release in striatal slices was examined, provided no evidence of autoreceptor subsensitivity in cocaine-sensitized animals. However, in contrast to these two studies, Yi and Johnson

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(36) found that sensitized animals had a marked reduction in the ability of the D_2 agonist, N-0437, to inhibit calcium-evoked DA release in synaptosomes from both the corpus striatum and nucleus accumbens. Thus, in order to help clarify this situation and to more closely examine autoreceptor sensitivity in the nucleus accumbens, which is the region primarily involved in the reward and motor stimulant properties of cocaine (15,25,26), we measured the ability of the D_2 agonist, quinpirole, to inhibit electrically stimulated DA release in slices prepared from the nucleus accumbens and striatum of cocaine-sensitized rats.

Apart from increased DA release, the enhancement in motor behavior and stereotypies following a cocaine challenge to sensitized animals could also be explained by an increased postsynaptic supersensitivity to dopamine. To date, binding studies have given conflicting evidence as to whether sensitized animals have an increased dopamine receptor sensitivity in dopamine terminal areas. For example, increases (33,34), decreases (12), and no change (9) have been reported for the binding of D_2 ligands to striatal homogenates in chronic cocaine-treated rats. However, an enhanced postsynaptic responsiveness to dopamine could result from an increased efficiency in the receptor to effector coupling, without any changes in receptor number or affinity. Thus, in addition to measuring DA release, we investigated the possibility of functional postsynaptic D_2-receptor supersensitivity by measuring the ability of quinpirole to inhibit the electrically stimulated release of acetylcholine (ACh) from slices of the nucleus accumbens and corpus striatum.

METHOD

Animals and Treatment Schedule

Female Sprague-Dawley rats (Texas Animal Specialties, Humble, TX), weighing 180–250 g, were administered cocaine (15 mg/kg) or saline twice per day for 9 days. Rats employed for the in vitro study were sacrificed on the 16th day, and the nucleus accumbens and striatum were dissected out. Rats employed for the behavioral study were given a saline challenge on the 15th day and a cocaine challenge on the 16th day. Behavior was rated on a six-point scale, modified from that described by Ellinwood and Balster (10), by an observer unaware of the previous injection schedule of each animal. The scale employed was as follows:

1. Lying down or asleep.
2. Feeding, drinking, or grooming.
3. Exploring the cage at normal levels of activity.
4. Exploring the cage with hyperactivity; little or no stereotypies.
5. Frequent stereotyped movements, although still exploring the cage.
6. Almost continuous stereotyped movements, mainly restricted to one place in the cage.

For each animal, the predominant behavior over a 1-min interval 15 and 30 min after the cocaine or saline injection was scored. The ratings obtained at these two intervals were then combined to give the cumulative score for each rat.

[^{3}H]DA and [^{14}C]ACh Release Assay

The rats were decapitated, their brains removed, and the nucleus accumbens and striatum dissected out as previously described (5). Following dissection, the tissue was chopped into 300 μm slices and the slices incubated for 10 min in 2 ml Krebs buffer (119.5 mM NaCl, 3.3 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 11 mM glucose, 0.03 mM ethylenediaminetetraacetic acid [EDTA], 0.6 mM ascorbate, pH 7.4), saturated with 95% O_2/5% CO_2, at 37°C. Subsequently, the slices were incubated in 1 ml of fresh buffer containing 1.5 μCi [^{3}H]DA and 10 μCi [^{14}C]choline for 18 min. The slices were then transferred to eight superfusion chambers (2–3 striatal slices or 3–4 accumbens slices per chamber). The slices were sandwiched between two platinum mesh screens positioned midway between two platinum electrodes. The electrodes were connected to a stimulator (Grass Instruments, Quincy, MA) via a chamber switching controller. Slices were superfused at 37°C with oxygenated Krebs buffer containing 10 μM hemicholinium-3 (to prevent reuptake of [^{14}C]choline hydrolyzed from released [^{14}C]ACh) at a rate of 0.25 ml/min; 3.3-min fractions were collected beginning 110 min after the start of superfusion. The tissue slices were subjected to two 3-min periods of electrical stimulation (S_1 and S_2) beginning 115 and 148 min after superfusion was started. In some cases a third 3-min period of electrical stimulation (S_3) was given at 181 min. Each stimulation period consisted of a train of unipolar, sawtoothed-shaped pulses (50 mA, 2 msec) at a rate of 0.3 sec^{-1}. When quinpirole or cocaine was included in the superfusion medium, it was added 17 min before S_2 or S_3, respectively. Sulpiride was added 22 min before S_2. All three drugs were left in the superfusion medium until the termination of the experiment. After the end of the superfusion, the slices were removed and their residual radioactivity determined.

The released radioactivity was calculated as fractional release × 100 (i.e., the radioactivity in each fraction was calculated as a percentage of the total radioactivity present in the tissue at the start of collection of that fraction). The enhanced overflow of radioactivity induced by electrical stimulation was expressed as the sum of the increased fractional release above baseline in the three fractions following the start of stimulation. To estimate the effect of different drugs on the electrically stimulated release of neurotransmitter, the stimulated overflow in the presence of the drug (S_2 or S_3) was divided by the stimulated overflow in their absence (S_1 or S_2). Although the released radioactivity is actually in the form of a mixture of neurotransmitters and metabolites, the stimulated release of [^{3}H] and [^{14}C] is considered representative of the release of DA and ACh since the metabolites are formed subsequent to transmitter release (6,16,24).

Statistical Analysis

Comparisons for the behavioral data were made using a Mann-Whitney *U*-test. Comparisons for the release data were

TABLE 1

BEHAVIORAL RATING OF CHRONIC COCAINE- OR SALINE-TREATED RATS FOLLOWING A CHALLENGE INJECTION OF COCAINE OR SALINE

Challenge	Saline Pretreatment	Cocaine Pretreatment
Saline	5 (4–6)	4 (3–6)*
Cocaine (15 mg/kg)	9 (8–10)	12 (9–12)†

Behavioral scores for each rat were calculated by taking the mean of the rating at 15- and 30-min timepoints following the challenge injection. Values represent the median (and range) from 6–7 rats.

*Not significantly different from saline-pretreated rats given a challenge saline injection. †$p < 0.05$ compared to saline-pretreated rats given a challenge cocaine injection.

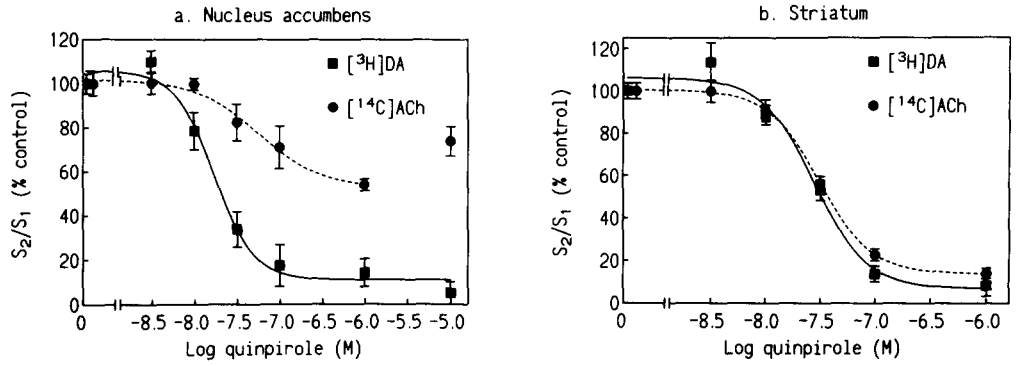

FIG. 1. Inhibition of electrically stimulated [^{3}H]DA and [^{14}C]ACh by quinpirole in (a) nucleus accumbens and (b) corpus striatum. Values are the means (± SEM) of 3-6 experiments.

made using Student's *t*-test. All statistical tests were two-tailed. IC_{50} values were calculated using a sigmoidal logistic equation with the assistance of an iterative curve-fitting program (ALLFIT), according to the method of De Lean et al. (8).

Drugs

(−)-Quinpirole hydrochloride and S(−)-sulpiride were purchased from Research Biochemicals Incorporated (Natick, MA). [^{3}H]DA (23 Ci/mmol) and [^{14}C]choline (53 mCi/mmol) were purchased from NEN Research Products (Boston, MA). Cocaine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO).

RESULTS

In comparison with rats pretreated with saline, rats pretreated with cocaine showed no differences in their response to a challenge injection of saline but were clearly enhanced in

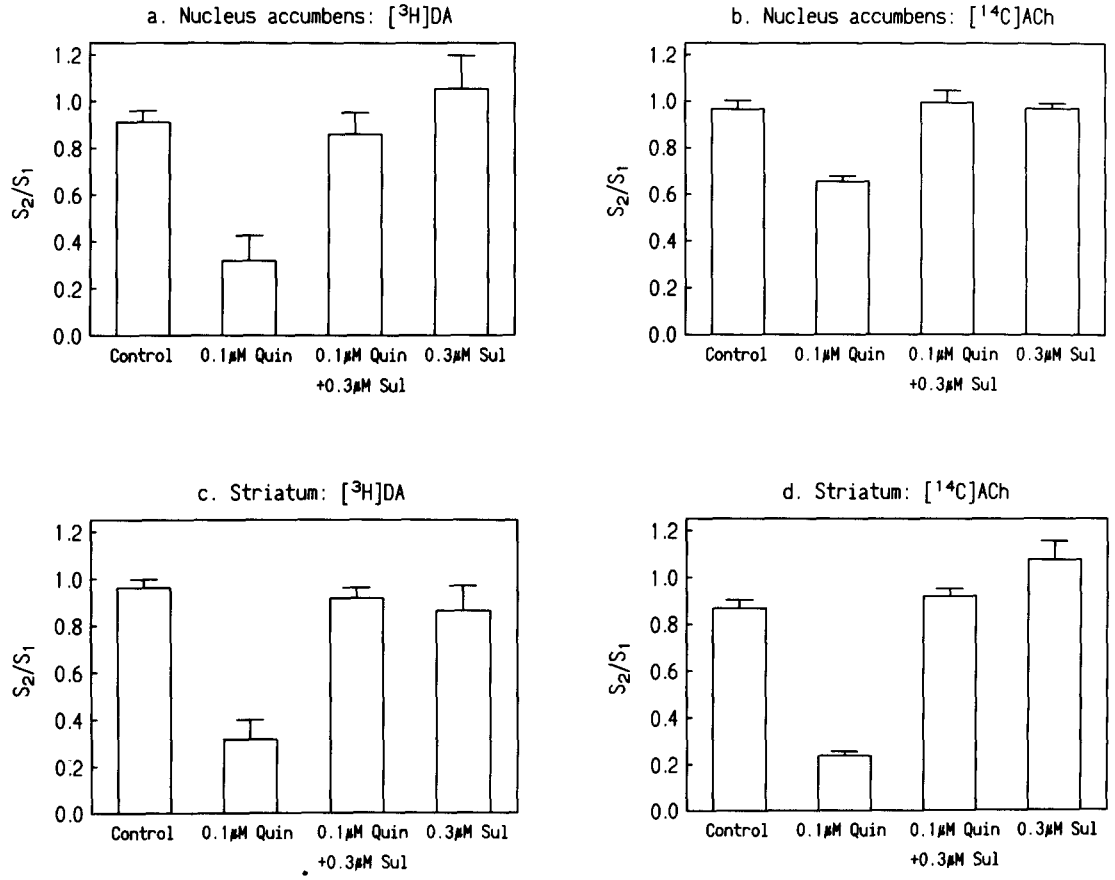

FIG. 2. Effect of sulpiride on the inhibition of electrically stimulated [^{3}H]DA and [^{14}C]ACh by quinpirole. (a) [^{3}H]DA release in the nucleus accumbens; (b) [^{14}C]ACh release in the nucleus accumbens; (c) [^{3}H]DA release in the corpus striatum; (d) [^{14}C]ACh release in the corpus striatum. Values are the means (± SEM) of 8-9 experiments.

their response to a challenge injection of cocaine (Table 1). When challenged with cocaine, almost all cocaine-pretreated rats were rated as either 5 or 6 at both the 15- and 30-min postinjection timepoints, whereas saline pretreated animals were rated as either 4 or 5 at these timepoints. Ratings of 6 were never seen in saline-pretreated animals. A second observer who rated the rats along with the first observer, but who, unlike the first observer, was aware of the previous treatment schedule of each rat, obtained similar behavior ratings (data not included).

Stimulation-evoked overflow of [^{3}H]DA and [^{14}C]ACh from accumbens and striatal slices was inhibited in a concentration-dependent manner by the D_2 agonist, quinpirole (Fig. 1a, b). Quinpirole inhibited the release of both transmitters from both brain areas with approximately equal potency (IC_{50} values as follows; nucleus accumbens: [^{3}H]DA, 15 nM; [^{14}C]ACh, 58 nM; striatum: [^{3}H]DA, 27 nM, [^{14}C]ACh, 29 nM). However, the degree of maximal inhibition of ACh release by quinpirole was much less in the nucleus accumbens than in the striatum.

The inhibition of [^{3}H]DA and [^{14}C]ACh release by 0.1 μM quinpirole (a near maximally effective concentration) was completely reversed by the D_2 antagonist, sulpiride, at a concentration of 0.3 μM (Fig. 2a-d). Sulpiride alone caused little or no enhancement of [^{3}H]DA or [^{14}C]ACh release, suggesting that the synaptic concentration of endogenous DA in the slice is not sufficient to significantly inhibit the release of either transmitter.

No differences were apparent in the absolute amounts of [^{3}H]DA or [^{14}C]ACh released by a single period of stimulation (S_1) in rats treated chronically with cocaine compared with rats treated with saline only (Table 2). There were also no significant differences between chronic cocaine- and saline-treated rats in the degree of inhibition of [^{3}H]DA or [^{14}C]ACh release by 80 nM quinpirole in either the nucleus accumbens or striatum (Table 3), thus suggesting that neither DA autoreceptors nor postsynaptic receptors on ACh neurons are subsensitive in rats treated chronically with cocaine.

In striatal slices that had not been exposed to quinpirole, the effect of the addition of 10 μM cocaine to the superfusion medium on electrically stimulated [^{3}H]DA and [^{14}C]ACh was examined (Table 4). In these slices, cocaine induced a 48% increase in [^{3}H]DA overflow. There was also a 60% decrease in [^{14}C]ACh release, presumably due to the enhancement in extracellular levels of endogenous DA in the slices by cocaine. However, there were no significant differences between chronic cocaine- and saline-treated rats in the degree of enhancement in [^{3}H]DA release or the inhibition of [^{14}C]ACh release by 10 μM cocaine in vitro.

TABLE 2

EFFECT OF CHRONIC COCAINE PRETREATMENT ON THE PERCENTAGE OF TISSUE STORES OF [^{3}H]DA OR [^{14}C]ACh RELEASED BY ELECTRICAL FIELD STIMULATION

	S_1-Fractional Release (%)	
Region/Radiolabel	Saline	Cocaine
Nucleus accumbens		
[^{3}H]DA	0.95 ± 0.09	1.03 ± 0.09
[^{14}C]ACh	3.08 ± 0.35	4.05 ± 0.51
Striatum		
[^{3}H]DA	1.84 ± 0.14	2.06 ± 0.17
[^{14}C]ACh	4.44 ± 0.52	4.49 ± 0.54

Values are means (±SEM) of 6-7 experiments. Values for cocaine pretreatment do not differ significantly from corresponding values for saline pretreatment.

TABLE 3

EFFECT OF CHRONIC COCAINE PRETREATMENT ON THE INHIBITION OF ELECTRICALLY EVOKED RELEASE OF [^{3}H]DA AND [^{14}C]ACh BY 80 nM QUINPIROLE

	S_2/S_1 (% control)	
Region/Radiolabel	Saline	Cocaine
Nucleus accumbens		
[^{3}H]DA	31.9 ± 4.4	21.0 ± 6.6
[^{14}C]ACh	76.5 ± 4.2	69.5 ± 5.2
Striatum		
[^{3}H]DA	19.8 ± 4.4	23.6 ± 6.8
[^{14}C]ACh	30.1 ± 2.6	33.4 ± 5.5

Values are means (±SEM) of 7-8 experiments. Values for cocaine pretreatment do not differ significantly from corresponding values for saline pretreatment.

DISCUSSION

This study utilized the inhibition of electrically stimulated [^{3}H]DA and [^{14}C]ACh release by quinpirole as markers for the sensitivity of D_2 presynaptic and postsynaptic receptors, respectively. Analysis of the inhibition curves suggests that the affinity of D_2 pre- and postsynaptic receptors for quinpirole is not different in either the nucleus accumbens or striatum. However, the maximal inhibition of ACh release by quinpirole was much less in the nucleus accumbens than in the striatum, suggesting that cholinergic neurons in the latter area are less susceptible to dopaminergic regulation, perhaps because of a more sparse innervation of these neurons.

Although complete dose-response curves for quinpirole inhibition were not obtained in chronically treated rats, the absence of any decrease in the inhibition of DA release by a submaximal concentration (80 nM) of quinpirole between cocaine- and saline-treated rats in either the nucleus accumbens or striatum strongly suggests that chronic cocaine treatment does not alter either the number or affinity of D_2 autore-

TABLE 4

EFFECT OF CHRONIC COCAINE TREATMENT ON THE POTENTIATION OF [^{3}H]DA RELEASE AND INHIBITION OF [^{14}C]ACh RELEASE BY 10 μM COCAINE IN STRIATAL SLICES

	S_3/S_2 (% control)	
Radiolabel	Saline	Cocaine
[^{3}H]DA	147.8 ± 9.0	128.0 ± 15.3
[^{14}C]ACh	40.1 ± 5.5	40.2 ± 5.2

Values are means (±SEM) of 5-6 experiments. Data for cocaine-pretreated rats are not significantly different from corresponding values for saline-pretreated rats.

ceptors in these areas. A similar conclusion was reached by Fitzgerald and Reid (11) in striatal slices, whereas Dwoskin et al. (9) found a slight supersensitivity of DA autoreceptors in striatal slices from chronic cocaine-treated rats. It should be noted, however, that both studies employed male rats, which are relatively difficult to sensitize compared with female rats (19, Snell and Johnson, unpublished observations). In fact, in the study by Fitzgerald and Reid (11), which did include behavioral data, the increase in locomotor response to cocaine in cocaine-pretreated rats did not reach significance, despite 14 days of treatment (10 mg/kg/day IP). In contrast to the results obtained by Dwoskin et al. (9) and Fitzgerald and Reid (11), Yi and Johnson (36) found that both accumbens and striatal release-regulating DA autoreceptors *were* subsensitive in sensitized female rats. In the latter investigation, DA release was evoked by calcium addition to synaptosomes. Calcium-evoked DA release is very sensitive to regulation by autoreceptors that are apparently linked to a hyperpolarizing potassium conductance (2,3, Yi and Johnson, unpublished observations). The discrepancy between the findings of Yi and Johnson (36) and those reported here suggests that inhibition of calcium-evoked DA release and the inhibition of electrically stimulated DA release do not involve precisely the same mechanism, and that these mechanisms are differentially affected by chronic cocaine treatment.

The failure to find a subsensitivity of release-regulating autoreceptors in the present study leaves open the question as to the cause of the increased extracellular dopamine levels following an acute cocaine challenge in sensitized animals, as measured by in vivo microdialysis in the nucleus accumbens either 1 day (18) or 2–4 days (4) after the cessation of chronic cocaine treatment. One possible explanation for the enhanced extracellular levels of dopamine is that synthesis-regulating autoreceptors or activity-regulating autoreceptors, neither of which were examined in the present study, are subsensitive in sensitized animals. In support of a subsensitivity in the latter type of receptor, Henry et al. (13) reported that A10 neurons in sensitized rats were subsensitive to the inhibitory effects of iontophoretically applied apomorphine on their firing rate. A second possibility is that the increased dopamine release is a consequence of an enhanced extracellular concentration of cocaine itself following a challenge injection in cocaine-sensitized animals, as reported by Pettit et al. (18). One important consideration in the above experiments, however, is the length of time elapsed since the termination of the chronic cocaine treatment. Both the subsensitivity of impulse-regulating autoreceptors and the enhanced cocaine levels following a challenge injection do not appear to last for more than about 1 week after the final cocaine injection (1,23), whereas the enhanced behavioral effects of a challenge injection of cocaine in sensitized animals are present even after 2 or more months (22,31).

An alternative explanation for the reported increase in extracellular DA levels following repeated cocaine administration is that the number or affinity of cocaine binding sites on the DA uptake transporter has been altered, leading to an enhanced ability of cocaine to inhibit DA uptake. This would result in an increase in the efflux of dopamine from superfused slices in the presence of cocaine. However, in the present study 10 μM cocaine did not cause a greater increase in electrically stimulated [^{3}H]DA in rats treated chronically with cocaine than those treated chronically with saline, thus arguing against a change in the cocaine binding site. This conclusion is also supported by an earlier study in which a similar chronic cocaine treatment was found to have no effect on the displacement of [^{3}H]GBR 12935 binding by cocaine or on total [^{3}H]GBR 12935 binding (37).

The inhibition of ACh release by quinpirole in the nucleus accumbens and striatum as well as the inhibition of ACh release by cocaine in the striatum was also identical between saline- and cocaine-treated rats, thereby suggesting that cholinergic neurons are not supersensitive to either quinpirole or endogenously released DA in sensitized rats. In contrast to these findings, Henry et al. (13) observed a significant supersensitivity to the inhibitory effect of iontophoretically applied DA in extracellular recordings from nucleus accumbens cells in cocaine-sensitized rats. However, since cholinergic neurons constitute only a small percentage of the cells in this nucleus, it is likely that the majority of the recordings were made from cell types other than cholinergic neurons. It would follow that supersensitivity to dopamine may occur only in these latter neuronal types and is not apparent in the cholinergic neurons.

Interestingly, although no reduction in either the magnitude of electrically evoked ACh and DA release or in the sensitivity of release-regulating DA receptors on dopamine and cholinergic neurons was observed in the study reported here, Cubeddu et al. (7) found a marked reduction in both these parameters in rabbit striatal slices 3 days after the cessation of chronic daily injections with the dopamine agonist bromocriptine. Why changes in DA and ACh release are seen following chronic treatment with a direct dopamine agonist, but not with the indirect agonist cocaine, remains to be determined.

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