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Chronic Cocaine Treatment Impairs the Regulation of Synaptosomal ^{3}H-DA Release by D_2 Autoreceptors

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YI, S.-J. AND K. M. JOHNSON. *Chronic cocaine treatment impairs the regulation of synaptosomal ^{3}H-DA release by D_2 autoreceptors.* PHARMACOL BIOCHEM BEHAV **36**(3) 457–461, 1990.—The effect of repeated administration of cocaine on presynaptic D_2 autoreceptor sensitivity in synaptosomes was studied. In rats treated chronically with saline, the dopamine D_2 agonist 2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin (N-0437) caused a significant inhibition of the Ca^{2+}-evoked ^{3}H-DA release from synaptosomes prepared from the nucleus accumbens and from the striatum; this effect was blocked by the D_2 antagonist sulpiride. However, chronic cocaine pretreatment abolished the effect of N-0437 in both areas, suggesting a subsensitivity of release-modulating terminal DA autoreceptors. Subsensitive DA autoreceptors would enhance stimulated DA release from mesolimbic and nigrostriatal terminals and may play a role in the behavioral sensitization observed in this paradigm.

Chronic cocaine DA autoreceptor DA release Behavioral sensitization

COCAINE produces effects similar to many other drugs classified as psychomotor stimulants and shares most of the psychomotor effects of amphetamine (26). Cocaine, unlike amphetamine, also has prominent local anesthetic effects; however, the local anesthetic properties of cocaine are not thought to be responsible for its psychomotor stimulant effects (7).

Like amphetamine, cocaine blocks the uptake of monoamines such as dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in to presynaptic terminals, but unlike amphetamine, has little effect on monoamine release except at very high concentrations (8). A critical role for DA in the psychomotor stimulant effects of cocaine was suggested by the observations that DA agonists have many of the same behavioral effects as cocaine and that DA antagonists and 6-hydroxydopamine lesions of dopaminergic pathways block these effects of cocaine (15). Administration of cocaine or amphetamine in mammals elicits a dose-dependent increase in spontaneous motor activity, and repeated intermittent administration of these drugs results in a progressive augmentation in locomotor activity and stereotypy (9, 20, 24), behaviors thought to be mediated by the mesolimbic and nigrostriatal DA pathways, respectively (5). This behavioral sensitization may play a role in the evolution and development of cocaine-induced paranoid psychoses like those reported for amphetamine (24,27).

Considering that dopaminergic systems undoubtedly play an important role in most of the amphetamine-like psychomotor stimulant effects of cocaine, it is thought that enhanced dopaminergic transmission may mediate behavioral sensitization. Robinson and Becker have reported that amphetamine-induced DA efflux in striatal slices prepared from rats repetitively administered amphetamine is greater than from the saline-pretreated rats (23). This effect is correlated temporally with the development of behavioral sensitization (16). Furthermore, other laboratories have found that amphetamine produced a greater stimulation of DA efflux in striatal slices prepared from rats behaviorally sensitized to cocaine or methamphetamine than for saline-pretreated rats (9, 19, 32).

The question addressed in the present study is whether there is a concomitant change in presynaptic regulation of DA release in nigrostriatal or mesolimbic DA pathways which could account for behavioral sensitization following repeated administration of cocaine. Bowyer and Weiner showed that ^{3}H-DA release evoked by the exposure of synaptosomes (isolated in the absence of Ca^{2+}) to 1.25 mM Ca^{2+} can be modulated by dopamine D_2 agonists and antagonists (2), presumably by acting on terminal autoreceptors. Therefore, the possibility that diminished autoreceptor function is associated with behavioral sensitization was tested in the present study by determining the ability of the D_2 receptor agonist N-0437 [2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin] to inhibit Ca^{2+}-evoked DA release in synaptosomes prepared from rats repeatedly administered cocaine.

METHOD

Because female rats have been reported to show a more consistent and robust sensitization than male rats (21), female Sprague-Dawley rats (Texas Animal Specialties, Humble, TX)

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were used in two independent experiments. Female rats weighing between 150 and 180 g were given daily injections of either cocaine (15 mg/kg twice a day for 7 days) or saline (1 ml/kg) intraperitoneally (IP). Seven days after the last injection, rats were acutely challenged with either saline or cocaine (15 mg/kg, IP) and decapitated 30 min later. Thus, rats were divided into four groups as follows: 1) chronic cocaine injection + acute cocaine challenge (cC-aC), 2) chronic cocaine + acute saline (cC-aS), 3) chronic saline + acute cocaine (cS-aC) and 4) chronic saline + acute saline (cS-aS). In the first experiment, release was measured in striatal synaptosomes, while in the second experiment the nucleus accumbens was used.

The dissected tissue was homogenized with a Teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at $1,000 \times g$. The supernatant was centrifuged at $17,500 \times g$ for 20 min. This crude synaptosomal pellet was resuspended in 30 volumes of Ca^{2+}-free Krebs-bicarbonate buffer (in mM; NaCl, 120.7; KCl, 3.3; $MgSO_4$, 1.2; KH_2PO_4, 1.2; EGTA, 0.1; $NaHCO_3$, 25; glucose, 11.5; EDTA, 0.03; ascorbic acid, 0.6) adjusted by pH 7.4 by bubbling with 95%–5% mixture of O_2 and CO_2, and equilibrated for 5 min at 37°C. ^{3}H-DA (3,4-[7-^{3}H]-dihydroxyphenylethylamine, 40 Ci/mmol, New England Nuclear) was then added at a final concentration of 25 nM and incubated for an additional 5 min. Synaptosomes were then placed on the top of GF/F glass fiber filters in superfusion chambers and were superfused for 20 min with Ca^{2+}-free buffer at 1 ml/min before starting collection of 1.5-min fractions of superfusate. At 36.5 min after the start of superfusion, the buffer was switched to one containing either 1.2 mM Ca^{2+} (striatum) or 0.6 mM Ca^{2+} (nucleus accumbens). The Ca^{2+}-containing buffer used to evoke ^{3}H-DA release was identical to the Ca^{2+}-free buffer except that Na^+ was decreased to maintain osmolarity. N-0437 and/or sulpiride were added at 26.5 min and remained until the end of the experiment. The efflux of radioactivity was calculated as percent fractional release, i.e., the radioactivity released in each superfusate fraction as a percent of total radioactivity present in the synaptosomes at that particular point in time. Ca^{2+}-evoked ^{3}H-DA release was measured by the sum of the increased fractional release above baseline in the six fractions following the addition of either 1.2 or 0.6 mM Ca^{2+}. Statistical significance of the effects of in vivo treatment with cocaine and in vitro N-0437 and sulpiride were determined by one- or two-way analysis of variance followed by Tukey's multiple comparison test. Cocaine hydrochloride was purchased from Sigma Chemical Co. and S(−)-sulpiride was purchased from Research Biochemicals Inc. N-0437 was a kind gift from Nelson Research, Irvine, CA.

RESULTS

Although we did not systematically rate behavior in this study, it was clear from our previous experience (9) that rats which were chronically administered cocaine were sensitized to the motor effects of cocaine. Also, after a 7-day withdrawal period, acute challenge with cocaine, but not saline, resulted in profound stereotypic sniffing and side-to-side head movement. This response was not observed in rats that were acutely challenged with cocaine 7 days after the cessation of chronic saline administration.

Figure 1A shows the effects of the D_2 agonist N-0437 and the D_2 antagonist sulpiride on Ca^{2+}-evoked ^{3}H-DA release from striatal synaptosomes obtained from rats challenged with saline 7 days after the last injection in a chronic saline regimen (cS-aS). Sulpiride (0.3 μM) did not cause any effect on Ca^{2+}-evoked ^{3}H-DA release. However, N-0437 (0.1 μM) produced a significant reduction (43%) of Ca^{2+}-induced ^{3}H-DA release and this effect was blocked by sulpiride (0.3 μM), indicating that this

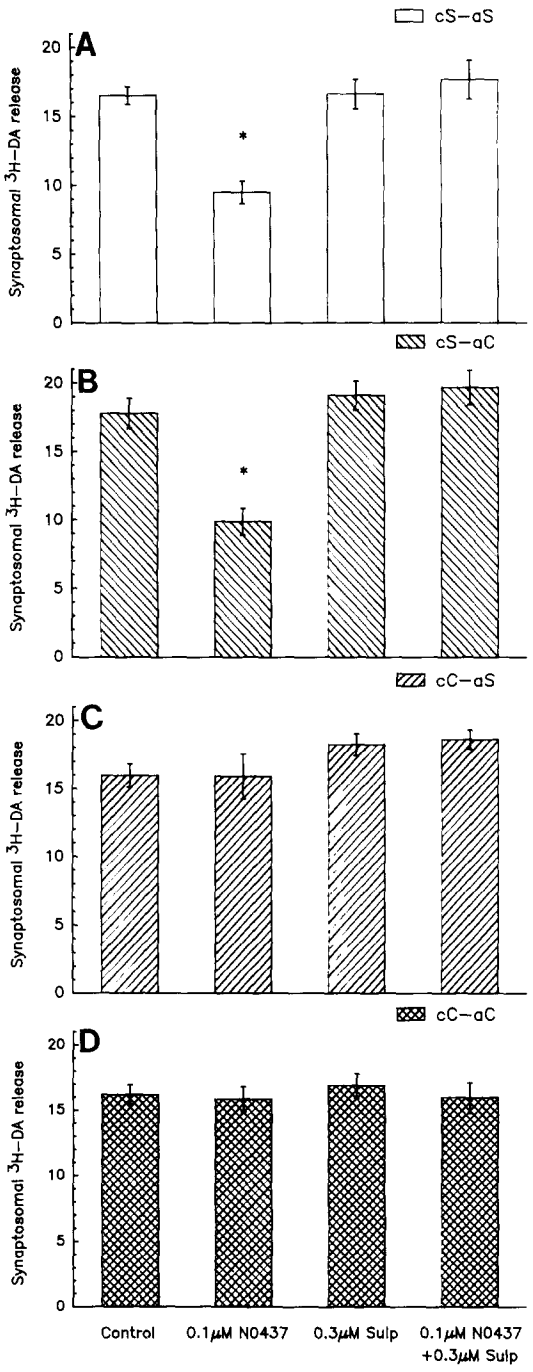

FIG. 1. Effects of N-0437 and sulpiride on Ca^{2+}-induced ^{3}H-DA release from striatal synaptosomes in the cS-aS- (A), cS-aC- (B), cC-aS- (C) and cC-aC- (D) treated rats. Each bar represents the mean ± S.E.M. of six independent experiments. *$p<0.05$ compared to control (one-way ANOVA followed by Tukey's post hoc test).

paradigm can be utilized to examine presynaptic D_2 autoreceptors as suggested by Bowyer and Weiner (2). The rationale for choosing 0.1 μM N-0437 is that when we constructed the concentration-response curve for N-0437 inhibition of Ca^{2+}-evoked ^{3}H-DA release, we found, as reported by others (29), a U-shaped curve with a maximal inhibitory effect at 0.1 μM (data

not shown). Because 0.3 μM sulpiride was the maximal concentration with no effect on either spontaneous or Ca^{2+}-induced ^{3}H-DA release, this concentration of sulpiride was used to block the effect of N-0437.

Figure 1C shows that chronic cocaine pretreatment (cC-aS) prevented the effect of N-0437 in inhibiting Ca^{2+}-induced ^{3}H-DA release from striatal synaptosomes, suggesting a subsensitivity of DA autoreceptors. This effect was not altered by acute cocaine challenge (cC-aC) (Fig. 1D). Furthermore, autoreceptor function following a single injection of cocaine was not altered (cS-aC) (Fig. 1B). Finally, sulpiride, either alone or in combination with N-0437, was not different from control in any of the four groups (Fig. 1A–D).

In synaptosomes from the nucleus accumbens, the paradigm was altered slightly in an attempt to decrease the variability and increase the degree of inhibition produced by N-0437. Reducing the concentration of Ca^{2+} from 1.2 mM to a submaximal value of 0.6 mM significantly reduced (39%) the evoked release, but did not significantly alter the inhibition (37%) produced by N-0437 (Fig. 2A). Furthermore, the nucleus accumbens was affected by cocaine in a manner exactly analogous to the striatum (Fig. 2A–D). That is, N-0437 inhibited Ca^{2+}-evoked ^{3}H-DA release in the cS-aS control group and in the acutely cocaine challenged group (cS-aC), but not in either of the two groups that received intermittent cocaine administration over a seven-day period.

As in the striatum, sulpiride, at a concentration capable of completely reversing the inhibitory effect of N-0437, had no effect by itself (Fig. 2A–D). This implies, that in this superfusion paradigm, there is no inhibitory "tone." This is most likely due to the fact that DA released from synaptosomes is carried away from the synaptic terminals before it has an opportunity to interact with DA autoreceptors. This would also account for the lack of enhanced release of DA under control conditions in the chronic cocaine-treated groups, in spite of the apparent development of subsensitive DA autoreceptors. That is, in this paradigm ^{3}H-DA release cannot be modulated by activation of autoreceptors by released endogenous DA because it is carried away by the superfusate. However, when N-0437 is present in the superfusion buffer, the autoreceptors are constantly stimulated to cause an inhibition of DA release. In this situation, the inhibitory "tone" produced by autoreceptor activation is apparent and can reflect cocaine-induced changes in the modulation of ^{3}H-DA release by DA autoreceptors.

DISCUSSION

Autoreceptor regulation of terminal DA release from striatal slices is generally a well accepted phenomenon. However, in striatal synaptosomes, this has been more difficult to document [cf. (3)]. Recently, it was proposed that Ca^{2+}-evoked release of ^{3}H-DA from synaptosomes isolated in the absence of Ca^{2+} could be utilized as a model for the study of autoreceptor regulation of DA release from nerve terminals (2). The precise mechanisms underlying either Ca^{2+}-evoked release or its inhibition by D_2 agonists are not yet clear. Similar to electrically evoked release of ^{3}H-DA from striatal slices (28), Ca^{2+}-evoked ^{3}H-DA release from striatal synaptosomes is inhibited by the sodium channel blocker tetrodotoxin (3,4). This suggests either that voltage-dependent sodium channels are spontaneously active and potentiate Ca^{2+}-induced release via further membrane depolarization (3) or that the addition of 1.2 mM Ca^{2+} itself depolarizes the membrane enough to activate these sodium channels. This would, in turn, potentiate voltage-dependent release. It has been postulated that the inhibition of Ca^{2+}-evoked ^{3}H-DA release by D_2 agonists involves activation of a K^+ conductance (3). Such an activation would hyperpolarize the membrane and reverse the depolarization initiated by the addition of Ca^{2+}. D_2 receptors previously have been shown to be linked to a K^+ conductance in substantia nigra (17). Such a mechanism would be consistent with the observation that DA release induced by high K^+ concentration is not subject to autoreceptor regulation (22).

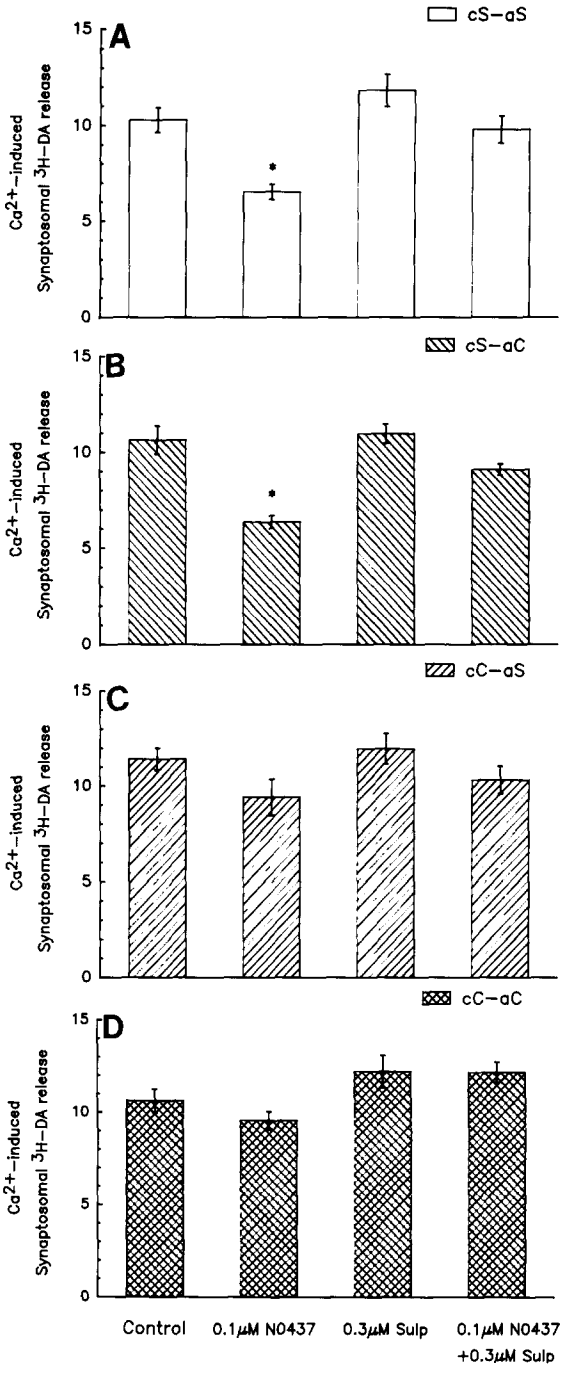

FIG. 2. Effects of N-0437 and sulpiride on Ca^{2+}-induced ^{3}H-DA release from synaptosomes obtained from the nucleus accumbens in the cS-aS- (A), cS-aC- (B), cC-aS- (C) and cC-aC- (D) treated rats. Each bar represents the mean ± S.E.M. of six independent experiments. *$p<0.05$ compared to control (one-way ANOVA followed by Tukey's post hoc test).

In the striatal synaptosomes, the potencies of pergolide, quinpirole and apomorphine as inhibitors of Ca^{2+}-evoked ^{3}H-DA release and the relative potencies of the D_2 antagonists l-sulpiride and domperidone as autoreceptor antagonists are consistent with their binding affinities for D_2 receptors in striatal membranes (2). Recently N-0437 has been shown to be a potent and selective D_2 agonist in vitro and in vivo using either brain dialysis or the γ-butyrolactone model of presynaptic autoreceptors (29,30). Therefore, the modulation of Ca^{2+}-evoked ^{3}H-DA release from striatal synaptosomes by N-0437 and sulpiride appears to reflect the regulation of DA release from terminals by presynaptic autoreceptors.

In this study, chronic cocaine treatment (cC-aS and cC-aC) prevented the inhibitory effect of N-0437 on Ca^{2+}-induced ^{3}H-DA release from synaptosomes prepared from either the striatum or the nucleus accumbens, suggesting that DA autoreceptors on nigrostriatal and mesolimbic terminals become subsensitive as a consequence of chronic cocaine treatment.

Down-regulation of somatodendritic DA autoreceptor function in the ventral tegmental area (A_{10}) and substantia nigra (A_9) after chronic administration of amphetamine or cocaine has been suggested in several studies (1, 10–13, 18, 32). A_9 and A_{10} DA cells in rats pretreated with repeated amphetamine are less responsive to the inhibitory effect of iontophoretic or systemically administered DA agonists (1, 13, 31). Consistent with autoreceptor subsensitivity, the spontaneous activity of A_{10} DA neurons is enhanced in chronic amphetamine-treated rats (31). Furthermore, it has been reported that after rats have been sensitized to cocaine, less DA is released from A_9- and A_{10}-containing tissue slices in response to K^+-depolarization than in tissue from nonsensitized rats (10). The decrease in depolarization-induced release of somatodendritic DA observed in amphetamine- and cocaine-pretreated rats would diminish the inhibition of action potential generation produced by these impulse-regulating autoreceptors. Regardless of whether subsensitivity of somatodendritic DA autoreceptors or reduced stimulation of these autoreceptors is most important in regulating cell firing during sensitization, both mechanisms would enhance DA release from the terminals and produce an increase in dopamimergic behaviors such as stereotypy and locomotion.

The present study suggests that not only DA autoreceptors on cell bodies, but also on DA terminals, become down regulated in rats treated chronically with cocaine. If the presynaptic D_2 release-modulating autoreceptors become subsensitive in response to repeated cocaine administration, this could also result in more DA release from the terminals in the striatum or nucleus accumbens, depending on the characteristics of the stimulus. This then may play a role in the development of sensitization to the locomotor and stereotypic effects of cocaine. Repeated administration of cocaine or amphetamine is also shown to decrease the sensitivity of DA autoreceptors regulating DA synthesis in striatal DA terminals (14). Thus, it is conceivable that both terminal synthesis and release are regulated by common autoreceptors. Down-regulation of both mechanisms would act in concert to increase dopaminergic transmission.

The data presented in this study are contradictory to those of Dwoskin *et al.* who found that repeated treatment with cocaine produced striatal D_2 autoreceptors supersensitive to pergolide (6). This discrepancy may be due to different injection schedules and/or doses of cocaine. For example, the authors cited above administered cocaine (10 mg/kg) once daily for either 8 or 14 days and sacrificed the rats 24 hours after the last injection. Another possibility is that inhibition of electrically evoked release of ^{3}H-DA from striatal slices may measure a different component of DA release or a different population of autoreceptors than measured here.

In summary, we have presented evidence that repetitive administration of cocaine, using a regimen known to produce behavioral sensitization, results in a down-regulation of DA autoreceptors which regulate Ca^{2+}-evoked synaptosomal ^{3}H-DA release. This phenomenon was observed in two independent experiments utilizing tissue from both striatum and nucleus accumbens. The down-regulation mechanism is unknown, but it could involve changes in the autoreceptor density or affinity or in the transduction mechanism. If the ultimate mechanism for regulation of DA release proves to be activation of a K^+ channel as previously postulated (3), the down-regulation mechanism could involve alterations in the number or functionality of these channels.

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