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Rapid Development of Dopaminergic Supersensitivity in Reserpine-treated Rats Demonstrated with ^{14}C-2-Deoxyglucose Autoradiography

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Dopaminergic denervation supersensitivity has been implicated in the pathogenesis of levodopa-induced dyskinesias, the most common and limiting side effect in the drug treatment of Parkinson's disease, yet the mechanisms that mediate altered drug sensitivity remain poorly understood. In animal models, one key component of denervation supersensitivity is the enhanced efficacy of selective D_1 agonists to stimulate locomotion. In rats with *chronic* dopamine depletion induced by 6-hydroxydopamine nigral lesion, the increased ability of D_1 agonists to stimulate regional cerebral glucose utilization (RCGU) in the substantia nigra pars reticulata (SNr) has provided a metabolic correlate to the heightened motor response. In this study, we used the stimulation of RCGU in the SNr as a sensitive *in vivo* assay of D_1 agonist effect to examine the time course of development of supersensitivity in rats following *acute* dopamine depletion with single doses of reserpine (5.0 mg/kg, i.p.) and α-methyl-*p*-tyrosine (AMPT; 100 mg/kg, i.p.). The stimulatory effect of the D_1 agonist SKF 38393 (30 mg/kg) on RCGU in the SNr was first enhanced 6 hr after reserpine/AMPT injection and was maximally enhanced at 12–24 hr (relative 2-deoxyglucose uptake increased 32–51%; $P < 0.05$). The response to SKF 38393 returned to control values 5 d after reserpine/AMPT injection. The single reserpine/AMPT injections depleted striatal dopamine to 1–2% of control values from 3–48 hr postinjection, whereas D_1 and D_2 dopamine receptor densities were unchanged at 24 hr. These results suggest that the heightened efficacy of D_1 agonists to stimulate RCGU, one index of dopaminergic denervation supersensitivity, correlates temporally with dopamine depletion but not with upregulation of dopamine receptor number. The development of supersensitive responses within 6–12 hr of dopamine depletion limits the potential mechanisms that mediate this phenomenon to processes that occur within this time frame. Extrapolation from these results suggests that intermittent dopamine depletion in patients with Parkinson's disease during the "off" state could result in enhanced functional sensitivity to subsequent agonist challenge and contribute to the disabling dyskinesias that often accompany the "on" state.

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Denervation supersensitivity refers to a state of enhanced responsiveness to a neurotransmitter after the surgical or pharmacological interruption of synaptic function. Dopaminergic denervation supersensitivity in the basal ganglia has been implicated in the pathogenesis of levodopa-induced dyskinesias, the most common and limiting side effect in the drug treatment of Parkinson's disease (Marsden et al., 1982; Agid et al., 1987). The mechanisms that mediate altered drug sensitivity in patients with Parkinson's disease remain poorly understood. In animal models of Parkinsonism, as in patients with Parkinson's disease, supersensitive motor responses have been observed following dopamine agonist administration. In rats with chronic dopamine depletion, the behavioral effects of D_1 and D_2 dopamine receptor stimulation change in two important ways as synthesized by Waddington and O'Boyle (1989): (1) D_1 agonists become full locomotor stimulants, in contrast to their minor motor stimulant effects in controls, and the response is blocked only by D_1, not D_2, antagonists; and 2) the motor effects of D_2 agonists are enhanced and are no longer blocked by D_1 antagonists. To summarize, in rats with chronic dopamine depletion, motor stimulation induced by both D_1 and D_2 agonists is enhanced (i.e., supersensitivity) and there is a loss of the normally present "cross-antagonism" (i.e., partial loss of D_1/D_2 functional linkage). These observations suggest that an improved understanding of denervation supersensitivity will require analysis of this complex shift in D_1/D_2 function.

The time course of the development of denervation supersensitivity may have important implications for its underlying mechanism. For example, if supersensitive drug responses develop within 24 hr of dopamine depletion, this would suggest that the physiological and biochemical changes that occur weeks to months following dopamine depletion, while perhaps of adaptive significance, are not of critical importance in determining drug sensitivity. Behavioral studies have suggested that the normally present "cross-antagonism" is lost within 24 hr of acute dopamine depletion. Breese and Mueller (1985) demonstrated that, in contrast to controls, the D_1 antagonist SCH 23390 no longer blocked locomotor stimulation induced by the D_2 agonist quinpirole in rats reserpinized 24 hr earlier. Studies of the time course of development of supersensitivity are less clear but have suggested that the motor-stimulating effects of D_1 agonists are enhanced 24–48 hr after reserpine injection (Arnt, 1985; Starr et al., 1987). While reserpine-induced monoamine depletion differs from selective dopaminergic cell loss, behavioral supersensitivity develops in a similarly rapid fashion (within 36–48 hr) after 6-hydroxydopamine (6-OHDA) nigral lesion (Neve et al., 1982). In this study, we use the stimulation of regional cerebral glucose utilization (RCGU) as a sensitive *in vivo* assay

of D_1 agonist effect (Trugman et al., 1989) to examine the time course of development of dopaminergic supersensitivity. The heightened efficacy of D_1 agonists to stimulate locomotion in dopamine-depleted animals has a regional metabolic correlate. In intact rats, D_1 agonists mildly increase RCGU in the substantia nigra pars reticulata (SNr; up 20%; Trugman et al., 1990). In contrast, in rats with chronic dopamine depletion induced by 6-OHDA lesion, D_1 agonists markedly increase RCGU in the SNr (up 100–200%; Trugman and Wooten, 1987). Therefore, D_1 agonist metabolic effects are enhanced in rats with *chronic* dopamine depletion, providing a quantitative measure of denervation supersensitivity. To determine the time course of development of enhanced D_1 agonist responses, we studied the effects of the D_1 agonist SKF 38393 on RCGU in rats following acute dopamine depletion with reserpine and α-methyl-*p*-tyrosine (AMPT). The primary aim of the experiments was to determine whether D_1 agonist–induced metabolic responses are enhanced within 24 hr of acute dopamine depletion. Once this was demonstrated, further experiments sought to identify the earliest time at which responses are enhanced, the time at which responses are maximally enhanced, and the time at which responses return to control levels following single doses of reserpine and AMPT. The experiments also sought to determine whether enhanced functional responses are accompanied by a change in dopamine receptor number and whether they correlate temporally with striatal dopamine depletion.

Materials and Methods

Animal preparation and drugs

All experiments were performed on male Sprague–Dawley rats weighing 250–300 gm. Central venous catheters were inserted under light halothane anesthesia the day before reserpine injection. The rats were fasted overnight prior to ^{14}C-2-deoxyglucose (2-DG) administration.

Reserpine (Sigma) was dissolved in 50 μl of glacial acetic acid and diluted with 10% propylene glycol; AMPT methyl ester HCl (Sigma) and (±)-SKF 38393 HCL (Research Biochemicals Inc., Natick, MA) were dissolved in water. Drugs were injected in a volume of 1.0–2.0 ml/kg body weight. Drug doses are expressed in terms of the weights of their salts.

Experimental design and data analysis

2-DG experiments. To determine whether D_1 agonist–induced RCGU effects are enhanced 24 hr after acute dopamine depletion, a dose–response study was performed. Rats were injected with reserpine (5.0 mg/kg, i.p., at time 0) and AMPT (100 mg/kg, i.p., at 23 hr) followed by SKF 38393 (1.0–30.0 mg/kg, i.v., at 24 hr). The controls were rats pretreated with vehicle followed by SKF 38393. The doses and timing of reserpine and AMPT injections were modified from a published protocol (Breese and Mueller, 1985) in which it was demonstrated that a similar drug treatment resulted in 98% depletion of striatal dopamine at 24 hr. To identify the earliest time at which RCGU effects are enhanced and the time of maximal enhancement, SKF 38393 (30 mg/kg, i.v.) was administered 3, 6, 12, 24, and 48 hr after reserpine (5.0 mg/kg, i.p.) injection. For these time points, AMPT (100 mg/kg, i.p.) was administered 1 hr prior to SKF 38393 injection. To determine the time at which D_1 agonist–induced metabolic responses return to control values after acute dopamine depletion, rats were injected with SKF 38393 (30 mg/kg, i.v.) 5, 10, and 25 d after injection of reserpine (5.0 mg/kg, i.p.) and AMPT (100 mg/kg, i.p., given 2 hr after reserpine).

For each of these protocols, rats were injected intravenously with ^{14}C-2-DG (8 μCi/100 gm body weight in 0.3–0.4 ml saline; 55 mCi/mM; American Radiolabeled Chemicals Inc., St. Louis, MO) 2 min after SKF 38393 administration. Unrestrained rats were studied in 23 × 35 cm cages. The rats were killed with a 50 mg/ml intravenous bolus of sodium pentobarbital 45 min after the ^{14}C-2-DG injection. The brains were rapidly removed and frozen in liquid Freon. Duplicate 20 μm coronal sections were taken every 100 μm, thaw mounted on coverslips, dried on a 40°C warming tray, and exposed to Kodak SB-5 x-ray film for 5 d. Film autoradiographs were analyzed with a Leitz variable aperture microdensitometer.

Data for glucose utilization were expressed as a ratio of gray matter to corpus callosum optical densities (relative 2-DG uptake; Mitchell and Crossman, 1984). Relative 2-DG uptake is linearly related to calculated rates of glucose utilization expressed as μmol/100 gm/min and accurately reflects changes induced by pharmacological and physiological stimuli (Sharp et al., 1983; Geary and Wooten, 1987). The data are summarized as mean ± SD and represent four to eight optical density measurements per brain region per animal, with four to eight rats per treatment group. The dose–response data were analyzed using a least-squares means analysis following a significant full two-way analysis of variance. The time course data were analyzed using a one-way analysis of variance followed by the Tukey studentized range test. We considered differences significant at $P < 0.05$.

Receptor autoradiography. Rats were injected with reserpine (5.0 mg/kg, i.p., at time 0) and AMPT (100 mg/kg, i.p., at 23 hr) and killed by decapitation at 24 hr. The brains were processed for quantitative *in vitro* receptor autoradiography as described (Trugman et al., 1986). Tissue sections were incubated with saturating concentrations of the D_1 antagonist ^{3}H-SCH 23390 (2 nM, 87 Ci/mmol; New England Nuclear) or the D_2 antagonist ^{3}H-raclopride (6 nM, 63 Ci/mmol; New England Nuclear); nonspecific binding was defined in the presence of 2 μM (+)-butaclamol. The mean values of ligand bound (measured B_{max}) for the reserpine- and vehicle-treated groups were compared using an independent *t* test.

Measurement of striatal dopamine concentration. Rats were injected with reserpine and AMPT according to the protocols described above and killed from 3 hr to 25 d following injection. Striata were dissected and tissue dopamine concentrations were measured using HPLC with electrochemical detection (Broaddus and Bennett, 1990).

Results

The stimulatory effects of SKF 38393 on RCGU in the SNr were enhanced 24 hr after reserpine/AMPT injection (Fig. 1). Relative 2-DG uptake in the SNr in response to SKF 38393 (10 and 30 mg/kg) was higher in reserpine/AMPT-treated rats than in controls [10 mg/kg: 2.78 ± 0.15 (±SD) vs 2.48 ± 0.07, $P = 0.005$; 30 mg/kg: 3.29 ± 0.24 vs 2.49 ± 0.24, $P = 0.0001$]. Relative 2-DG uptake in the striatum in response to SKF 38393 was not higher in reserpine/AMPT-treated rats than in controls (30 mg/kg: 3.27 ± 0.27 vs 3.44 ± 0.35, $P = 0.36$).

The stimulatory effects of SKF 38393 (30 mg/kg) on RCGU in the SNr were first enhanced 6 hr after reserpine/AMPT injection and were maximally enhanced at 12–24 hr (relative 2-DG uptake increased 32–51%; Figs. 2, 3). Five days after reserpine/AMPT injection, the response to SKF 38393 did not differ significantly from control values. The reserpine/AMPT injections resulted in a profound depletion of striatal dopamine that was of rapid onset and long duration. Striatal dopamine was reduced to 1–2% of control value [control, 48 ± 5 (±SD) pmol/mg tissue] from 3–48 hr postreserpine and recovered to 13%, 25%, and 31% of control values at 5, 10, and 25 d, respectively. Twenty-four hours after reserpine/AMPT injection, D_1 and D_2 dopamine receptor densities in the striatum and SNr did not differ from control values (Fig. 4).

Behavioral responses to drug administration were observed but not quantified. Rats injected with reserpine (5.0 mg/kg, i.p.) became cataleptic within 60–90 min, demonstrating akinesia and ptosis. Twenty-four hours after reserpine/AMPT, SKF 38393 (10 and 30 mg/kg) dramatically reversed the catalepsy within 60 sec of intravenous administration; the rats opened their eyes, became mobile, and demonstrated facial and body grooming, sniffing, and chewing. Catalepsy was similarly reversed when SKF 38393 was administered at the 6 and 12 hr time points. When SKF 38393 was injected 3 hr after reserpine/AMPT, the animals aroused for approximately 15–20 min and then returned to an akinetic state.

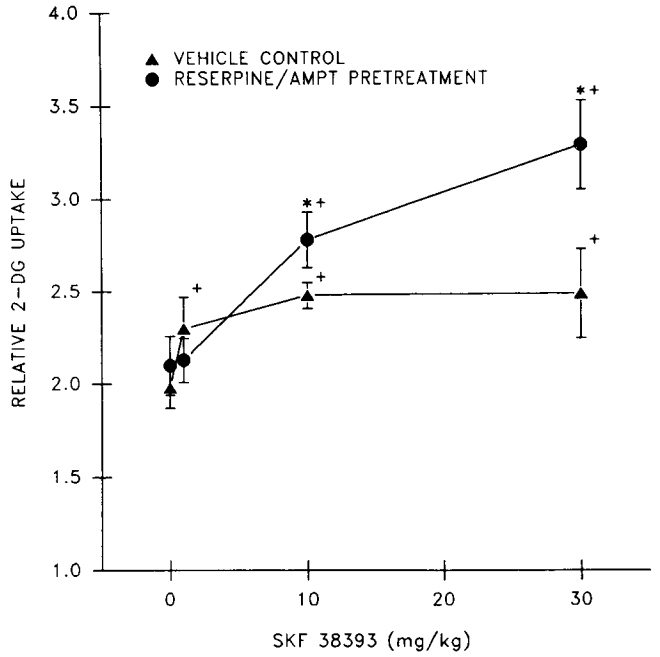

Figure 1. Dose–response analysis of D_1 agonist–induced metabolic effects in the SNr 24 hr after reserpine/AMPT injection. Relative 2-DG uptake in response to SKF 38393 (10 and 30 mg/kg) was higher in reserpine/AMPT-treated rats (*circles*) than in controls (*triangles*). Values are means ± SD for four to eight rats per treatment group. The *asterisks* indicate a difference ($P < 0.05$) from the vehicle control group treated with the same dose of SKF 38393. The *pluses* indicate a difference from rats that received the same pretreatment (reserpine/AMPT or vehicle) followed by SKF 38393 vehicle (SKF 38393, 0 mg/kg).

Discussion

This study demonstrates that D_1 agonist–induced metabolic responses are enhanced within 24 hr of acute dopamine depletion in rats. Twenty-four hours after reserpine/AMPT injection, the dose–RCGU response curve for the D_1 agonist SKF 38393 is shifted to the left with an increase in maximal response, fulfilling the criteria for denervation supersensitivity (Fig. 1; Fleming and Trendelenburg, 1961). The metabolic effects are first enhanced 6 hr after reserpine/AMPT injection, are maximally enhanced at 12–24 hr, and return to control values by 5 d. The reserpine/AMPT combination profoundly depleted striatal dopamine from 3–48 hr postinjection, whereas D_1 and D_2 dopamine receptor densities were unchanged at 24 hr. These results suggest that the heightened efficacy of D_1 agonists to stimulate RCGU, one index of dopaminergic denervation supersensitivity, correlates temporally with dopamine depletion and not with upregulation of dopamine receptor number.

The novel finding in this study is that D_1 agonist–induced metabolic responses are enhanced within 6 hr of dopamine depletion. We have confidence in this result because RCGU increases have been shown to provide a sensitive and valid measure of D_1 agonist effect and because the result is consistent with prior behavioral studies. In rats with chronic dopamine depletion, D_1 agonists dose-dependently increase RCGU in the SNr and the response is blocked by D_1 antagonists (Trugman and Wooten, 1987; Trugman et al., 1989). The recent demonstration that striatonigral neurons selectively express D_1 receptors (Gerfen et al., 1990; Harrison et al., 1990; Le Moine et al., 1991), along with the recognition that RCGU reflects primarily activity in nerve terminals (Kadekaro et al., 1985), supports the interpretation that RCGU increases in the SNr reflect a direct stimulation of striatonigral neurons. The rapid development of dopaminergic denervation supersensitivity has been demonstrated previously using behavioral measures of drug effect. Costall and Naylor (1973) showed that the intensity and duration of apomorphine-induced stereotyped behavior are enhanced within 6 hr of reserpine injection; similarly, locomotor activity induced by D_1 agonists is potentiated 24–48 hr after reserpine injection (Arnt, 1985; Starr et al., 1987). By suggesting that D_1 receptor stimulation results in increased rates of glucose utilization with-

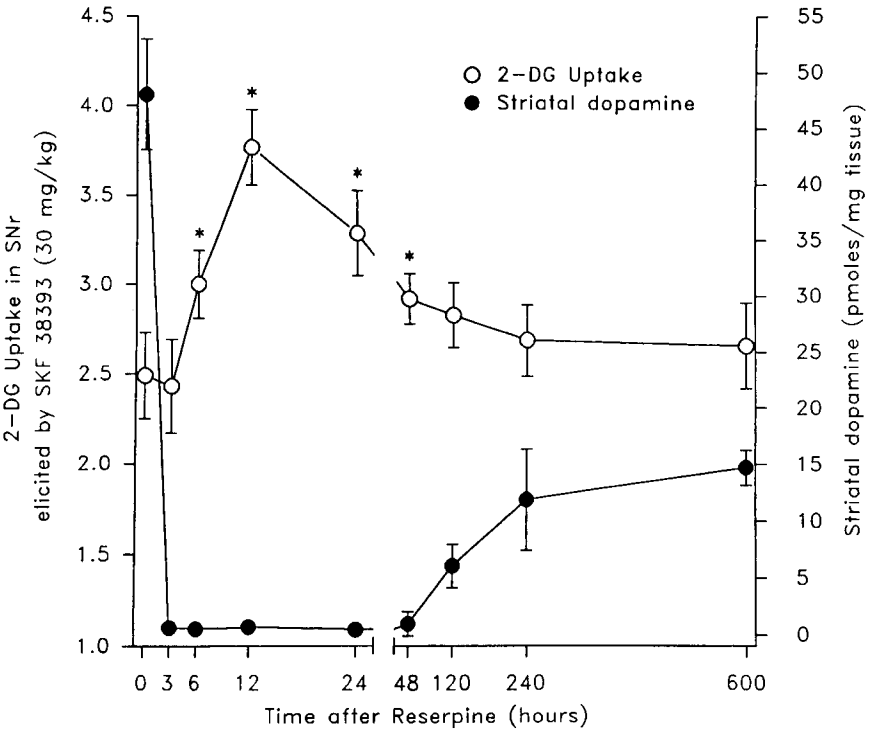

Figure 2. The metabolic response to SKF 38393 (30 mg/kg) in the SNr and striatal dopamine concentration as a function of time after reserpine/AMPT injection. Values are means ± SD for four to eight rats per treatment group. The *asterisks* indicate a difference ($P < 0.05$) from non-reserpine-treated rats injected with SKF 38393 (30 mg/kg, time 0). The error bars (SD) for dopamine concentrations at 3–24 hr are less than the size of the data point.

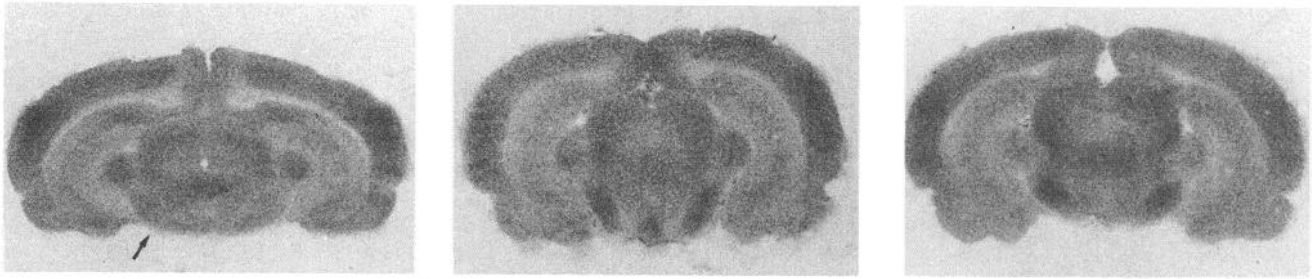

Figure 3. ^{14}C-2-DG autoradiographs through the midbrain at the level of the SNr (*arrow*) illustrating glucose utilization in response to SKF 38393 (30 mg/kg) injection. Increased uptake of ^{14}C-2-DG in the SNr is observed in rats treated with reserpine/AMPT 6 or 12 hr earlier in comparison to naive rats.

in striatonigral neurons within 6 hr of dopamine depletion, the present study adds functional and anatomical specificity to prior behavioral work.

The demonstration of enhanced metabolic responses to D_1 stimulation within 6 hr of dopamine depletion has important implications for the mechanism of denervation supersensitivity. Altered neurotransmitter function, including changes in peptide (Young et al., 1986), synthetic enzyme (Vernier et al., 1988), and dopamine receptor (Gerfen et al., 1990) mRNA levels, has been extensively documented in animals with chronic dopamine depletion. One question is whether these changes are primarily adaptive responses to dopamine loss or whether they are of critical importance in the regulation of sensitivity to dopamine receptor stimulation. Clearly, changes that evolve over weeks to months do not mediate the enhanced effects of D_1 receptor stimulation observed within 6–12 hr of dopamine depletion.

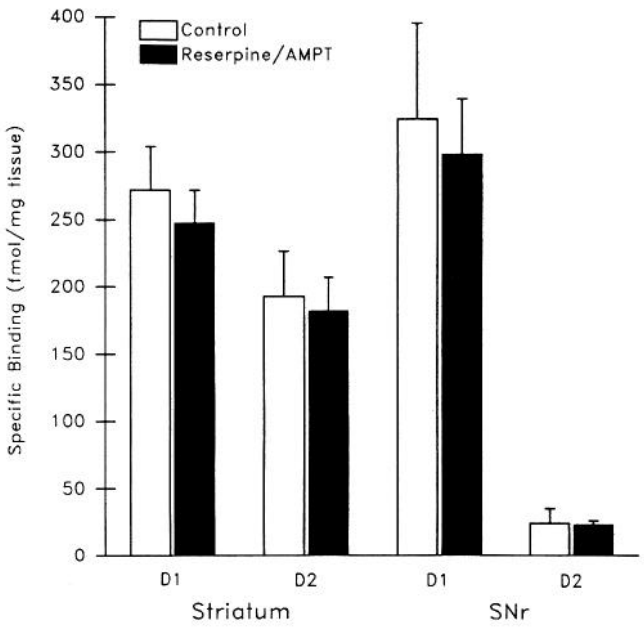

Figure 4. Effect of reserpine/AMPT treatment on D_1 and D_2 receptor densities. Binding values of ^{3}H-SCH 23390 (D_1 antagonist, 2 nM) and ^{3}H-raclopride (D_2 antagonist, 6 nM) represent means ± SD for three or four rats per treatment group. Binding did not differ in rats injected with reserpine/AMPT 24 hr previously compared to vehicle-injected controls (P values ranged from 0.38 to 0.64).

The present study underscores the need to search for biochemical and physiological changes that correlate temporally with altered functional drug response.

The results suggest a complex relationship between enhanced functional responses to D_1 stimulation and the extent and duration of striatal dopamine depletion. The fact that metabolic responses are first enhanced 6 hr after reserpine injection, yet striatal dopamine is markedly depleted by 3 hr, suggests that the processes that mediate the altered functional response require approximately 4–6 hr to develop. The response peak at 12–24 hr suggests that duration of dopamine depletion is a determinant factor in the drug response, but the attenuated response at 48 hr (when dopamine levels are still profoundly depleted), compared to 12–24 hr, argues against a tight correlation between enhanced metabolic responses and the duration of dopamine depletion. Perhaps a clearer relationship would emerge if RCGU responses were correlated with extracellular levels of dopamine measured *in vivo* using microdialysis. The normalization of the D_1 agonist response at the 5 d time point, when striatal dopamine was 13% of control level, suggests that this modest degree of recovery of dopaminergic function is sufficient to restore normosensitivity to D_1 stimulation.

We found that D_1 and D_2 dopamine receptor number were unchanged 24 hr after reserpine injection, suggesting that increases in receptor density do not account for enhanced sensitivity to dopamine agonists in states of dopamine depletion. The results support the findings of Breese et al. (1987), who found no change in the binding characteristics of D_1 and D_2 antagonist ligands in 6-OHDA–lesioned rats with documented behavioral supersensitivity to D_1 and D_2 agonists. Small decrements (approximately 10–20%) in striatal D_1 receptor density (Marshall et al., 1989) and mRNA levels (Gerfen et al., 1990) have been reported in rats with long-term dopamine depletion, but it remains unclear how these changes could mediate enhanced functional responses to D_1 stimulation. Alternative hypotheses of denervation supersensitivity are needed.

The data presented here suggest a model of denervation supersensitivity based on neuronal interaction in the striatum. GABA-utilizing medium spiny neurons constitute >90% of intrinsic striatal neurons, are the major target of dopamine input, and are the primary striatal projecting neurons (Smith and Bolam, 1990). Evidence suggests that the majority of striatonigral neurons express the D_1 receptor (Gerfen et al., 1990) and the majority of striatopallidal neurons express the D_2 receptor (Le Moine et al., 1991); the percentage of striatal cells that express

both D_1 and D_2 receptors is not known. We propose that neurons expressing D_1 receptors and neurons expressing D_2 receptors are functionally linked, or coupled, through the actions of dopamine. The anatomic basis for this linkage may be a dual innervation by midbrain dopamine neurons, local axon collaterals, or interneurons. The rapid shift in drug sensitivity following reserpine/AMPT treatment suggests that dopamine depletion, per se, results in the breakdown of this functional linkage, in supersensitive responses to D_1 and D_2 stimulation, and in the loss of "cross-antagonism" demonstrable in behavioral studies. The mechanisms by which dopamine may couple distinct populations of striatal output neurons remain to be elucidated.

The demonstration of supersensitive metabolic responses to D_1 stimulation within 6 hr of dopamine depletion may have implications for the pathogenesis and treatment of clinical fluctuations in Parkinson's disease. Many patients with advanced Parkinson's disease cycle from mobility ("on") to immobility ("off"), with states in between, every 2–3 hr throughout the day, and it is likely that these cycles are associated with extremely high and low striatal dopamine concentrations alternating over the course of hours. Therefore, these patients likely experience acute intermittent dopamine depletion daily. Extrapolation from the results presented here suggests that this intermittent dopamine depletion could result in enhanced functional sensitivity to subsequent agonist challenge and perhaps contribute to the disabling dyskinesias that often accompany the "on" state. One corollary of the present hypothesis is that *continuous* replacement with dopamine, or concomitant D_1 and D_2 stimulation, should restore functional linkage and normosensitivity to a dopamine-denervated system and ameliorate the severity of levodopa-induced dyskinesias while maintaining near-normal patient mobility. Experimental (Winkler and Weiss, 1989) and clinical (Mouradian et al., 1990) observations support this possibility.

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