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Effects of Chronic Cocaine Administration on the Serotonergic System in the Rat Brain

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JOHNSON, R. G., D. FIORELLA AND R. A. RABIN. *Effects of chronic cocaine administration on the serotonergic system in the rat brain.* PHARMACOL BIOCHEM BEHAV 46(2) 289–293, 1993.—Male Sprague-Dawley rats received injections of cocaine (20 mg/kg/dose, IP) every 12 h for 14 days and were sacrificed on the 15th day. The chronic cocaine treatment caused an increase in the levels of serotonin [5-hydroxytryptamine (5-HT)] and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the hippocampus. 5-HIAA levels in the frontal cortex were also increased, but 5-HT levels were unaltered by the chronic cocaine treatment. Similarly, striatal levels of 5-HT and 5-HIAA were unchanged by repeated administration of cocaine. Chronic cocaine administration did not alter the density of [^{3}H]8-OH(DPAT), [^{3}H]mesulergine, or [^{3}H]ketanserin binding in the hippocampus, choroid plexus, and frontal cortex, respectively. Furthermore, repeated injection of cocaine did not alter serotonergic-mediated inhibition of adenylate cyclase activity. Thus, repeated administration of cocaine causes region-specific alterations in 5-HT levels but does not change the properties of the 5-HT$_{1A}$, 5-HT$_{1C}$, or 5-HT$_2$ receptors.

Cocaine Serotonin Adenylate cyclase 5-HT$_{1A}$ receptor 5-HT$_{1C}$ receptor 5-HT$_2$ receptor

ALTHOUGH cocaine was isolated from coca leaves in 1855 (34), the neurochemical basis for the behavioral effects of cocaine are still not well defined. Cocaine has been shown to inhibit the presynaptic uptake of the catecholamine neurotransmitters dopamine and norepinephrine as well as 5-hydroxytryptamine (5-HT) (11,25,26). Cocaine binds with highest affinity to the 5-HT transporter followed by dopamine and norepinephrine transporters (24). Systemic administration of cocaine reversibly depressed spontaneous firing of the serotonergic neurons in the dorsal raphe nucleus (5,21). Similarly, microiontophoretic application of cocaine decreased the firing of serotonergic neurons and potentiated the inhibitory effect of 5-HT in the dorsal raphe nucleus (5). This decrease in firing presumably occurs because of the inhibition of 5-HT reuptake, which increases the synaptic concentration of the neurotransmitter with a subsequent activation of the somatodendritic autoreceptors. Interestingly, in the nucleus accumbens 5-HT-mediated depolarization is more sensitive to the potentiating effect of cocaine than either the hyperpolarizing or depolarizing effect of dopamine (31).

Repeated administration of cocaine elicits a neuroadaptation that is manifested as a decrease in some physiological and behavioral effects but an increased sensitivity of other responses to subsequent drug challenge (22). The neurochemical mechanisms responsible for these changes are not clear. Repeated cocaine administration has been reported to increase dopamine concentrations and decrease dopamine synthesis in the nucleus accumbens (2,9). An increase in the density of the dopamine D_2 receptor in the nucleus accumbens, as well as a decrease in the density of striatal D_1 receptors, have been reported after repeated administration of cocaine (10,19). However, the reports on changes in dopamine receptors after repeated administration of cocaine have been inconsistent (7,10,19). Chronic administration of cocaine also has been reported to increase the density of whole brain β-adrenergic receptors as well as the stimulation of cyclic adenosine monophosphate (cAMP) content by norepinephrine (1). Because of the paucity of data, the effects of repeated administration of cocaine on the serotonergic system are unclear. A 5-day treatment with 10 mg/kg cocaine was reported to decrease septal caudate 5-HT content as well as the activity of the soluble form of tryptophan hydroxylase, which is the rate-limiting enzyme in 5-HT biosynthesis (29). However, Yeh and DeSouza (35) reported that 40 mg/kg cocaine for 8 days did not alter 5-HT content in any brain region examined (e.g., the frontal cortex, hippocampus, striatum, hypothalamus, midbrain, and pons medulla). Interestingly, the activity of the platelet 5-HT transporter was lower in patients who abused cocaine compared to normal controls (6).

Because of the lack of information regarding the effects of chronic cocaine on 5-HT receptors, the present study was undertaken to determine the effects of repeated administra-

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tion of cocaine on the properties of the 5-HT_{1A}, 5-HT_{1C}, and 5-HT_2 receptors. In addition, levels of 5-HT and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) were also measured.

METHOD

Male Sprague–Dawley rats (190–275 mg) were injected with cocaine (20 mg/kg, IP) every 12 h for 14 days. Control animals received equivalent volumes of physiological saline (pH 7.4). Twelve hours after the final injection, rats were sacrificed by decapitation and brain areas dissected according to Glowinski and Iversen (8).

Levels of 5-HT and 5-HIAA were determined according to a modification of the method of Kumar et al. (12). Briefly, the frontal cortex, hippocampus, and striatum were homogenized (Dounce tissue grinder) in a solution containing 48 mM Tris-HCl (pH 7.4), 33.6 μM $HClO_4$, and 30 ng/ml *N-w*-methyl-5-hydroxytryptamine oxalate as an internal standard. Homogenates were centrifuged at 40,000 × *g* for 15 min at 4°C, and the resultant supernatants were frozen at −70°C until use. 5-HT and 5-HIAA levels were determined by reverse-phase high-performance liquid chromotography (HPLC) using a μBONDAPAK C_{18} 3.9 × 300-mm column (Waters Associates, Inc.) and an LC-4 amphoteric electrochemical detector (Bioanalytical Systems, Inc.). Samples were eluted from the HPLC column with a mobile phase containing 0.1 M trichloroacetic acid, 0.01 M sodium acetate, 0.1 mM EDTA, and 20% methanol, pH 3.85, and the separated biogenic amines were measured by electrochemical detection after oxidation at 0.6 V. For striatal tissue, a flow rate of 1.0 ml/min was used, while a flow rate of 1.2 ml/min was used for frontal cortex and hippocampal tissues. Peaks were identified and quantified by comparing retention times and peak heights with known standards. Data are expressed as ng biogenic amine/mg supernatant protein.

Receptor binding assays were carried out by modification of a previously described method (33). In brief, tissues were homogenized (Dounce tissue grinder) in 50 mM Tris-HCl (pH 7.4) and centrifuged at 40,000 × *g* for 15 min at 4°C. The resulting pellets were resuspended in the Tris buffer, and the samples were incubated at 37°C for 15 min to remove endogenous 5-HT (15). The samples were then centrifuged at 40,000 × *g* for 15 min and again resuspended in Tris buffer. This procedure was repeated and the final pellets were resuspended in a final volume of 14 ml containing 50 mM Tris (pH 7.4), 4 mM $MgCl_2$, 10 μM pargyline, and 0.1% ascorbic acid. Binding assays were carried out in a final volume of 0.5 ml containing the above Tris buffer, various concentrations of radioligand (0.5–5.0 nM [^{3}H]8-OH(DPAT) for the hippocampus; 0.1–5.0 nM [^{3}H]ketanserin for the frontal cortex; 0.5–8.0 nM [^{3}H]mesulergine for the choroid plexus), and appropriate drugs. Incubations were started by the addition of 400 μl tissue and carried out for 30 min at either 37°C (for [^{3}H]8-OH(DPAT) and [^{3}H]mesulergine) or 30°C (for [^{3}H]ketanserin). In preliminary studies, these conditions resulted in equilibrium binding at all radioligand concentrations. Incubations were terminated with a Brandel cell harvester and the filters rinsed twice with cold 50 mM Tris (pH 7.4). The amount of bound radioactivity was measured by liquid scintillation spectrophotometry after incubating the filters in scintillation cocktail overnight. Specific binding was defined as the difference in radioactivity bound in the absence and presence of 10 μM cianserin for [^{3}H]ketanserin binding or 10 μM 5-HT for [^{3}H]8-OH(DPAT) and [^{3}H]mesulergine binding. The data were analyzed by nonlinear regression using the program EBDA/LIGAND (Elsevier BIOSOFT).

TABLE 1

EFFECT OF A 14-DAY TREATMENT WITH COCAINE (20 mg/kg IP, b.i.d.) ON 5-HT AND 5-HIAA LEVELS IN THE HIPPOCAMPUS, FRONTAL CORTEX, AND STRIATUM

	5-HT* (ng/mg protein)	5-HIAA (ng/mg protein)
Hippocampus		
Control (n = 9)	79 ± 17	58 ± 9
Cocaine treated (n = 10)	134 ± 17†	109 ± 17†
Frontal cortex		
Control (n = 10)	84 ± 12	38 ± 4
Cocaine treated (n = 9)	102 ± 11	51 ± 3†
Striatum		
Control (n = 9)	224 ± 55	154 ± 35
Cocaine treated (n = 9)	168 ± 19	140 ± 16

*Data are expressed as means ± SEM.
†$p < 0.05$ (Student's t-test).

For adenylate cyclase assays, the hippocampus was homogenized (Dounce tissue grinder) in ice-cold 2 mM Tris-HCl (pH 7.5) containing 2 mM EGTA, 300 mM sucrose, and 2 mM dithiothreitol. The homogenates were centrifuged at 40,000 × *g* for 10 min at 4°C. The resultant pellets were resuspended in the Tris buffer and again centrifuged at 40,000 × *g* for 10 min. This procedure was repeated and the final pellet was resuspended in the Tris buffer (20 mg tissue/ml). Adenylate cyclase assays were carried out at 30°C in a final volume of 200 μl containing 50 mM Tris-HCl (pH 7.5), 5 mM cAMP, 2 mM $MgCl_2$, 0.1 mM adenosine triphosphate (ATP) (1–2 μCi [α-^{32}P]ATP), 4 mM theophylline, 10 μM pargyline, 10 mM creatine phosphate, 0.1 mg/ml creatine phosphokinase, 50 μM guanosine triphosphate (GTP), 100 mM NaCl, and appropriate drugs. The reaction was stopped after 10 min by the addition of 200 μl 50 mM Tris-HCl (pH 7.5) containing 5 mM ATP and 10% SDS. The samples were then boiled for 5 min

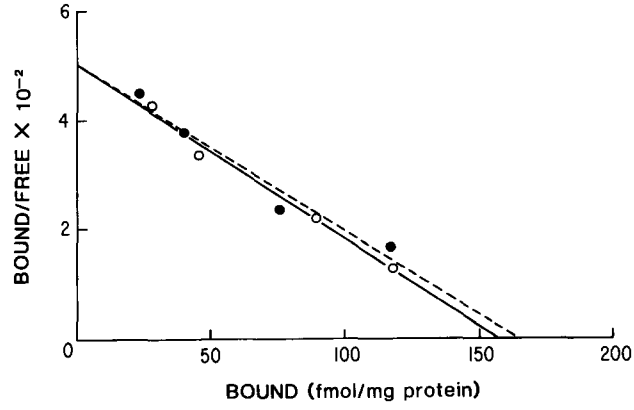

FIG. 1. Effects of a 14-day treatment with cocaine (20 mg/kg, IP, b.i.d.) on [^{3}H]8-OH(DPAT) binding in the hippocampus. Equilibrium saturation experiments were carried out with 0.5–5.0 nM [^{3}H]8-OH-DPAT. The data are plotted by the method of Scatchard (27) and are representative of six similar experiments (control, ○ – ○; cocaine-treated, ● – ●). For this particular experiment, B_{max} was 157 and 164 fmol/mg protein for control and cocaine-treated animals, respectively; K_d was 1.8 and 2.4 nM for control and cocaine-treated animals, respectively.

TABLE 2

REPEATED ADMINISTRATION OF COCAINE ON [^{3}H]8-OH-DPAT BINDING IN THE HIPPOCAMPUS, [^{3}H]KETANSERIN IN THE FRONTAL CORTEX, AND [^{3}H]MESULERGINE IN THE CHOROID PLEXUS

	B_{max} (fmol/mg protein)	K_d (nM)	Hill Coefficient
[^{3}H]8-OH-DPAT			
Control	175 ± 12	2.2 ± 0.4	1.00 ± 0.003
Cocaine treated	188 ± 13	2.8 ± 0.9	1.01 ± 0.0002
[^{3}H]Ketanserin			
Control	349 ± 27	5.3 ± 1.3	0.99 ± 0.003
Cocaine treated	277 ± 26	2.8 ± 0.7	1.02 ± 0.014
[^{3}H]Mesulergine			
Control	138 ± 15	3.1 ± 0.6	0.95 ± 0.029
Cocaine treated	155 ± 32	3.1 ± 0.8	0.97 ± 0.009

Data are expressed as mean ± SEM for four to nine animals.

and [^{3}H]cAMP (approx. 15,000 cpm) was added to monitor recovery. [^{32}P]cAMP was isolated by sequential chromatography on Dowex cation exchanger and neutral alumina as previously described (23).

Protein content was determined by the method of Lowry et al. (13) using bovine serum albumin (BSA) fraction V as the standard.

Materials

[α-^{32}P]ATP, [^{3}H]cAMP, [^{3}H]ketanserin, and [^{3}H]8-OH(DPAT) were obtained from Dupont/New England Nuclear (Boston, MA). N^6-methyl[^{3}H]mesulergine was obtained from Amersham Corp. (Arlington Heights, IL). Cocaine and all other chemicals were obtained from common commercial sources.

RESULTS

The effects of a 14-day treatment with cocaine (20 mg/kg, b.i.d.) on 5-HT and 5-HIAA levels are shown in Table 1. The repeated injection of cocaine caused a 70% increase in hippocampal 5-HT levels and an 88% increase in 5-HIAA levels. Although 5-HIAA levels were also increased in the frontal cortex after the cocaine treatment, 5-HT levels in the frontal cortex were unchanged. Similarly, the repeated injection of cocaine did not alter 5-HT or 5-HIAA levels in the striatum.

Possible alterations in the hippocampal 5-HT$_1$A receptor were investigated by measuring [^{3}H]8-OH(DPAT) binding. A one-site model best described the binding of [^{3}H]8-OH(DPAT) in the hippocampus (Fig. 1). Repeated administration of cocaine did not alter either the affinity of the receptor for the radioligand (K_d) or the density of [^{3}H]8-OH(DPAT) binding sites (B_{max}) (Table 2). The properties of the 5-HT$_{1A}$ receptor were further studied by measuring serotonergic inhibition of adenylate cyclase activity. Repeated injection of cocaine did

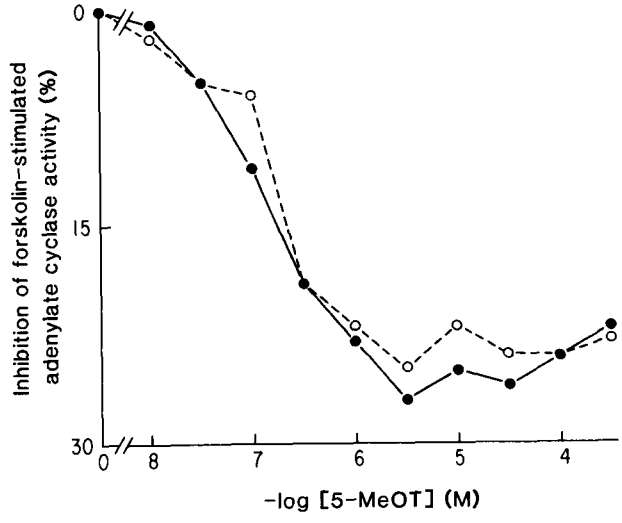

FIG. 2. Effect of repeated administration of cocaine on serotonergic inhibition of adenylate cyclase activity in the hippocampus. Adenylate cyclase activity was measured in the presence of 10 μM forskolin. Data are expressed as the percent inhibition of the forskolin-stimulated enzyme activity by 5-methoxytryptamine (5-MeOT) and are plotted as the mean of seven animals (control, ○—○; cocaine-treated, ●—●).

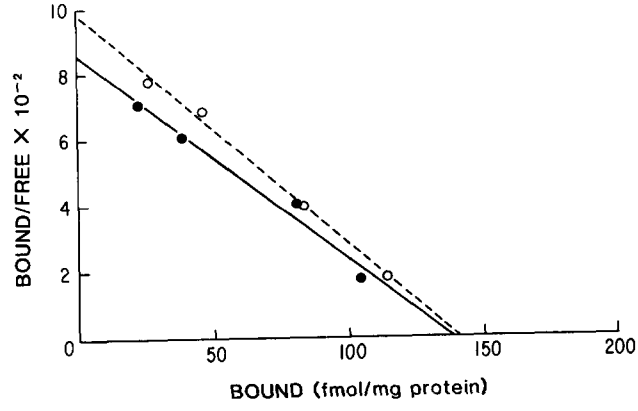

FIG. 3. Effects of chronic cocaine administration on [^{3}H]mesulergine binding in the choroid plexus. Equilibrium saturation experiments were carried out with 0.5–8.0 nM [^{3}H]mesulergine. Data are plotted by the method of Scatchard (27) and are representative of five similar experiments (control, ○—○; cocaine-treated, ●—●). For this particular experiment, B_{max} was 141 and 138 fmol/mg protein for control and cocaine-treated animals, respectively; K_d was 2.4 and 2.8 nM for control and cocaine-treated animals, respectively.

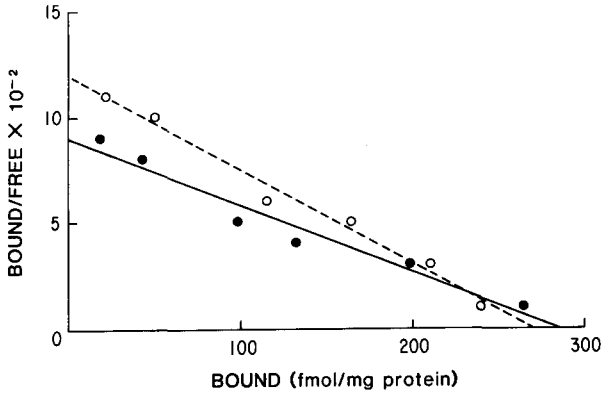

FIG. 4. Effects of repeated injection of cocaine on [^{3}H]ketanserin binding in the frontal cortex. Equilibrium saturation experiments were carried out with 0.1–5.0 nM [^{3}H]ketanserin. Data are plotted by the method of Scatchard (27) and are representative of nine similar experiments. (control, ○ – ○; cocaine-treated, ● – ●). For this particular experiment, B_{max} was 275 and 289 fmol/mg protein for control and cocaine-treated animals, respectively; K_d was 1.0 and 1.4 nM for control and cocaine-treated animals, respectively.

not change basal adenylate cyclase activity (51 ± 6 and 49 ± 6 pmol cAMP/mg protein/min for control and cocaine-treated animals, respectively). Similarly, stimulation of adenylate cyclase activity by forskolin was not altered by chronic administration of cocaine (233 ± 27 and 234 ± 25 pmol cAMP/mg protein/min for control and cocaine-treated animals, respectively). Maximum inhibition of forskolin-stimulated adenylate cyclase activity by the 5-HT$_1$ agonist 5-methoxytryptamine (5-MeOT) was 25 ± 1% (Fig. 2). The maximal inhibitory effect of 5-MeOT on hippocampal adenylate cyclase activity was not changed by the 14-day treatment with cocaine (23 ± 0.7%). Similarly, the concentration of 5-MeOT resulting in half-maximal inhibition of adenylate cyclase activity was not altered by repeated injection of cocaine; IC_{50} was 0.09 ± 0.02 μM for control animals and 0.14 ± 0.03 μM for cocaine-treated rats (Fig. 2).

Possible effects of chronic cocaine administration on the 5-HT$_{1C}$ and 5-HT$_2$ receptors were investigated by measuring binding of [^{3}H]mesulergine to the choroid plexus (Fig. 3) and binding of [^{3}H]ketanserin to the frontal cortex (Fig. 4), respectively. Repeated administration of cocaine did not alter the affinity of the receptor for the radioligands or the density of [^{3}H]ketanserin and [^{3}H]mesulergine binding sites (Table 2).

DISCUSSION

In the present study, the effects of a 14-day treatment with 20 mg/kg cocaine b.i.d. on the brain serotonergic system were investigated. Repeated injection of cocaine appears to result in region-specific alterations in 5-HT levels. Thus, in the present study an increase in 5-HT levels was observed in the hippocampus but not in the frontal cortex or striatum. Conversely, 7-day treatment with 10 mg/kg cocaine decreased 5-HT levels in the septum-caudate region (29). Yeh and DeSouza (35) did not find any change in 5-HT levels in the striatum, frontal cortex, or hippocampus after chronic administration of cocaine, but these investigators used a shorter treatment period than the present study (8 vs. 14 days in the present study).

In many systems, an inverse relationship has been shown between synaptic levels of the neurotransmitter and the density of the corresponding neurotransmitter receptor. For example, chronic blockade of norepinephrine reuptake by the tricyclic antidepressant desmethylimipramine decreased the density of cortical β_1-adrenergic receptors (14). Similarly, the density of cortical 5-HT$_2$ receptors was decreased by chronic administration of antidepressants (28). Cocaine can increase the synaptic levels of 5-HT by inhibiting its reuptake into nerve terminals (3,4,11,26), but repeated injection of cocaine failed to alter the properties of the 5-HT$_{1A}$ receptor. Nor did cocaine change the properties of the 5-HT$_2$ family of receptors, which includes the 5-HT$_{1C}$ and 5-HT$_2$ receptors (20). This lack of a change does not appear to be due to an insufficient dosage and length of drug treatment because changes in hippocampal 5-HT levels were observed and dopamine receptor density was reported to be altered with a lower dose and/or a shorter treatment period (10,19).

Chronic administration of the serotonergic uptake blockers, fluoxetine and zimelidine, was reported to reduce 5-HT$_{1A}$-mediated inhibition of hippocampal adenylate cyclase activity (18). Because chronic administration of the antidepressant imipramine decreased serotonergic inhibition of hippocampal adenylate cyclase activity without altering [^{3}H]8-OH-DPAT binding (17), this effect would appear to alter adenylate cyclase through the GTP binding protein rather than a change in the properties of the 5-HT$_{1A}$ receptor. Repeated injection of cocaine, however, did not alter serotonergic inhibition of hippocampal adenylate cyclase activity. This result is in agreement with the results of Varrault et al. (32), who found that the hippocampal 5-HT$_{1A}$ receptor coupled to adenylate cyclase is not readily desensitized. Chronic administration of cocaine also did not alter basal adenylate cyclase activity or forskolin stimulation of the enzyme. Although a decrease in the levels of the GTP-binding protein $G_i\alpha$ was reported after chronic administration of cocaine (16), this response was not a generalized phenomena but was only observed in discrete brain regions. Similarly, the increase in basal adenylate cyclase activity after chronic injection of cocaine appears to be a region-specific effect because it was only observed in the nucleus accumbens (30).

Although repeated administration of cocaine has been shown to result in both behavioral tolerance and sensitization (22), the present study indicates these responses do not appear to involve the 5-HT$_{1A}$, 5-HT$_{1C}$, or 5-HT$_2$ receptors located in the hippocampus, choroid plexus, or frontal cortex, respectively.

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