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EFFECTS OF ACUTE AND SUBACUTE ADMINISTRATION OF COCAINE ON DOPAMINERGIC SYSTEMS IN THE RAT STRIATUM

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ABSTRACT: *The characteristics of dopamine uptake, D-1 and D-2 receptors after acute and subacute cocaine administration were determined in striatum from WKY and SHR. Cocaine was administered either acutely (40 mg/kg, s.c.) or twice daily (20 mg/kg, s.c.) for 3 and 7 days in 9-wk old WKY and SHR. Rats were sacrificed 30 min, 2 or 24 h after the single injection and 18 h after the last administration to the subacutely treated group. The changes in dopamine uptake, dopamine uptake sites, D-1 and D-2 receptors were determined using (^{3}H)dopamine, (^{3}H)-GBR-12935, (^{3}H)SCH-23390 and (^{3}H)sulpiride, respectively. In acutely treated rats, significant increases in V_{max} of dopamine uptake were observed 30 min after the cocaine injection in both strains without changes in K_m values. The in vitro IC_{50} for cocaine was significantly decreased 30 min in WKY and 2 h in SHR. However, that for in vitro GBR-12909 was significantly increased 30 min and 2 h in both strains. Also densities of (^{3}H)-GBR-12935 binding sites were significantly increased 30 min and 2 h without changes in their K_d. Significant increases in D-2 receptor density were observed 30 min, 2 or 24 h after acute injection in both strains without changes in their affinities. The density of D-1 receptor was significantly decreased 30 min after the injection in WKY, but not in SHR. In subacutely treated rats, a significant increase in K_m of dopamine uptake was observed in 7-day treated SHR. The in vitro IC_{50} for GBR-12909 was significantly increased in 3-day treated WKY. The density of D-1 receptors was significantly increased in 3- and 7-day treated WKY, but not in SHR. The affinity of both binding sites remained unchanged. The results suggest that cocaine administration alters dopamine uptake, characteristics of dopamine uptake sites and dopamine receptor binding characteristics in rat brain. Furthermore, D-1 and D-2 dopamine receptors appear to be differently regulated.*

Keywords: *Cocaine, SHR and WKY, Dopamine uptake, Dopamine uptake sites, Dopamine receptors.*

INTRODUCTION

The compulsive non-medical use of cocaine has been increasing during the last decade. While other systems may also be involved in cocaine-induced toxicity, its specific central activity may be related to interference with uptake and synthesis of catecholamines and indolamines (Koe, 1976; Reith *et al.*, 1983). However, specific behavioral effects of cocaine (*e.g.* locomotor stimulation, stereotypy, hallucination *etc.*) have been attributed to alterations in dopaminergic functions (Galambos *et al.*, 1967; Fekete and Borsey, 1971). The pharmacological effects of this psychomotor stimulant are exerted primarily via blockade of reuptake of the catecholamines, norepinephrine and dopamine, such that the amount of these neurotransmitters in the synapse is increased. Thus cocaine acts indirectly as a dopamine agonist (Dackis and Gold, 1985) and the dopamine uptake rate might be affected by cocaine itself as well as by elevated synaptic dopamine level. Extracellular dopamine levels, as measured by microdialysis techniques, have been noted to increase in a dose-dependent fashion following cocaine administration (Church *et al.*, 1987; Nicolaysen *et al.*, 1988). It has also been reported that exogenous dopamine can affect the dopaminergic neuronal activity, including dopamine release and its subsequent catabolism (Arbilla *et al.*, 1985; Chang and Ramirez, 1989).

Cocaine administration has been reported to alter the binding characteristics of dopaminergic receptors, although there has been little consensus to published observations. Acute administration of cocaine has been shown to increase (Memo *et al.*, 1981) and to have minimal effects (Dwoskin *et al.*, 1988; Goeders and Kuhar, 1987) on dopaminergic receptor density in multiple tissues. A similar wide variation in the documented effects of cocaine on striatal dopaminergic receptors has been reported following subacute administration of this agent (Dwoskin *et al.*, 1988; Goeders and Kuhar, 1987; Trulson and Ulissey, 1987). Thus, a systemic analysis of cocaine on dopaminergic systems is desirable.

It has been reported that brain dopamine systems participate in the regulation of hypertension (Van Den Buuse *et al.*, 1986a). The characteristics of dopamine uptake and receptors in various brain regions differ between spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto rats (WKY) (Bhargava, 1984; Chiu *et al.*, 1982; Le Fur *et al.*, 1981, 1983; Lim *et al.*, 1989; Myers *et al.*, 1981). Recently, hepatotoxicity (Watanabe *et al.*, 1987) and behavioral (Van Den Buuse and De Jong, 1989) effects of dopaminergic drugs, including the dopamine uptake inhibitors, GBR-12935 and cocaine, were shown to differ between SHR and WKY. Thus dopamine uptake complex and dopaminergic neuronal activities in these two rat strains might be affected differently by acute and/or subacute administration.

The objective of the present review was to delineate changes in the characteristics of brain dopamine uptake complex and dopamine D-1 and D-2 receptors in SHR and WKY following acute and subacute administration of cocaine.

MATERIALS AND METHODS

Materials

The tritium-labeled ligands, (^{3}H)dopamine (specific activity, 39 Ci/mmol), (^{3}H)GBR-12935 (specific activity, 36.2 Ci/mmol) and (^{3}H)sulpiride (specific activity, 78.6 Ci/mmol) were purchased from New England Nuclear (Boston, MA). The ligand, (^{3}H)SCH-23390 (specific activity, 85 Ci/mmol) was obtained from Amersham Corp. (Arlington Heights, IL). Unlabeled GBR-12909 and (-)sulpiride were obtained from Research Biochemicals, Inc. (Natick, MA) and unlabeled SCH-23390 was provided by Schering Corp. (Bloomfield, NJ). All other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO).

Animal Treatment

Eight-weeks old male WKY and SHR were obtained from Taconic Farms (Germantown, NY). After arrival, the rats were housed in groups of four per cage in a temperature-controlled animal room with automatic 12 hr light-dark cycles for 7 days prior to treatment. The acutely-treated rats received single injections of cocaine hydrochloride (40 mg/kg, sc) or saline (1 ml/kg, sc) and were killed 30 min, 2 or 24 hr after the injections. The subacutely-treated rats received either cocaine hydrochloride (20 mg/kg, sc) or an equivalent volume (1 ml/kg, sc) of saline twice daily (8.30 A.M. and 5.30 P.M.) for 3 or 7 days and were sacrificed 16-18 hr after the last injection. In protocols of receptors assay involving daily administration of cocaine for 7 days, an additional group of animals received a challenge dose of cocaine, 40 mg/kg, sc., 18 h after the last daily injection. This group of animals was sacrificed 30 min after the administration of the challenge dose of cocaine. At the appropriate times, the rats were decapitated and brains were rapidly removed. The striata were dissected out according to the procedure of Glowinski and Iversen (1966).

(^{3}H)Dopamine Uptake

Striatal tissue was homogenized gently by hand using a glass homogenizer and synapsomes were prepared. The specific (^{3}H)dopamine uptake in synaptosomes were performed according to Haberland and Hetey (1987) within 4 hrs of sacrifice. The concentration used were: 0.2 uM (^{3}H)dopamine, 10^{-8} to 10^{-5} M cocaine and 10^{-10} to 5×10^{-8} GBR-12909.

(^{3}H)GBR-12935, (^{3}H)SCH-23390 and (^{3}H) Sulpiride Binding Assay

Membranes for dopamine uptake site binding assay were prepared and specific binding of dopamine uptake site ligand, (^{3}H)GBR-12935, was determined according to the method of Andersen (1987). Membranes for D-1 receptor binding assay were prepared according to the method of Zukin *et al.* (1974) and specific binding of D-1 receptor ligand, (^{3}H)SCH-23390, was determined according to Porceddu *et al.* (1986). Membranes for D-2 receptor binding assay were prepared and specific binding of D-2 receptor ligand, [^{3}H]sulpiride, was determined according to Carboni *et al.* (1985). The protein content was determined by the method of Lowry *et al.* (1951). Using bovine serum albumin as a standard.

RESULTS AND DISCUSSION

Involvement of the Dopamine Uptake Complex in Cocaine-induced Toxicity in SHR and WKY

Differential responses of WKY and SHR to drug agents, particularly antihypertensive compounds, have been well documented. Moreover, important differences in brain dopamine levels (Van den Buuse *et al.*, 1984; Versteeg *et al.*, 1976) have been documented. Also, Myers *et al.* (1981) has reported that the dopamine uptake in 6-week-old animals in SHR was lower than that in WKY, however, there was no difference between the two strains at 9-10 weeks old. Recently we examined the differences in dopamine uptake (Table 1) and the characteristics of dopamine uptake sites between two strains using (^{3}H)dopamine and (^{3}H)GBR-12935, respectively. We have found that the rate of the dopamine uptake in striata from SHR is higher than that in WKY, however, the characteristics of dopamine uptake sites are not different from each other. Since Iversen (1974) has reported that the synaptic concentration of dopamine is regulated, in large part, via the uptake of the transmitter; and since it is generally agreed that the depletion of dopamine in striatum by the injection of 6-hydroxydopamine causes increases in the number of dopamine receptors, the higher dopamine uptake rate in SHR, by decreasing synaptic dopamine, contributes to the higher densities of the dopamine receptors in the striata. Although the exact role of striatal dopaminergic activity in the hyperactivity and hypertension of SHR are not known, Van den Buuse *et al.* (1986b) has reported that degeneration of the substantia nigra in SHR attenuates the development of hypertension. Thus, the higher dopamine uptake might be related to the hyperactivity and hypertension of SHR.

It is well accepted that cocaine inhibits dopamine uptake (Dackis and Gold, 1985; Hadfield and Nugent, 1983; Nicolaysen *et al.*, 1988) and that this inhibition is competitive (Hadfield and Nugent, 1983; Tuomisto and Tuomisto, 1987). Missale *et al.* (1985) have reported that the velocities of the dopamine uptake in striatum are decreased by acute cocaine treatment. However, they also reported the velocity of the dopamine uptake in nucleus accumbens was increased by acute and subacute cocaine treatment. However, after acute-cocaine administration (40 mg/kg, sc.) to both WKY and SHR, we found that the velocities of the dopamine uptake were elevated 30 min, but not 2 and 24 hr (Table 2). This was further substantiated that cocaine-induced increase (Table 3) in the number of binding sites for (^{3}H)GBR-12935, which is reported to bind to the dopamine uptake site (Bonnet and Costentin, 1986; Andersen, 1987).

Table 1. K_m and V_{max} values for dopamine uptake and IC_{50} of the *in vitro* cocaine effects on dopamine uptake in the striatum of WKY and SHR

	K_m (μM)	V_{max} (μM/mg protein/2.5 min)	IC_{50} (μM)
WKY	0.336 ± 0.026	0.136 ± 0.001	1.832 ± 0.010
SHR	0.360 ± 0.005	0.157 ± 0.007*	1.706 ± 0.079

*$p < 0.05$ compared to the WKY values.
The values are mean ± S.E. of 4 separate experiments each performed in duplicate.

Table 2. Effects of acute cocaine treatment (40 mg/kg, s.c.) on DA uptake in rat striatum

	WKY		SHR	
	K_m	V_{max}	K_m	V_{max}
control	0.237 ± 0.017	0.155 ± 0.012	0.205 ± 0.015	0.208 ± 0.011#
30 min	0.218 ± 0.010	0.213 ± 0.007**	0.174 ± 0.010#	0.258 ± 0.014#*
control	0.306 ± 0.012	0.189 ± 0.006	0.309 ± 0.014	0.206 ± 0.004
2 h	0.338 ± 0.016	0.209 ± 0.012	0.362 ± 0.012	0.222 ± 0.012
24 h	0.310 ± 0.019	0.217 ± 0.019	0.377 ± 0.031	0.191 ± 0.008

Units: $K_m = \mu M$, V_{max} = nmol/mg protein/2.5 min.
Rats were sacrificed at the indicated time after injection of cocaine.
*$p < 0.05$, **$p < 0.01$ compared to the respective control value.
#$p < 0.05$ compared to the WKY value.
The values are mean ± S.E. of four separate experiments each performed in duplicate.

Table 3. Effects of acute cocaine treatment (40 mg/kg, s.c.) on the characteristics of DA uptake sites ([^{3}H]GBR-12935) in rat striatum

	WKY		SHR	
	K_d	V_{max}	K_d	V_{max}
control	1.548 ± 0.042	848.7 ± 21.3	1.474 ± 0.050	856.1 ± 23.9
30 min	1.559 ± 0.061	976.6 ± 44.6*	1.385 ± 0.064	977.1 ± 10.8**
control	1.958 ± 0.161	840.5 ± 26.3	1.982 ± 0.172	942.6 ± 34.1
2 h	1.876 ± 0.058	1007.8 ± 40.9*	2.331 ± 0.123#	1077.0 ± 19.7*
24 h	2.150 ± 0.226	980.1 ± 90.5	2.255 ± 0.325	947.4 ± 93.7

Rats were sacrificed at the indicated time after injection of cocaine.
Unit: K_d = nM, B_{max} = pmol/g protein.
*$p < 0.05$, **$p < 0.01$ compared to the respective control value.
#$p < 0.05$ compared to WKY value.
The values are mean ± S.E. of five separate experiments each performed in duplicate.

Table 4. Effects of subacute cocaine treatment (20 mg/kg, s.c. twice daily) on DA uptake in rat striatum

	WKY		SHR	
	K_m	V_{max}	K_m	V_{max}
control	0.208 ± 0.009	0.138 ± 0.003	0.221 ± 0.008	0.152 ± 0.003#
7 days	0.201 ± 0.005	0.141 ± 0.003	0.230 ± 0.011	0.167 ± 0.011
control	0.298 ± 0.016	0.130 ± 0.004	0.309 ± 0.010	0.165 ± 0.008##
7 days	0.302 ± 0.006	0.123 ± 0.008	0.411 ± 0.027*	0.138 ± 0.013

Rats were sacrificed 18 h after the last administration of cocaine (twice daily, 20 mg/kg, s.c.)
Unit: $K_m = \mu M$, V_{max} = nmol/mg protein/2.5 min.
*$p < 0.05$ compared to the respective control value.
#$p < 0.05$, ##$p < 0.01$ compared to the WKY value.
The values are mean ± S.E. of four separate experiments each performed in duplicate.

Table 5. Effects of subacute cocaine treatment (20 mg/kg, s.c. twice daily) on the characteristics of DA uptake sites ([^{3}H]GBR-12935) in rat striatum

	WKY		SHR	
	K_d	V_{max}	K_d	V_{max}
control	1.628 ± 0.032	849.4 ± 29.1	1.539 ± 0.070	917.8 ± 20.9
3 days	1.510 ± 0.075	787.2 ± 23.5	1.505 ± 0.090	881.7 ± 24.7*
7 days	1.509 ± 0.065	853.4 ± 30.2	1.391 ± 0.053	858.8 ± 24.8

Rats were sacrificed 18 h after the last injection of cocaine (twice daily, 20 mg/kg).
Unit: K_d = nM, B_{max} = pmol/g protein.
*$p < 0.05$ compared to WKY value.
The values are mean ± S.E. of five separate experiments each performed in duplicate.

However, after subacute administration, there were no change in the dopamine uptake (Table 4) and the dopamine uptake sites (Table 5). Altar and Marshall (1988) have reported that striatal dopamine uptake is unaltered during the adult life span of the rat despite significant losses of striatal dopamine and suggest that the preservative dynamics of the dopamine uptake in striatum are very active. Nicolaysen *et al.* (1988) have reported that the dopamine uptake rate under competitive inhibition by cocaine does not differ from the steady state rate since the dopamine concentration was elevated. Recently Chang and Ramirez (1989) reported that exogenous dopamine infusion in rat striatum induced an increase in DOPAC output and nomifensine only partially blocked the increase in DOPAC output and had little effect on dopamine-induced increase in HVA output. Therefore, cocaine-induced small increase in the synaptic dopamine levels might cause an increase in the dopamine uptake in order to maintain the neuronal balance.

Sershen *et al.* (1984) have reported that the number of dopamine uptake sites and cocaine binding sites are similarly reduced in the striatum of MPTP-treated mice. Although cocaine inhibits dopamine uptake through either the dopamine recognition site itself or via another component of the transport mechanism is debatable (Calligaro and Eldefrawi, 1988; Galloway, 1988; Kennedy and Hanbauer, 1983), after acute cocaine administration the potencies of the dopamine uptake inhibitors, cocaine and GBR-12909, were affected in opposite directions; *i.e.*, cocaine potency was increased whereas that of GBR-12909 was decreased (Table 6). However, after subacute administration there were no different (Table 7). It suggests that the binding sites of two dopamine uptake inhibitors might be different within the dopamine uptake complex and that presynaptic dopaminergic terminals are altered during cocaine treatment.

Involvement of Dopamine Receptors in Cocaine-induced Toxicity in WKY and SHR.

Several investigators (Bhargava, 1984; Chiu *et al.*, 1982; Le fur *et al.*, 1981; Lim *et al.*, 1989) have reported that the densities of D-1 and D-2 receptors in striatum are significantly higher in SHR than in WKY. However, it has been reported that spiperone can bind to serotonin receptors as well as D-2 receptors (List and Seeman, 1981; Schnellmann *et al.*, 1984; Seeman *et al.*, 1984). When the more selective agent,

Table 6. Effects of acute cocaine treatment (40 mg/kg, s.c.) on the *in vitro* IC_{50}s of cocaine and GBR-12909 on dopamine uptake in rat striatum

	IC_{50} for cocaine (μM)		IC_{50} for GBR-12909 (nM)	
	WKY	SHR	SKY	SHR
control	1.140 ± 0.077	1.063 ± 0.091	3.437 ± 0.140	3.626 ± 0.151
30 min	0.903 ± 0.039*	0.926 ± 0.030	4.202 ± 0.248*	4.472 ± 0.304*
control	1.061 ± 0.104	1.195 ± 0.101	3.569 ± 0.336	3.420 ± 0.309
2 h	0.913 ± 0.126	0.874 ± 0.055*	6.255 ± 0.603**	5.536 ± 0.529*
24 h	1.116 ± 0.064	1.175 ± 0.040	3.484 ± 0.389	4.995 ± 0.580

Rats were sacrificed at the indicated time after injection of cocaine.
*$p < 0.05$, **$p < 0.01$ compared to the respective control values.
The values are mean ± S.E. of five separate experiments each performed in duplicate.

Table 7. Effects of subacute cocaine treatment (20 mg/kg, s.c. twice daily) on *in vitro* IC_{50}s of cocaine and GBR-12909 on dopamine uptake in rat striatum

	IC_{50} for cocaine (μM)		IC_{50} for GBR-12909 (nM)	
	WKY	SHR	WKY	SHR
control	0.930 ± 0.077	1.048 ± 0.092	3.327 ± 0.115	3.336 ± 0.300
3 days	1.001 ± 0.079	1.101 ± 0.132	4.271 ± 0.368*	3.580 ± 0.315
control	1.103 ± 0.132	1.188 ± 0.093	3.618 ± 0.210	3.686 ± 0.509
7 days	1.179 ± 0.124	1.172 ± 0.131	3.214 ± 0.263	4.070 ± 0.437

Rats were sacrificed 18 h after the last injection of cocaine (twice daily, 20 mg/kg).
*$p < 0.05$ compared to the respective control value.
The values are mean ± S.E. of five separate experiments each performed in duplicate.

Table 8. Effect of *in vitro* cocaine on the characteristics of D-1 and D-2 receptors in rat striatum

		WKY		SHR	
		K_d	B_{max}	K_d	B_{max}
D-1	control	0.629 ± 0.045	835.3 ± 15.2	0.629 ± 0.039	966.4 ± 39.2#
	1 μM	0.669 ± 0.024	833.9 ± 16.3	0.649 ± 0.020	991.5 ± 21.8
	10 μM	0.668 ± 0.007	825.0 ± 21.8	0.664 ± 0.010	969.1 ± 23.2
	100 μM	0.676 ± 0.025	821.2 ± 12.0	0.643 ± 0.009	940.7 ± 32.8
D-2	control	3.770 ± 0.023	376.2 ± 6.9	3.756 ± 0.034	385.1 ± 18.7
	10 μM	3.655 ± 0.021	380.5 ± 6.1	3.645 ± 0.166	383.5 ± 17.7
	100 μM	3.861 ± 0.126	384.7 ± 11.9	4.094 ± 0.052**	395.8 ± 13.9

Units; K_d (nM), B_{max} (pmol/g protein).
**$p < 0.01$ compared to the respective control value.
#$p < 0.05$ compared to corresponding WKY value.
Each value represents the mean ± 1 S.E.M. of five determinations, each performed in duplicate.

(^{3}H)sulpiride, was used in the determination of D-2 receptors, no difference in the characteristics of D-2 receptors was noted between the two strains. While a higher density of D-1 receptors (defined (^{3}H)SCH-23390) in SHR than in WKY was obtained (Table 8). This indicate that the high density of dopamine receptors in SHR might be due to a high density of the D-1 dopamine receptor subtype.

It is well accepted that cocaine inhibits dopamine uptake in nerve terminals. The increase in synaptic dopamine concentration that would be expected from such as action may play a role in the alteration of dopaminergic receptors (Pitts and Marwah, 1988). Some investigators have reported that dopamine receptors were changed after acute (Memo *et al.*, 1981) and subacute (Goeders and Kuhar, 1987; Trulson and Ulissey, 1987) administration of cocaine. However, other investigators have shown no alteration of dopamine receptors after either acute (Goeders and Kuhar, 1987) or subacute (Dwoskin *et al.*, 1988) administration of cocaine. The discrepancy of results concerning dopamine receptors might be due to prcedural difference, such as dose levels, duration of dosing and sacrifice time after the last administration of cocaine, between different studies. Therefore, we determined the changes in dopamine receptors after systemic administration of cocaine. Changes in the densities of D-1 and D-2 receptors differed following acute treatment with cocaine (Table 9). Since addition of cocaine in striatal homogenates *in vitro* was shown not to affect characteristics of dopamine receptors at reasonable concentrations (Table 8), the changes in dopamine receptors binding characteristics are probably not due to direct actions of cocaine. Increases in D-2 and decreases in D-1 receptor densities were observed. It has been reported that dopaminergic D-1 and D-2 receptors were differentially affected by prolonged L-DOPA treatment (Parenti *et al.*, 1986). It has been reported that the release of dopamine is modulated by inhibitory autoreceptors (Parker and Cubeddu, 1985) and that the dopamine autoreceptor is of the D-2 type (Stool and Kebabian, 1984), although

Table 9. Effect of acute cocaine treatment (40 mg/kg, s.c.) on the characteristics of D-1 and D-2 receptors in rat striatum

		WKY		SHR	
		K_d	B_{max}	K_d	B_{max}
D-1	control	0.366±0.007	1495.1±46.7	0.383±0.024	1607.4±53.4
	30 min	0.378±0.011	1342.1±29.2*	0.405±0.012	1669.5±70.6##
D-1	control	0.450±0.047	1428.5±23.6	0.424±0.032	1563.7±17.5##
	2 h	0.461±0.046	1551.1±20.8	0.459±0.036	1609.9±90.1
	24 h	0.426±0.050	1561.8±59.9	0.433±0.025	1647.3±36.0
D-2	control	4.384±0.362	226.5±13.7	4.444±0.391	202.5± 6.5
	30 min	4.179±0.408	306.5± 8.4**	3.993±0.359	249.0±13.5#,*
	2 h	4.338±0.305	344.4±11.6**	4.156±0.416	296.3±16.2#,**
	24 h	4.093±0.294	304.1±12.9**	4.047±0.216	287.4± 6.3**

Each Rat was sacrificed at the indicated time after injection of cocaine.
Units; K_d (nM), B_{max} (pmol/g protein).
*$p<0.05$, **$p<0.01$ compared to the respective control value.
#$p<0.05$, ##$p<0.01$ compared to corresponding WKY value.
Each value represents the mean ± 1 S.E.M. of four or five determinations, each performed in duplicate.

the roles and localizations of dopamine subtype D-1 and D-2 are controversial (Fage and Scatton, 1986; Quimet *et al.*, 1984). Barnett and Kuczenski (1986) have reported that acute administration of amphetamine or methylphenidate promoted a rapid desensitization of dopamine-stimulated adenylate cyclase in the striatum, which is a selective index of D-1 receptor function. However, subacute treatment with cocaine was observed to produce an early decrease in the maximum binding density of both D-1 and D-2 receptors (Table 10). Also continued administration of cocaine produced increases in the maximum binding densities of D-1 receptors, while those of D-2 receptors remained comparable to saline treated controls (Table 11). It has been reported that tyrosine hydroxylase activity, which is the rate-limiting enzyme for dopamine synthesis, was significantly reduced (Trulson *et al.*, 1986) and pergolide (a

Table 10. Effect of a challenge dose of cocaine on the characteristics of D-1 and D-2 receptors in rat striatum in rats previously receiving a subacute dosage regimens of cocaine

		WKY		SHR	
		K_d	B_{max}	K_d	B_{max}
D-1	control	0.417 ± 0.036	877.4 ± 58.0	0.443 ± 0.025	993.6 ± 60.1
	treated	0.407 ± 0.023	831.6 ± 36.5	0.462 ± 0.031	809.4 ± 14.9*
D-2	control	2.904 ± 0.069	291.4 ± 6.5	3.147 ± 0.139	279.4 ± 3.7
	treated	2.941 ± 0.105	246.8 ± 10.2**	3.508 ± 0.091	302.9 ± 12.6

Rats were sacrificed 30 min following administration of cocaine (40 mg/kg, s.c.).
The challenge dose was administered 18 h following the last regularly scheduled administration of cocaine under the subacute treatment regimen (twice daily, for 7 days, 20 mg/kg, s.c.).
Units; K_d (nM), B_{max} (pmol/g protein).
*$p < 0.05$, **$p < 0.01$ compared to the respective control value.
Each value represents the mean ± 1 S.E.M. of five determinations, each performed in duplicate.

Table 11. Effect of subacute cocaine treatment (20 mg/kg, s.c. twice daily) on the characteristics of D-1 and D-2 receptors in rat striatum

		WKY		SHR	
		K_d	B_{max}	K_d	B_{max}
D-1	control	0.483 ± 0.057	1463.4 ± 11.8	0.608 ± 0.114	1594.9 ± 24.8##
	3 days	0.597 ± 0.095	1633.0 ± 42.0*	0.618 ± 0.113	1647.2 ± 55.5
D-1	control	0.555 ± 0.021	1282.6 ± 50.1	0.523 ± 0.016	1521.5 ± 27.3##
	7 days	0.505 ± 0.010	1544.1 ± 67.1*	0.531 ± 0.012	1487.6 ± 46.5
D-2	control	3.527 ± 0.079	253.6 ± 5.7	3.500 ± 0.103	252.3 ± 3.6
	3 days	3.317 ± 0.066	262.7 ± 4.1	3.660 ± 0.094	243.3 ± 7.3
	7 days	3.423 ± 0.105	265.9 ± 6.3	3.559 ± 0.048	258.4 ± 4.5

Each rats was sacrificed 18 h after the last injection of cocaine (twice daily, 20 mg/kg, s.c.).
Units; K_d (nM), B_{max} (pmol/g protein).
*$p < 0.05$ compared to the respective control value.
$p < 0.01$ compared to corresponding WKY value.
Each value represents the mean ± 1 S.E.M. of four or five determinations, each performed in duplicate.

D-2 agonist)-induced release of dopamine was decreased (Dwoskin *et al.*, 1988) after subacute administration of cocaine. The D-1 receptor was found to show a considerably faster turnover than did the D-1 receptor following administration of the irreversible non-selective dopamine receptor antagonist, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (Fuxe *et al.*, 1987). Thus, early decreases in the density of D-1 receptors result from cocaine-induced increases in synaptic dopamine concentration. Subsequent increases in D-1 receptor number may reflect reactive decreases in dopamine release. However, analysis of the decreases in D-2 receptor number is complicated by the localization of D-2 receptors at both postsynaptic and presynaptic sites.

The observed changes indicate that two strains of rats show different sensitivities to cocaine and that WKY are more sensitive than SHR with respect to cocaine-induced changes in dopamine receptors. Recently, Van den Buuse and De Jong (1989) have reported that administration of dopaminergic agents produced greater responses in WKY than in SHR in the open field behavioral tests. But the precise cause for these differential responses remain to be clarified.

In summary, cocaine is known to inhibit the uptake of catecholaminergic nerve terminal. Acute and subacute cocaine administration in the rats produces the changes in the dopaminergic parameters, such as the increased density of dopamine uptake sites, the changed densities of D-1 and D-2 receptors. Although the possibility of the involvement of other neuronal system by cocaine cannot be excluded, cocaine-induced small increase in the synaptic dopamine levels might alter the presynaptic dopamine terminals and cause an increase in the dopamine uptake in order to maintain the neuronal balance. However, the exact sites of action of cocaine and the altered sites in the dopamine uptake complex remained to be further studied. Furthermore, changes in D-1 and D-2 receptor densities following cocaine administration indicate that cocaine-induced toxicities might be due to the accumulation of the synaptic dopamine in the dopaminergic system. The changes in the characteristics of D-1 and D-2 receptors were somewhat different after cocaine administration and the regulatory process in the differential changes of D-1 and D-2 receptors after cocaine administration might be due to the different roles and localization of dopamine subtype D-1 and D-2.

Although the precise cause for the different responses between WKY and SHR need to be further investigated, the comparison between two strains of rats revealed that the rate of dopamine uptake and D-1 receptor density in the dopamine nerve system were higher in SHR than in WKY. After cocaine administration, WKY are more sensitive than SHR with respect to the change in dopamine receptors.

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