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Selective D_1 and D_2 Dopamine Agonists Differentially Alter Basal Ganglia Glucose Utilization in Rats with Unilateral 6-Hydroxydopamine Substantia Nigra Lesions

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The relative roles of D_1 and D_2 dopamine receptor stimulation in mediating the antiparkinsonian effects of dopaminergic drugs remain unclear. To determine the functional metabolic consequences of selective dopamine receptor stimulation, we used 2-deoxyglucose (2-DG) autoradiography to examine the effects of the D_1 agonist SKF-38393 and the D_2 agonist LY-171555 on regional cerebral glucose utilization (RCGU) in rats with unilateral 6-hydroxydopamine (6-OHDA) substantia nigra lesions. SKF-38393 (0.5–25.0 mg/kg) and LY-171555 (0.01–5.0 mg/kg) produced indistinguishable behavioral responses, including vigorous contralateral rotation. Treatment with each drug similarly increased glucose utilization, dose-dependently, in the parafascicular thalamus, subthalamic nucleus, deep layers of the superior colliculus, and lateral midbrain reticular formation ipsilateral to the nigral lesion; glucose utilization was decreased in the ipsilateral lateral habenula. By contrast, the D_1 and D_2 agonists differentially altered glucose utilization in the entopeduncular nucleus (EP) and the substantia nigra pars reticulata (SN_r). SKF-38393, 5.0 and 25.0 mg/kg, increased glucose utilization 127 and 275%, respectively, in the pars reticulata ipsilateral to the lesion. LY-171555, 1.0 and 5.0 mg/kg, caused maximal contralateral turning, yet did not alter glucose utilization in the ipsilateral SN_r. The glucose utilization response of the ipsilateral EP paralleled that of the SN_r demonstrating large increases following administration of SKF-38393 and minimal change following the use of LY-171555. The results demonstrate that the selective D_1 agonist reproduces the marked glucose utilization increases (2–3-fold above control values) in the EP and SN_r that were previously observed using L-DOPA and apomorphine in this model, whereas the selective D_2 agonist does not. Because both nuclei are selectively rich in D_1 receptors, with D_1:D_2 ratios of 20–30:1, the data suggest that the glucose utilization increases observed with L-DOPA result, at least in part, from a direct stimulation of D_1 receptors in these nuclei and do not reflect an exclusive drug effect on striatal dopamine receptors. Given the magnitude of the glucose utilization response, the findings suggest that D_1 receptors in the EP and SN_r become functionally supersensitive following 6-OHDA substantia nigra lesion. The ability of selective D_1 and D_2 agonists to differentially regulate metabolic activity in these 2 major basal ganglia output nuclei may be of physiologic and therapeutic significance.

Degeneration of dopaminergic neurons in the substantia nigra and the resultant dopamine deficiency in the basal ganglia represent the critical neuropathological and neurochemical correlates of Parkinson's disease (Hornykiewicz, 1982). The most effective therapy for Parkinson's disease remains dopamine replacement, in the form of precursor L-DOPA or direct-acting dopamine agonists (e.g., bromocriptine, pergolide). Some fundamental questions remain regarding the mechanism of action of these drugs: (1) Which dopamine receptors (i.e., anatomic localization or receptor subtype) need to be stimulated to achieve an antiparkinsonian effect? (2) Subsequent to dopamine receptor stimulation, which neural circuits are activated to mediate these effects?

In an attempt to answer this second question, the 2-deoxyglucose (2-DG) autoradiographic method of measuring regional cerebral glucose utilization (RCGU) has been used to identify brain regions physiologically altered by dopaminergic drugs. L-DOPA and apomorphine (a D_1 and D_2 agonist) produce indistinguishable RCGU patterns when administered systemically to rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra, a classical animal model of Parkinson's disease (Ungerstedt et al., 1973). This pattern is characterized by marked RCGU increases (~200%) in the entopeduncular nucleus (EP; homolog of the primate medial pallidum) and substantia nigra pars reticulata (SN_r) ipsilateral to the nigral lesion, and moderates RCGU changes (~10–50%) in other brain regions (Wooten and Collins, 1983; Trugman and Wooten, 1986). It has been hypothesized that these profound glucose utilization changes in the EP and SN_r reflect primarily increased physiological activity in the axon terminals of striatal projection neurons (Trugman and Wooten, 1986). This is consistent with studies suggesting that the striatum is the primary site of dopamine receptor supersensitivity and dopaminergic drug action following the loss of nigral dopamine neurons (Ungerstedt, 1971; Siggins et al., 1976; Creese et al., 1977).

In recent years, it has become clear that endogenous dopamine interacts with 2 distinct receptors, D_1 and D_2, as identified by both biochemical and pharmacological criteria (Stoof and Kebabian, 1984). Stimulation of the D_1 receptor increases adenylate cyclase activity, while stimulation of the D_2 receptor inhibits this enzyme (Kebabian and Calne, 1979; Onali et al.,

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Table 1. Behavioral observations made during the 45 min ^{14}C-2-DG circulation time in rats with unilateral 6-OHDA substantia nigra lesions

	Saline control	SKF-38393			LY-171555			
		0.5 mg/kg	5.0 mg/kg	25.0 mg/kg	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg
Contralateral rotations/min	0.0 ± 0	0.0 ± 0	0.0 ± 0	7.0 ± 1.5	0.0 ± 0	0.5 ± 0.2	3.1 ± 0.9	3.9 ± 0.3
Postural asymmetry	0	0	+	++	0	+	++	++
Facial grooming	0	+	+	0	0	+	0	0

Controls are lesioned rats treated with saline (n = 6). The experimental groups consist of lesioned rats treated with SKF-38393 or LY-171555 (n = 3). Behavior was observed for 60 sec every 5 min and 360° contralateral rotations were expressed as means ± SD. Postural asymmetry was graded as absent (0), mild (+; 10°–30° head tilt), or marked (++; tight head to tail posture). Facial grooming was rated as absent (0) or present (+). The administration of both D_1- and D_2-selective agonists resulted in comparable behavioral effects over the indicated dose ranges.

1985). Quantitative receptor autoradiography has revealed distinct, yet overlapping, neuroanatomical distributions of D_1 and D_2 receptors (Boyson et al., 1986; Dawson et al., 1986; Savasta et al., 1986). At present, the functional role of each receptor subtype in normal and pathological states is inadequately understood. Experimental and clinical data have suggested that dopaminergic drugs alter motor behavior and achieve antiparkinsonian effects via D_2-receptor stimulation (Schachter et al., 1980;

Table 2. Relative 2-DG uptake in rats with left-sided unilateral 6-OHDA substantia nigra lesions

Brain region	Side	Saline control	SKF-38393		
			0.5 mg/kg	5.0 mg/kg	25.0 mg/kg
Nucleus accumbens	L	2.67 ± 0.35	2.93 ± 0.29	2.61 ± 0.26	2.61 ± 0.34
	R	2.80 ± 0.35	3.21 ± 0.45	2.56 ± 0.26	2.71 ± 0.45
Striatum	L	3.23 ± 0.22	3.51 ± 0.40	3.10 ± 0.09	3.49 ± 0.35
Dorsal	R	3.35 ± 0.37	3.85 ± 0.72	3.40 ± 0.31	3.68 ± 0.28
Ventral	L	3.27 ± 0.25	3.56 ± 0.20	3.73 ± 0.45	3.81 ± 0.18
	R	3.20 ± 0.31	3.57 ± 0.35	3.45 ± 0.43	3.82 ± 0.28*
Lateral	L	3.21 ± 0.27	3.53 ± 0.26	3.63 ± 0.48	4.29 ± 0.15**
	R	3.26 ± 0.34	3.73 ± 0.45	3.51 ± 0.45	4.11 ± 0.17**
Medial	L	3.07 ± 0.25	3.27 ± 0.27	3.18 ± 0.22	3.26 ± 0.24
	R	3.22 ± 0.37	3.57 ± 0.52	3.32 ± 0.26	3.42 ± 0.33
Globus pallidus	L	2.48 ± 0.18	2.74 ± 0.31	3.18 ± 0.87	3.06 ± 0.27
	R	2.07 ± 0.22	2.25 ± 0.25	2.23 ± 0.30	2.73 ± 0.10**
Motor cortex	L	3.07 ± 0.35	3.44 ± 0.28	2.87 ± 0.30	3.19 ± 0.31
	R	3.36 ± 0.49	3.39 ± 0.36	3.08 ± 0.40	3.51 ± 0.30
Somatosensory cortex	L	3.19 ± 0.37	3.73 ± 0.48	3.33 ± 0.13	4.00 ± 0.62
	R	3.42 ± 0.50	3.74 ± 0.31	3.40 ± 0.43	4.33 ± 0.40
Anterior cingulate cortex	L	3.49 ± 0.46	4.14 ± 0.41	3.26 ± 0.49	3.47 ± 0.19
	R	3.65 ± 0.45	4.19 ± 0.62	3.42 ± 0.51	3.68 ± 0.21
Entopeduncular nucleus	L	1.71 ± 0.34	1.86 ± 0.18	2.67 ± 0.17**	4.92 ± 0.21**
	R	1.83 ± 0.43	1.91 ± 0.11	1.81 ± 0.16	2.28 ± 0.16
Lateral habenular nucleus	L	4.80 ± 0.65	4.16 ± 0.51	3.13 ± 0.59**	2.64 ± 0.43**
	R	3.92 ± 0.35	4.23 ± 0.57	4.45 ± 1.14	4.72 ± 0.65
Parafascicular nucleus, thalamus	L	3.22 ± 0.43	3.44 ± 0.31	3.56 ± 0.60	4.85 ± 0.79**
	R	3.30 ± 0.53	3.55 ± 0.49	3.41 ± 0.51	4.27 ± 0.64
Ventroposterior thalamus	L	3.03 ± 0.31	3.35 ± 0.17	3.54 ± 0.76	3.60 ± 0.26
	R	3.11 ± 0.35	3.39 ± 0.38	3.50 ± 0.88	3.49 ± 0.18
Subthalamic nucleus	L	3.07 ± 0.43	3.39 ± 0.26	4.15 ± 0.69*	4.25 ± 0.27*
	R	3.45 ± 0.45	3.48 ± 0.35	3.38 ± 0.40	3.80 ± 0.37
Pretectal area	L	3.56 ± 0.43	3.65 ± 0.68	3.48 ± 0.39	4.39 ± 0.47*
	R	3.76 ± 0.51	3.87 ± 0.47	3.55 ± 0.36	4.44 ± 0.39
Substantia nigra pars reticulata	L	1.98 ± 0.13	2.37 ± 0.30	4.49 ± 0.53**	7.43 ± 0.39**
	R	2.09 ± 0.16	2.20 ± 0.15	2.58 ± 0.33*	3.06 ± 0.32**
Deep layers of superior colliculus	L	3.05 ± 0.41	3.37 ± 0.37	3.27 ± 0.75	4.50 ± 0.66**
	R	3.22 ± 0.36	3.51 ± 0.37	3.12 ± 0.65	3.70 ± 0.34
Lateral midbrain reticular formation	L	2.77 ± 0.31	3.06 ± 0.13	3.50 ± 0.55	3.98 ± 0.26**
	R	2.90 ± 0.36	2.92 ± 0.31	3.17 ± 0.56	3.61 ± 0.23

Controls are lesioned rats treated with saline (n = 6). The experimental groups consist of lesioned rats treated with SKF-38393 or LY-171555 (n = 3) at the indicated doses. Data are means ± SD of the ratio of gray to white matter optical density (OD_R). Dunnett's test (df = 7,19) was used to compare experimental group OD_R values to control values for each brain region. Statistical significance is indicated: * $p < 0.05$; ** $p < 0.01$.

Seeman, 1980). Studies employing recently developed selective D_1 and D_2 agonists and antagonists, however, have suggested that the D_1 receptor mediates some of the behavioral effects of dopaminergic drugs both in normal animals and in those with 6-OHDA or reserpine-induced dopamine depletion (Rosengarten et al., 1983; Molloy and Waddington, 1984; Arnt, 1985; Braun and Chase, 1985; Breese et al., 1985a, b).

To determine the functional metabolic consequences of selective dopamine receptor stimulation, we have examined the effects of the D_1 agonist SKF-38393 (Setler et al., 1978; Sibley et al., 1982) and of the D_2 agonist LY-171555 (Tsuruta et al., 1981) on RCGU in rats with unilateral nigral lesions. We present evidence that these selective agonists, while producing similar glucose utilization patterns in multiple brain regions, differentially alter glucose utilization in the EP and SN_r.

Table 2. Extended

LY-171555			
0.01 mg/kg	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg
2.97 ± 0.33	2.76 ± 0.37	2.71 ± 0.22	3.10 ± 0.40
3.15 ± 0.38	2.83 ± 0.47	2.78 ± 0.29	2.95 ± 0.33
3.53 ± 0.44	3.26 ± 0.42	3.46 ± 0.35	3.47 ± 0.34
3.60 ± 0.35	3.34 ± 0.38	3.39 ± 0.37	3.53 ± 0.22
3.43 ± 0.28	3.52 ± 0.36	3.46 ± 0.24	3.53 ± 0.57
3.40 ± 0.22	3.45 ± 0.23	3.36 ± 0.29	3.30 ± 0.29
3.42 ± 0.35	3.32 ± 0.30	3.63 ± 0.48	3.64 ± 0.26
3.43 ± 0.35	3.43 ± 0.16	3.35 ± 0.34	3.47 ± 0.25
3.30 ± 0.24	3.21 ± 0.42	3.42 ± 0.30	3.46 ± 0.27
3.34 ± 0.23	3.36 ± 0.42	3.45 ± 0.33	3.43 ± 0.14
2.54 ± 0.21	2.56 ± 0.22	2.79 ± 0.35	2.87 ± 0.29
2.08 ± 0.11	2.25 ± 0.13	2.50 ± 0.27*	2.43 ± 0.15
2.89 ± 0.30	2.90 ± 0.24	3.56 ± 0.67	3.73 ± 0.15
3.05 ± 0.33	3.05 ± 0.33	3.59 ± 0.60	3.78 ± 0.27
3.02 ± 0.44	3.64 ± 0.38	4.23 ± 0.92*	4.35 ± 0.33*
3.24 ± 0.29	3.86 ± 0.60	4.70 ± 0.78**	4.78 ± 0.25**
3.61 ± 0.58	3.68 ± 0.33	3.99 ± 0.30	4.20 ± 0.23
3.68 ± 0.43	3.70 ± 0.38	4.05 ± 0.40	4.38 ± 0.22
1.77 ± 0.14	1.96 ± 0.31	2.57 ± 0.28**	2.56 ± 0.17**
1.81 ± 0.20	2.02 ± 0.31	2.71 ± 0.64**	2.44 ± 0.09
4.71 ± 0.65	3.71 ± 0.75	3.30 ± 0.59**	3.08 ± 0.14**
4.45 ± 0.61	3.75 ± 0.37	4.18 ± 0.45	3.59 ± 0.19
3.20 ± 0.56	3.88 ± 0.35	4.42 ± 0.81*	4.43 ± 0.55*
3.24 ± 0.55	3.73 ± 0.43	4.04 ± 0.43	4.02 ± 0.55
3.12 ± 0.75	3.72 ± 0.40	3.92 ± 0.66	3.58 ± 0.23
3.12 ± 0.64	3.75 ± 0.42	3.80 ± 0.33	3.53 ± 0.15
3.16 ± 0.44	4.01 ± 0.16	4.99 ± 0.91**	5.23 ± 0.70**
3.52 ± 0.37	4.15 ± 0.18	5.01 ± 0.67**	5.12 ± 0.51**
3.21 ± 0.39	3.40 ± 0.24	3.82 ± 0.16	4.31 ± 0.27
3.61 ± 0.44	3.69 ± 0.57	3.96 ± 0.30	4.31 ± 0.22
2.09 ± 0.27	2.11 ± 0.32	2.39 ± 0.16	2.53 ± 0.14
2.06 ± 0.27	2.31 ± 0.31	2.60 ± 0.25*	2.42 ± 0.05
3.00 ± 0.40	3.68 ± 0.57	4.31 ± 0.73*	4.17 ± 0.30*
3.03 ± 0.41	3.64 ± 0.33	4.02 ± 0.63	3.77 ± 0.35
2.84 ± 0.36	3.15 ± 0.52	3.60 ± 0.69*	3.12 ± 0.18
2.78 ± 0.42	3.09 ± 0.14	3.51 ± 0.41	3.06 ± 0.19

Materials and Methods

Animal preparation, drugs, and 2-DG autoradiography. All experiments were performed on male Sprague-Dawley rats weighing 250–300 gm. Following pretreatment with desipramine hydrochloride, 25 mg/kg, i.p. (Sigma Chemical Co., St. Louis, MO), unilateral, left-sided, 6-OHDA (Sigma) lesions of the substantia nigra pars compacta (SN_c) were performed as previously described (Wooten and Collins, 1981). Six-hydroxydopamine hydrobromide (6.0 μg/2.0 μl of 0.5% ascorbic acid in saline) was injected over 3 min at the following stereotactic coordinates: bregma −5.0 mm AP, 1.6 mm L, −8.0 mm DV (Paxinos and Watson, 1982). Rats were tested 10 d later with apomorphine hydrochloride (Sigma), 0.5 mg/kg, i.p., to determine lesion efficacy. Only rats that turned a minimum of 5 rotations/min at the peak action of apomorphine were used in subsequent 2-DG studies, performed 4–6 weeks after lesioning.

Racemic (RS) SKF-38393 (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride; Research Biochemicals, Wayland, MA) was dissolved in NaCl, 77 mM, containing 10% (vol/vol) propylene glycol. LY-171555 [*trans*-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-^{1}H(or ^{2}H)-pyrazolo-3,4-g-quinoline, monohydrochloride] (quinpyrrole; Lilly Research Laboratories, Indianapolis, IN) was dissolved in saline. Each rat received 25 μCi of ^{14}C-2-deoxyglucose (55 μCi/mmol; American Radiochemical, St. Louis, MO) reconstituted in saline. All drugs, vehicle, and isotope were injected intravenously in a volume of 1 ml/kg body weight. Drug doses are expressed in terms of the weights of their salts.

^{14}C-2-DG autoradiography was performed according to the method of Sokoloff et al. (1977). The experimental groups consisted of unilateral nigral-lesioned rats treated with SKF-38393 or LY-171555. The control group consisted of lesioned rats treated with saline. On the experimental day, after the rats had fasted overnight, a central venous catheter was inserted under 1% halothane anesthesia. After 3 hr of recovery, rats were injected with a drug followed by ^{14}C-2-DG 1 min later. Unrestrained rats were studied in 23 × 35 cm cages. Behavioral observations, which included observation of the number of 360° contralateral rotations, were recorded for 60 sec every 5 min. Postural asymmetry was graded as absent (0), mild (+; 10–30° head tilt), or marked (++; tight head to tail position). Facial grooming was rated as absent (0) or present (+). Forty-five minutes after the ^{14}C-2-DG injection, the rats were killed with a 50 mg/ml intravenous bolus of sodium pentobarbital. The brains were rapidly removed, frozen in liquid freon, and mounted on brass chucks. Duplicate 20 μm coronal sections were taken every 140 μm, thaw-mounted on coverslips, dried on a 60°C warming tray, and exposed to Kodak SB-5 x-ray film for 6 d. Film autoradiographs were analyzed with a Leitz variable aperture microdensitometer.

Data analysis. Data for glucose utilization were expressed as a ratio of gray matter optical density (OD) to white matter (corpus callosum) OD (OD_R) (Sharp et al., 1983; Mitchell and Crossman, 1984). The data represent the mean ± SD of a minimum of 4 measurements per brain region per animal. All OD values were between 0.05 and 0.9 and were therefore on the linear part of the OD-versus-tissue equivalent ^{14}C curve (Sharp et al., 1983). Analysis of variance revealed no difference among groups for the corpus callosum OD values ($df = 7,19$).

Dunnett's multiple t test was used to compare OD_R data from the experimental groups to those of controls. A test of homogeneity of slopes was used to compare the regression lines of the log dose–response data. A paired t test was used to compare ipsilateral and contralateral OD_R values in the lesioned controls. Statistical significance was taken as $p < 0.05$.

Results

Behavioral observations

Behavioral observations made during the 45 min circulation time of the ^{14}C-2-DG are summarized in Table 1. The doses of both SKF-38393 and LY-171555 produced effects ranging from minimal behavioral change to vigorous contralateral rotation. In those rats that received the higher doses, turning behavior always began within 30–60 sec of completion of the intravenous injection. Locomotor activity was minimal in those rats that didn't turn; they generally remained stationary throughout the experimental period. Intermediate doses of both drugs produced mild postural asymmetry without contralateral rotation. At these

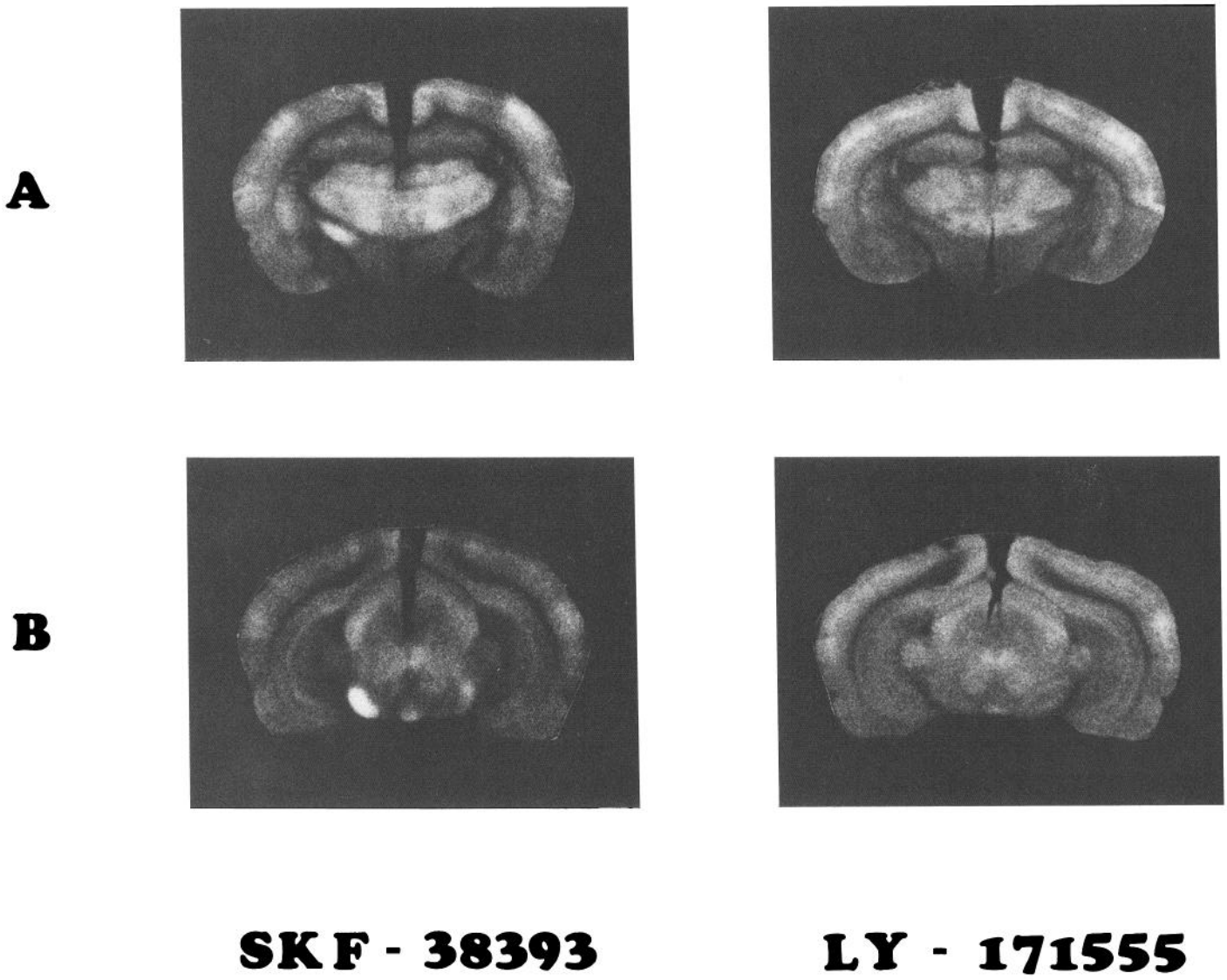

Figure 1. ^{14}C-2-deoxyglucose (2-DG) reversed-image autoradiographs (printed directly from x-ray film) depicting RCGU patterns in the unilateral nigral-lesioned rat treated with SKF-38393, 25 mg/kg (D_1 agonist), and LY-171555, 1.0 mg/kg (D_2 agonist). The SN_c lesion is on the *left side,* as are the RCGU changes noted below. *Light areas* indicate high 2-DG uptake, while *dark areas* correspond to low 2-DG uptake. RCGU is markedly increased in the entopeduncular nucleus (*A*) and substantia nigra pars reticulata (*B*) ipsilateral to the SN_c lesion following D_1-, but not D_2-agonist treatment.

doses, a distinctive facial grooming behavior, using predominantly the forelimb contralateral to the substantia nigra lesion, was noted. This behavior was elicited by both drugs. At doses of each drug that elicited vigorous contralateral turning, facial grooming was not observed. As indicated in Table 1, the administration of SKF-38393 and LY-171555 produced comparable behavioral effects over the indicated dose ranges.

Regional cerebral glucose utilization

The effects of the substantia nigra lesion alone (control) and the effects of SKF-38393 and LY-171555 on RCGU are presented in Table 2. The substantia nigra lesion resulted in characteristic RCGU changes in several brain regions ipsilateral to the lesion: globus pallidus (up 20%), lateral habenula (up 22%), subthalamic nucleus (down 11%), and multiple cortical regions (down 5–10%). These findings are consistent with prior reports (Kozlowski and Marshall, 1980; Wooten and Collins, 1981).

Both D_1 (SKF-38393) and D_2 (LY-171555) agonists produced dose-dependent RCGU changes in selected brain regions. SKF-38393, 0.5 mg/kg—a dose associated with minimal behavioral change—did not alter glucose utilization in any region studied. Administration of SKF-38393, 5.0 mg/kg resulted in mild postural asymmetry and contralateral facial grooming; it increased RCGU in the ipsilateral EP (up 56%), SN_r (up 127%), and subthalamic nucleus (up 35%), and decreased RCGU in the ipsilateral lateral habenula (down 35%). RCGU was also increased in the contralateral SN_r (up 23%). SKF-38393, 25.0 mg/kg, caused continuous contralateral circling and RCGU changes of greater magnitude in the same regions: EP (up 188%), ipsilateral SN_r (up 275%), contralateral SN_r (up 46%), subthalamic nucleus (up 38%), and lateral habenula (down 45%). In addition, RCGU was increased in other brain regions ipsilateral to the lesion: parafascicular thalamus (up 51%), pretectal area (up 23%), deep layers of superior colliculus (up 48%), and lateral midbrain re-

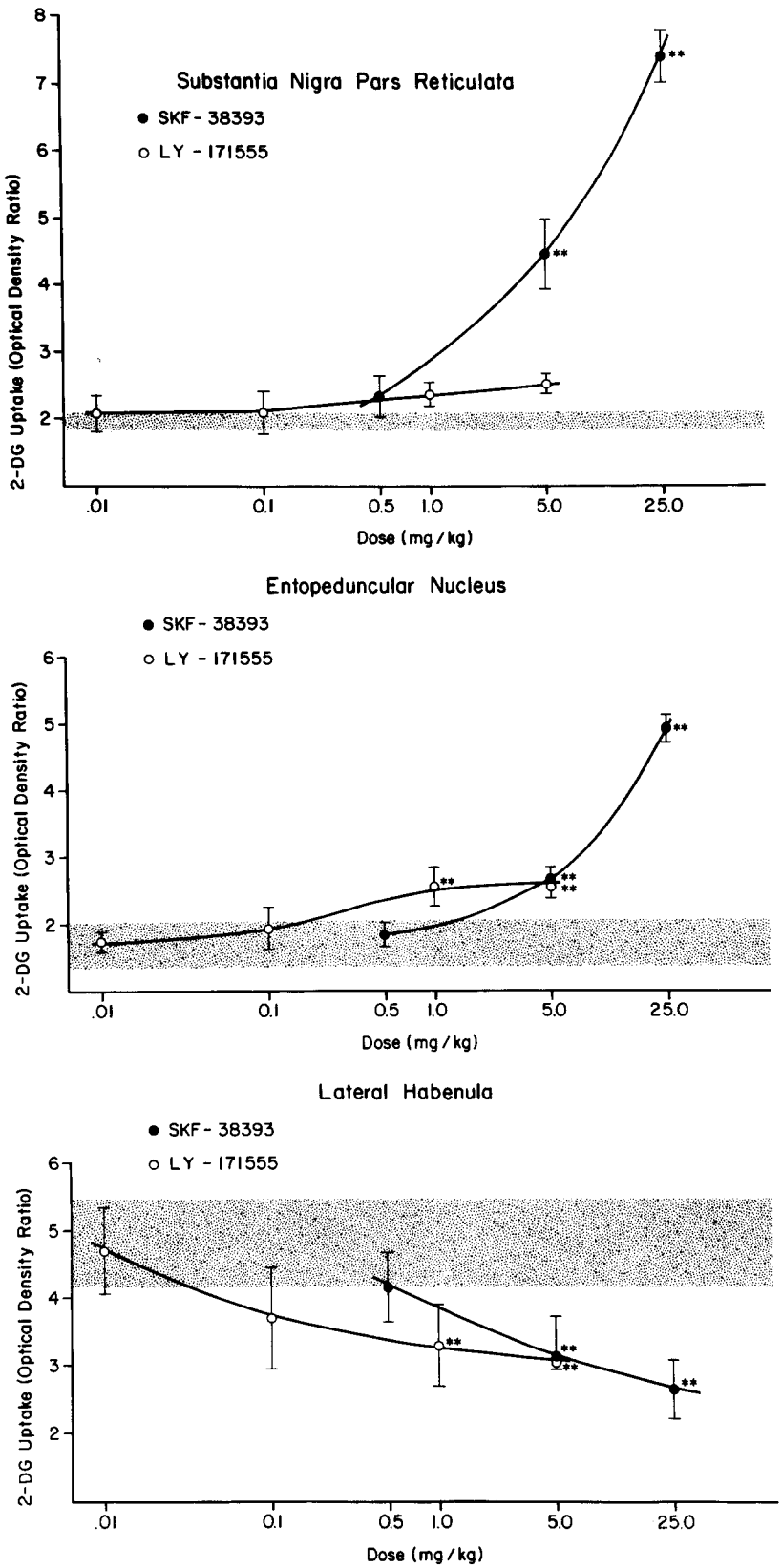

Figure 2. Log dose–response curves for 2-DG uptake in the substantia nigra pars reticulata (SN_r), entopeduncular nucleus (EP), and lateral habenula ipsilateral to the 6-OHDA SN_c lesion. Lesioned rats were administered SKF-38393 (D_1 agonist) or LY-171555 (D_2 agonist) intravenously ($n = 3$). The *shaded area* indicates 2-DG uptake in the control group (lesioned rats given saline; $n = 6$). For both the SN_r and EP, the slopes of the D_1 and D_2 dose–response curves differ ($p < 0.001$), indicating that 2-DG uptake in these nuclei is differentially altered by these drugs. The slopes of the dose-response curves in the lateral habenula do not differ, indicating that 2-DG uptake in this nucleus is altered in a similar manner by both D_1 and D_2 agonists. Optical-density ratios significantly different from control values are indicated as follows: *, $p < 0.05$; **, $p < 0.01$.

ticular formation (up 44%). At this dose, RCGU was also increased in the lateral striatum bilaterally (ipsilateral, up 34%; contralateral, up 26%).

LY-171555, 0.01 mg/kg, produced no behavioral changes and did not alter RCGU. Administration of LY-171555, 0.1 mg/kg, resulted in mild postural asymmetry, grooming, and minimal turning behavior. This dose altered RCGU in several regions, including the lateral habenula and subthalamic nucleus, but none of the changes reached statistical significance. LY-171555, at doses of 1.0 and 5.0 mg/kg, caused continuous con-

tralateral turning and similar RCGU changes. RCGU changes were noted in ipsilateral regions, including parafascicular thalamus, where it was up 37%, lateral habenula (down 31%), deep layers of superior colliculus (up 41%), and lateral midbrain reticular formation (up 30%). RCGU changes were noted bilaterally in the following regions: somatosensory cortex (left, up 33%; right, up 37%); EP (L, up 50%; R, up 48%); and subthalamic nucleus (L, up 63%; R, up 45%). The similar magnitudes of the behavioral and RCGU responses to LY-171555, 1.0 and 5.0 mg/kg, suggest that these doses are at the plateau of the dose–response curve.

Statistical analysis of log dose–response data allowed us to compare the RCGU responses to SKF-38393 and LY-171555 in individual brain regions. Most brain regions, including the lateral habenula, parafascicular thalamus, subthalamic nucleus, and deep layers of superior colliculus, responded in a similar manner to both SKF-38393 and LY-171555; the slopes of the dose–response curves for the D_1 and D_2 agonists in these brain regions were not different. The parallel dose–response curves for the lateral habenula are illustrated in Figure 2 (bottom panel). In contrast, SKF-38393 and LY-171555 produced dramatically different RCGU patterns in 2 critical basal ganglia nuclei: the EP and SN_r. SKF-38393, 5.0 and 25.0 mg/kg, increased RCGU in the ipsilateral SN_r 127 and 275%, respectively. LY-171555, even at doses that produced continuous turning, never significantly altered RCGU in the SN_r. In the ipsilateral EP, SKF-38393, 5.0 and 25.0 mg/kg, increased RCGU 56 and 188%, respectively. LY-171555, 1.0 and 5.0 mg/kg, increased RCGU 50% in this same brain region. Representative autoradiographs are presented in Figure 1. Figure 2 demonstrates graphically the similar RCGU responses of the SN_r and EP to the D_1 and D_2 agonists, and shows that the slopes of the D_1 and D_2 dose–response curves in these nuclei are different ($p < 0.001$).

The combination of 2-DG studies with behavioral analysis allowed for a correlation of RCGU responses with turning behavior. Only 2 brain regions, the parafascicular nucleus of the thalamus and the deep layers of the superior colliculus, demonstrated RCGU changes that correlated exclusively with turning. Other regions, including the EP, lateral habenula, and subthalamic nucleus, demonstrated RCGU changes at drug doses associated with postural asymmetry, without overt contralateral rotation. Vigorous turning behavior was produced by LY-171555 without a significant RCGU change in the SN_r.

It is of interest to note that certain brain regions that have been implicated in dopamine-mediated locomotor behavior did not demonstrate any RCGU changes upon administration of either SKF-38393 or LY-171555. These regions include the nucleus accumbens, motor cortex, and ventroposterior thalamus. RCGU in the globus pallidus ipsilateral to the nigral lesion showed a tendency to increase with both D_1 and D_2 agonists, but these changes did not reach statistical significance. RCGU in the striatum, the nucleus considered to be the major site of action of dopaminergic drugs following nigral lesion, was moderately increased in the lateral quadrant with treatment by SKF-38393 (25 mg/kg) (up 30% bilaterally), but remained unchanged following the administration of LY-171555.

Discussion

The 2-DG autoradiographic method provides a powerful means for simultaneously surveying metabolic activity in multiple brain regions and correlating these changes with behavior. In an effort to identify the neural circuits activated by the selective stimulation of D_1 and D_2 receptors, we have studied the effects of D_1 (SKF-38393) and D_2 (LY-171555) dopamine agonists on RCGU in rats with unilateral 6-OHDA SN_c lesions. The pharmacologic selectivity of these drugs has been determined by extensive *in vitro* biochemical investigation (Setler et al., 1978; Tsurata et al., 1981; Sibley et al., 1982; Onali et al., 1985). *In vivo* data on the inhibition of prolactin secretion suggest that pharmacologic specificity at D_1 and D_2 receptors is maintained at the doses used in this study (Setler et al., 1978; Bach et al., 1980). The use of both SKF-38393 and LY-171555 resulted in broad and comparable ranges of behavioral and RCGU responses. While both drugs produced similar RCGU changes in several brain regions, including the lateral habenula, subthalamic nucleus, deep layers of the superior colliculus, and parafascicular thalamus, RCGU was differentially altered in the EP and the SN_r. Given the strategic role of these nuclei as the dual source of basal ganglia efferents to premotor centers (Graybiel and Ragsdale, 1979), the ability of selective D_1 and D_2 agonists to differentially regulate metabolic activity in these 2 nuclei may be of pathophysiologic and therapeutic significance.

Two key questions arise in interpreting the present findings: (1) What is the electrophysiological correlate of the RCGU changes in the EP and SN_r consequent to drug administration?, and (2) upon systemic administration, where do these drugs primarily act to produce their effects? In rats with unilateral SN_c lesions, both apomorphine (a mixed D_1 and D_2 agonist) and L-DOPA (a precursor to dopamine) induce contralateral rotation and marked RCGU increases in the EP and SN_r (up ~200%) (Wooten and Collins, 1983; Trugman and Wooten, 1986). Electrophysiological studies have demonstrated that, in 6-OHDA-lesioned rats, systemically administered apomorphine profoundly and consistently inhibits the firing of identified SN_r output neurons (Waszczak et al., 1984). On the basis of evidence that the striatum is the primary site of supersensitivity following SN_c lesion, it has been hypothesized that the dramatic RCGU increases in the EP and SN_r reflect primarily a direct drug effect on striatal dopamine receptors (Trugman and Wooten, 1986). Accordingly, the RCGU increases were thought to represent increased metabolic activity in the axon terminals of inhibitory striatoentopeduncular and striatonigral neurons. This speculation is consistent with known electrophysiological observations (Waszczak et al., 1984). Our present results demonstrate that administration of the selective D_1 agonist SKF-38393 reproduces the RCGU increases in the EP and SN_r previously observed with apomorphine and L-DOPA, whereas the selective D_2 agonist LY-171555 does not.

Recently, the effects of D_1 and D_2 agonists on SN_r neuronal activity have been reported (Weick and Walters, 1987). When administered to rats with unilateral 6-OHDA lesions, SKF-38393 (10 mg/kg, i.v.) was found to mimic the inhibitory effects of apomorphine upon SN_r neuronal activity, although the magnitude of the average inhibition was not as great. LY-171555 (1.0 mg/kg, i.v.) was much less effective in producing inhibition. The D_1 antagonist SCH-23390 was effective in reversing the inhibitory effects of apomorphine, whereas pretreatment with the D_2 antagonist YM-09151-2 altered only minimally the apomorphine-induced inhibition. The electrophysiological and 2-DG studies of apomorphine and selective dopamine agonists complement each other. It is clear that one electrophysiological correlate of the marked RCGU increase in the SN_r observed with apomorphine and SKF-38393 is profound inhibition of SN_r neuronal activity. Together, these studies suggest that the

D_1 receptor plays a significant role in mediating the effects of apomorphine on neuronal activity and glucose utilization in the SN_r.

Recent receptor-localization studies have contributed to our understanding of where these dopaminergic drugs may be acting. Both the EP and SN_r have large numbers of D_1 receptors and few D_2 receptors, with D_1:D_2 ratios of 18:1 and 36:1, respectively (Boyson et al., 1986). Lesion studies have suggested that the D_1 receptors in the EP and SN_r are located on the terminals of afferents from the striatum (Altar et al., 1986; Barone and Chase, 1986; Porceddu et al., 1986; Wamsley et al., 1986). What might be the physiological role for these D_1 receptors? Morphologic studies have confirmed the existence of dopamine in dendrites of SN_c neurons, which course ventrally to densely innervate the SN_r (Björklund and Lindvall, 1975). Dopamine is physiologically and pharmacologically releasable from this dendritic pool, and its release attenuates the inhibition of SN_r output neurons evoked by electrical stimulation of the striatonigral GABAergic pathway (Cheramy et al., 1981; Waszczak and Walters, 1986). Electrophysiologic evidence suggests that this modulatory role of dopamine in the SN_r may be mediated by the D_1 receptor (Matthews and German, 1986). Interpreted in the context of the electrophysiological and receptor-localization studies, our data suggest that the RCGU increases in the EP and SN_r observed after the administration of apomorphine, L-DOPA, or SKF-38393 result, at least in part, from a direct action on D_1 receptors in these nuclei and may not reflect an exclusive drug effect at the striatal level.

Supersensitivity to the behavioral effects of dopamine agonists, characterized by a left shift in the dose–response curve, occurs in patients with Parkinson's disease, and has been demonstrated following SN_c lesion in rats (Ungerstedt, 1971; Uretsky and Schoenfeld, 1971; Hornykiewicz, 1982). Because of the major axonal projection of SN_c dopaminergic neurons to the striatum, much work has been directed toward demonstrating the existence and the molecular mechanisms of supersensitivity to dopamine in this nucleus (Siggins et al., 1976; Creese et al., 1977). Less attention has been directed to the SN_r as a potential site of supersensitivity to dopamine following SN_c lesion. The ability of iontophoretically applied dopamine to attenuate SN_r responses to GABA is increased 40% following 6-OHDA nigral lesion, providing electrophysiologic evidence of a supersensitive dopaminergic effect in the SN_r (Waszczak and Walters, 1984). Our data suggest that a supersensitive RCGU response to D_1-receptor stimulation exists in the EP and SN_r following SN_c lesion.

In the present study, as in prior 2-DG studies of dopamine agonists, the RCGU responses of the EP paralleled the responses of the SN_r (Fig. 2). These 2 nuclei have similar spontaneous firing patterns, nerve cell morphology, and afferent and efferent connections, suggesting that they represent a single nucleus divided by the internal capsule (DeLong and Georgopoulos, 1982). In addition, they share similar D_1:D_2 receptor profiles (Boyson et al., 1986). The presence of large numbers of D_1 receptors in the EP suggests a local physiological role for dopamine, yet no dopaminergic neural processes have been demonstrated terminating in this nucleus. Our RCGU data suggest that dopaminergic drugs alter metabolic activity in the EP in part via direct stimulation of D_1 receptors within the nucleus, and further indicate that studies aimed at elucidating a physiologic role for dopamine in this nucleus, while technically difficult, might yield important information.

The D_1 receptor has been identified by both biochemical and pharmacological criteria, yet its physiological role in brain function is debated (Stoof and Kebabian, 1984). In normal rats, the selective D_1 agonist SKF-38393 does not produce typical stereotyped chewing or gnawing, nor does it increase locomotor behavior; it does result in a nonstereotyped grooming behavior (Molloy and Waddington, 1984). In rats with 6-OHDA SN_c lesions, administration of SKF-38393 results in contralateral rotation indistinguishable from that produced by apomorphine or L-DOPA (Setler et al., 1978). Recent work has suggested that both the locomotor activity and self-mutilating behavior induced by L-DOPA in rats treated neonatally with 6-OHDA are mediated by functionally supersensitive D_1 receptors (Breese et al., 1985a, b). Thus, behavioral studies clearly indicate a supersensitive response to D_1-receptor stimulation in rats with 6-OHDA lesions of dopaminergic neurons. It has been reported that SKF-38393 does not alter RCGU in naive animals (Palacios and Wiederhold, 1985). By contrast, we report that administration of SKF-38393 to rats with 6-OHDA SN_c lesions results in dose-dependent RCGU changes in multiple brain regions, and in marked RCGU increases in the EP and SN_r. This is consistent with other evidence that the RCGU response to dopaminergic drugs varies with the state of sensitivity to dopamine (Palacios and Wiederhold, 1986). The mechanisms that underlie this shift in the dose–RCGU-response curve to SKF-38393 after 6-OHDA lesion remain to be determined. Our RCGU results complement the behavioral studies and further support a role for the D_1 receptor in mediating some of the effects of L-DOPA in rats with 6-OHDA lesions.

It has been suggested, on the basis of behavioral and lesion studies, that D_1 and D_2 agonists produce contralateral rotation in the 6-OHDA rat model by the selective activation of anatomically distinct striatal efferent pathways (Herrera-Marschitz and Ungerstedt, 1984a, b). Inherent in the interpretation of these studies is the assumption that the striatum is the sole site of dopamine receptor supersensitivity and dopaminergic drug action following 6-OHDA SN_c lesion. Our results suggest that, in addition to the striatum, the EP and SN_r may be major sites of action of those dopaminergic drugs capable of stimulating the D_1 receptor (e.g., apomorphine, L-DOPA). Our data do not directly confirm or refute the hypothesis proposed by Herrera-Marschitz and Ungerstedt (1984a, b), but they do suggest that these additional sites of drug action need to be incorporated into future models of the functional neuroanatomy of turning.

In this study, the parafascicular nucleus of the thalamus and the deep layers of the superior colliculus were the 2 brain regions where significant RCGU changes correlated exclusively with rotational behavior. The parafascicular nucleus receives afferents from the SN_r (Beckstead et al., 1979) and projects to the striatum (Jones and Leavitt, 1974); rats with unilateral lesions of the parafascicular nucleus turn ipsilaterally in response to apomorphine (Ahlenius et al., 1982). Our RCGU data support a role for the parafascicular nucleus, in conjunction with dopamine-dependent basal ganglia circuits, in turning behavior. Metabolic activity is also increased in the deep layers of the superior colliculus during turning induced by either D_1 or D_2 agonists. Similar RCGU changes have been described consequent to the use of systemic L-DOPA (Trugman and Wooten, 1986) and intrastriatal dopamine (Brown and Wolfson, 1983). Together, these RCGU studies further support a role of the deep layers of the superior colliculus in postural control (DiChiara et al., 1982).

The results of this study have potential clinical implications. Our results indicate that D_1 and D_2 dopamine agonists differentially alter glucose utilization in the EP and SN_r in rats with SN_c lesions. This assumes importance partly because these 2 regions serve as the major output nuclei of the basal ganglia (Graybiel and Ragsdale, 1979). Bromocriptine, a dopaminergic ergot used in combination with L-DOPA for advanced Parkinson's disease, is both a D_2 agonist and a D_1 antagonist (Markstein, 1981). Our results raise the possibility that the antagonist actions on D_1 receptors in the EP and SN_r may contribute to the therapeutic efficacy of bromocriptine in ameliorating L-DOPA-induced dyskinesias and motor fluctuations. The demonstration of the differential regulation of metabolic activity in the EP and SN_r by D_1 and D_2 agonists provides a rationale for the trial of dopamine receptor subtype-selective drugs in clinical disorders of the basal ganglia.

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