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Nigrostriatal dopaminergic denervation enhances dopamine D_4 receptor binding in rat caudate–putamen

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Abstract

Radioligand binding to dopamine (DA) D_4 receptors was examined in adult rat forebrain 5 weeks after unilateral 6-hydroxydopamine (6-OHDA) lesioning of substantia nigra to remove ascending nigrostriatal dopaminergic projections. D_4 receptor binding was increased by up to 47% in denervated caudate–putamen (CPu) in rats that rotated away from the lesioned side with apomorphine challenge, with lesser changes in rats that failed to rotate with apomorphine. Functional significance of D_4 receptor upregulation induced by the lesions was investigated by examining behavioral effects of the highly selective D_4 agonist CP-226,269 and antagonist CP-293,019. Neither agent induced rotation at doses as high as 30 mg/kg ip. Pretreatment with the D_4 antagonist CP-293,019 did not affect rotation induced by either a D_1-like (SKF-38393) or D_2-like receptor (quinpirole) agonist. These findings provide the first evidence that D_4 receptors can be upregulated by nigrostriatal dopaminergic denervation. They also suggest that, unlike D_1 and D_2 receptors, D_4 receptors do not play a pivotal role in rotational behavior in rats with unilateral dopaminergic lesions.

Keywords: Apomorphine; Autoradiography; Dopamine; D_2; D_4; 6-Hydroxydopamine; Receptors; Rotational behavior

1. Introduction

Dopamine (DA) D_2-like receptor family includes three subtypes (D_2, D_3 and D_4) that share extensive similarities in molecular structure, signaling pathway and pharmacology (Bunzow et al., 1998; Sokoloff et al., 1990; Tarazi and Baldessarini, 1999a,b). Regulation of D_2 receptors is best characterized (Seeman, 1981). Prolonged treatment of rats with drugs that block D_2 receptors, or removal of nigrostriatal DA projections with 6-hydroxydopamine (6-OHDA) results in upregulation and supersensitivity of D_2 receptors in caudate–putamen (CPu) (Creese et al., 1977; Florijn et al., 1997; Heikkila et al., 1981; Lisovoski et al., 1992; Qin et al., 1994; Tarazi et al., 1997a,c). Plasticity of D_2 receptors presumably reflects pharmacodynamic effects of DA receptor antagonists (Neve and Neve, 1997; Seeman, 1981) and may contribute to their typical neurological side effects (Baldessarini and Tarsy, 1979).

Regulation of D_3 receptors differs from that of D_2 receptors (Levant, 1997). In contrast to upregulation of D_2 receptors, DA denervation with 6-OHDA produces substantial losses of D_3 receptors (Levesque et al., 1995). Repeated treatment with antipsychotic agents has generated inconsistent results, with either increases or no change in D_3 receptor levels (Buckland et al., 1993; Fishburn et al., 1994; Levèsque et al., 1995; Tarazi et al., 1997a; Wang et al., 1996).

D_4 receptor levels can be increased by repeated administration of various types of antipsychotic agents, including atypical antipsychotics, such as clozapine, that somewhat preferentially block D_4 receptors (Florijn et al., 1997; Schoots et al., 1995; Tarazi et al., 1997a,c). Repeated treatment with stimulant drugs that release endogenous catecholamines, however, fails to alter D_4 receptors (Zhang et al., 2000), suggesting that D_4 receptors are more responsive to deprivation than to excesses of DA. Recently, we reported that D_4 receptors in CPu were not changed 1 week after 6-OHDA lesions of the rat nigrostriatal pathway, suggesting that presynaptic receptors on DA terminals (if existing at all) do not constitute a major proportion of D_4 receptors in this brain region (Tarazi et al., 1998). How-

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ever, upregulation of postsynaptic receptors requires synthesis of new receptors, and therefore might take longer to become evident.

Accordingly, we assessed D_4 receptor concentrations in rat forebrain 5 weeks after 6-OHDA lesions of the nigrostriatal DA pathway to further test the hypothesis that D_4 receptors can be upregulated in response to reduced availability of endogenous DA. Effects of 6-OHDA lesions on radioligand binding to D_1-like (D_1/D_5) and D_2-like (D_2/D_3/D_4) receptors were also examined for comparison with responses of D_4 receptors. A unique behavioral consequence of unilateral 6-OHDA lesions of the nigrostriatal DA pathway is contralateral rotation upon challenge with direct DA agonists (Creese at al., 1977; Heikkila et al., 1981; Ungerstedt and Arbuthnott, 1970). Agents used to induce rotation in these studies, such as apomorphine and quinpirole, however, are also active at D_4 receptors (Van Tol et al., 1991), raising the possibility that D_4 receptors might also be implicated in rotational behavior. Novel D_4 receptor-selective agonist CP-226,269 and antagonist CP-293,019 were used in the present study to evaluate involvement of this particular receptor subtype.

2. Materials and methods

2.1. Radioligands and chemicals

[^{3}H]Nemonapride (85.5 Ci/mmol), [^{3}H]*R*-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT; 87 Ci/mmol) and [^{3}H]SCH-23390 (81.4 Ci/mmol) were from New England Nuclear (NEN; Boston, MA). Tritium-sensitive Hyperfilm and tritium autoradiography standards were from Amersham (Arlington Heights, IL). D-19 developer and fixative were from Eastman-Kodak (Rochester, NY). *R*(−)-apomorphine hydrochloride, 1,3-ditolylguanidine (DTG), *cis*-flupenthixol dihydrochloride, 6-OHDA hydrobromide, ketanserin tartrate, *S*(−)-pindolol, *S*(−)-raclopride tartrate, *R*(+)-SKF-38393 hydrochloride and *S*(−)-sulpiride were from Sigma-Research Biochemicals International (Sigma-RBI; Natick, MA). Quinpirole dihydrochloride was generously donated by Eli Lilly Laboratories (Indianapolis, IN), as were CP-226,269 and CP-293,019 by Pfizer Research Laboratories (Groton, CT). All other drugs and chemicals were purchased from Fisher Scientific (Dallas, TX) or Sigma Chemicals (St. Louis, MO).

2.2. Unilateral 6-OHDA lesions

Animal procedures were approved by the McLean Hospital Institutional Animal Care and Use Committee, in compliance with federal and state regulations. Adult male Sprague–Dawley rats (Charles River, Wilmington, MA) initially weighing 220–250 g were maintained individually under a 12-h artificial light/dark schedule (on, 0700–1900 h) with free access to standard rat chow and tap water. Rats were pretreated with the monoamine oxidase inhibitor pargyline hydrochloride (30 mg/kg ip) 60 min prior to microinfusion of 6-OHDA under anesthesia with sodium pentobarbital (60 mg/kg ip). 6-OHDA (20 μg free base in 2 μl of 0.9% saline containing 1 mM ascorbic acid) was injected to substantia nigra compacta over 2 min (additional 5 min allowed for equilibrium) using the following coordinates: A–P = −5.8, D–V = 8.0, L = 2.0 mm, with incisor bar set at 3.0 mm below zero (Paxinos and Watson, 1998). Rats were allowed 5 weeks to recover from the surgery before sacrifice or behavioral testing.

2.3. Behavioral testing

Rotational behavior was monitored visually in a clear Plexiglas hemispherical chamber (21 cm radius) by an experienced observer between 1000 and 1600 h. Five weeks after the lesions, some rats were screened for rotational behavior with apomorphine challenge (0.5 mg/kg). Rats displaying contralateral rotations were used to further test other agents in a randomized sequence. All test agents were given intraperitoneally in a vehicle of 0.9% saline or 30% 2-hydroxypropyl-β-cyclodextrin, in sessions separated by at least 72 h. The number of complete (360°) rotations was accumulated for 30 min (5–35 min after injection, except 20–50 min with SKF-38393 to compensate for its slower onset of activity). Rats were decapitated 72 h after the last testing session.

2.4. DA transporter and receptor autoradiography

After decapitation, rat brain was quickly removed and frozen in β-methylbutane on dry ice. Coronal sections (10 μm) were prepared in a cryostat at −17°C, thaw-mounted on gelatin-coated microscopic slides and stored at −80°C until quantitative autoradiographic assays. Lesions were verified by quantifying DA transporter using [^{3}H]β-CIT, as detailed previously (Kula et al., 1999a). Briefly, after 60-min preincubation in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl and 4 mM $MgCl_2$, brain sections were incubated at room temperature for another 60 min in fresh buffer containing 2 nM [^{3}H]β-CIT. Non-specific binding was determined using excess GBR-12909 (1 μM). D_1-like, D_2-like and D_4 receptors were assayed in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ (Tarazi et al., 1997a,b,c, 1998).

D_1-like receptors were assayed with 1 nM [^{3}H]SCH-23390 plus 40 nM ketanserin to mask serotonin 5-$HT_{2A/2C}$ sites. Non-specific binding was determined by 1 μM *cis*-flupenthixol.

D_2-like (D_2/D_3/D_4) binding was assayed with 1 nM [^{3}H]nemonapride in the presence of 0.5 μM 1,3-ditolylguanidine and 0.1 μM pindolol to block σ and 5-HT_{1A} sites. Non-specific binding was determined with 10 μM *S*(−)-sulpiride.

D_4 receptors were assayed with 1 nM [^{3}H]nemonapride with 300 nM *S*(−)-raclopride to occupy D_2/D_3 sites, and other masking agents (0.5 μM DTG and 0.1 μM pindolol) used in D_2-like receptor assay. Non-specific binding was determined with 10 μM *S*(−)-sulpiride.

After 1-h incubation, sections were washed twice for 5 min in ice-cold buffer, rinsed in deionized water and air-dried. Dried sections were exposed to Hyperfilm-[^{3}H] for 2 weeks at 4°C. Radioligand binding was quantified with a computerized image analyzer (Image Research, St. Catherines, Ontario) and converted to nanoCuries per milligram tissue using [^{3}H] reference standards, with specific binding expressed in femtomoles per milligram tissue.

2.5. Statistical analysis

Data were analyzed by ANOVA with post-hoc Dunnett's *t* test at defined degree of freedom and reported as means ± S.E.M.

3. Results

3.1. Effects of 6-OHDA lesions on DA transporter and receptor binding

Initial experiments were conducted in eight rats that were sacrificed 5 weeks after the lesions without behavioral testing to avoid potential influence by exposure to drugs that alter DA neurotransmission. 6-OHDA lesions produced >90% losses of DA transporter labeled with [^{3}H]β-CIT in ipsilateral CPu, in comparison to the intact side (Table 1). DA transporter binding was also reduced in ipsilateral nucleus accumbens septi (NAc) by 44.9%, apparently due to diffusion of 6-OHDA from the primary target substantia nigra to the adjacent ventral tegmental area.

D_4 receptor binding was increased by 63.7% and 62.5% in lateral and medial CPu, respectively, in comparison to the intact side (Table 2). D_2-like receptor binding was increased by 47.8% and 49.5% in lateral and medial CPu, respectively. Neither D_4 nor D_2-like receptors in NAc were affected by the lesions. D_1-like receptors in CPu and NAc were not affected (data not shown).

Another 12 rats with unilateral 6-OHDA lesions were used for behavioral testing. Five weeks after lesioning, the rats were challenged with the mixed D_1/D_2 agonist apomorphine (0.5 mg/kg). Seven of 12 rats displayed robust contralateral rotation (rotators); the remaining five did not rotate or show noticeable postural bias (non-rotators). Losses of DA transporter binding in denervated CPu tended to be greater in rotators than in non-rotators (95.0% and 91.8% vs. 89.2% and 84.9%, in lateral and medial CPu, respectively; Table 1), although the differences were not statistically significant. DA transporter binding was also reduced moderately in NAc (by 49.1% in rotators vs. 34.0% in non-rotators).

In rotators, D_4 receptor binding in CPu was significantly higher on the lesioned side than the intact side (47.1% and 34.1% in lateral and medial parts, respectively; Table 2). Effects of the lesions on D_4 receptors in non-rotators were considerably smaller in magnitude and confined to lateral CPu (22.3% vs. 47.1% in rotators; $P<.01$). D_4 receptor levels in NAc were not significantly altered in either rotators or non-rotators. D_4 receptor binding in the intact side did not differ between rats that rotated upon apomorphine challenge and lesioned rats that were never exposed to DA agonists. However, the magnitude of D_4 receptor binding increase in denervated CPu was significantly smaller in rotators that received DA agonists during the behavioral testing than in rats that were never exposed to DA agonists (47.1 ± 3.5% vs. 63.7 ± 3.0% in lateral CPu, $P<.05$; 34.1 ± 4.1% vs. 62.5 ± 3.1% in medial CPu, $P<.01$).

In rotators, D_2-like receptor binding in CPu was also significantly higher on the lesioned side than the intact side (40.9% and 33.2% in lateral and medial parts, respectively), with only a statistically non-significant increase in non-rotators. D_2-like receptor binding in NAc was not affected in any group. Similar to D_4 receptors, the increase in D_2-like

Table 1
Dopamine transporter binding in rat forebrain after unilateral 6-OHDA lesions

	CPu/lateral	CPu/medial	Nucleus accumbens
Naive rats			
Contralateral	192.3 ± 10.5	156.0 ± 7.3	66.3 ± 6.4
Ipsilateral	15.4 ± 2.8 **(92.0%)** **	18.7 ± 3.4 **(88.0%)** **	36.5 ± 5.1 **(44.9%)** **
Rotators			
Contralateral	178.8 ± 7.0	148.4 ± 5.8	60.5 ± 5.1
Ipsilateral	8.9 ± 1.6 **(95.0%)** **	12.2 ± 2.5 **(91.8%)** **	30.8 ± 4.5 **(49.1%)** **
Non-rotators			
Contralateral	181.5 ± 12.5	149.3 ± 12.7	62.4 ± 7.9
Ipsilateral	19.6 ± 8.9 **(89.2%)** **	22.6 ± 10.1 **(84.9%)** **	41.2 ± 6.6 **(34.0%)** *

Data are specific binding of [^{3}H]β-CIT (fmol/mg tissue) in mean ± S.E.M.
Numbers in parentheses indicate percent losses of transporter binding on the lesioned side.
* $P<.05$ by post-hoc Dunnett's *t* test after ANOVA.
** $P<.01$ by post-hoc Dunnett's *t* test after ANOVA.

Table 2
Dopamine receptor binding in rat forebrain after unilateral 6-OHDA lesions

	CPu/lateral	CPu/medial	Nucleus accumbens
D_2-like receptors			
Naive rats			
Contralateral	250.5 ± 9.2	188.3 ± 8.0	160.2 ± 5.5
Ipsilateral	370.3 ± 11.7 **(+47.8%)** **	281.6 ± 10.4 **(+49.5%)** **	155.2 ± 6.3 **(−3.1%)**
Rotators			
Contralateral	237.9 ± 6.9	178.5 ± 7.4	141.2 ± 6.2
Ipsilateral	334.3 ± 5.2 **(+40.9%)** **	237.7 ± 9.1 **(+33.2%)** **	130.0 ± 5.4 **(−7.8%)**
Non-rotators			
Contralateral	233.5 ± 12.0	171.1 ± 8.4	154.7 ± 6.1
Ipsilateral	272.6 ± 11.6 **(+16.7%)**	188.0 ± 15.2 **(+9.9%)**	144.3 ± 8.5 **(−6.5%)**
D_4 receptors			
Naive rats			
Contralateral	44.1 ± 3.0	33.6 ± 1.7	32.8 ± 2.4
Ipsilateral	72.2 ± 4.9 **(+63.7%)** **	54.6 ± 4.0 **(+62.5%)** **	30.6 ± 3.1 **(−6.7%)**
Rotators			
Contralateral	41.4 ± 2.2	31.4 ± 1.3	25.7 ± 2.1
Ipsilateral	60.9 ± 2.9 **(+47.1%)** **	42.1 ± 2.6 **(+34.1%)** **	23.3 ± 1.6 **(−9.3%)**
Non-rotators			
Contralateral	38.6 ± 2.4	29.8 ± 1.9	30.6 ± 2.6
Ipsilateral	47.2 ± 2.7 **(+22.3%)** *	33.0 ± 2.4 **(+10.7%)**	29.6 ± 3.7 **(−3.3%)**

Data are specific binding of [^{3}H]nemonapride (fmol/mg tissue) in mean ± S.E.M.
Numbers in parentheses indicate percent change of receptor binding in comparison to the intact side.
* $P < .05$ by post-hoc Dunnett's t test after ANOVA.
** $P < .01$ by post-hoc Dunnett's t test after ANOVA

receptor binding in rotators was significantly less than in rats never exposed to a DA agonist (40.9 ± 4.7% vs. 47.8 ± 4.4% in lateral CPu, $P > .05$; 33.2 ± 2.6% vs. 49.5 ± 4.1% in medial CPu; $P < .01$).

3.2. Effects of D_4 ligands on rotational behaviors

Rats that rotated with apomorphine challenge also displayed robust contralateral rotation in response to the D_1-like receptor agonist SKF-38393 and the D_2-like agonist quinpirole (Table 3). Neither the D_4 selective agonist CP-226,269 nor the D_4 antagonist CP-293,019 induced rotation at doses of 10 and 30 mg/kg. Moreover, pretreatment with 30 mg/kg D_4 antagonist CP-293,019 did not alter rotational responses to SKF-38393 (1.0 mg/kg) or quinpirole (0.3 mg/kg) given 30 min later.

Table 3
Rotation induced by dopamine receptor agents in rats with unilateral 6-OHDA lesions

Test agents (mg/kg)	Rotations/30 min ± S.E.M.
Apomorphine (0.5)	188 ± 47
SKF-33893 (1.0)	272 ± 61
Quinpirole (0.3)	203 ± 33
CP-226,269 (10 and 30)	inactive
CP-293,019 (10 and 30)	inactive
CP-293,019 (30) + SKF-38393 (1.0)	253 ± 50[a]
CP-293,019 (30) + Quinpirole (0.3)	216 ± 29[a]

Complete contralateral rotations were counted for 30 min following intraperitoneal injection of test agents ($n = 7$ rats/condition).
[a] Responses to SKF-38393 or quinpirole after D_4 antagonist CP-293,019 pretreatment did not differ significantly from those with SKF-38393 or quinpirole alone.

4. Discussion

Unilateral 6-OHDA lesions of the rat nigrostriatal DA pathway significantly increased D_4 receptor binding in the ipsilateral CPu. In view of previous studies on the upregulation of D_4 receptors after prolonged antipsychotic treatment (Florijn et al., 1997; Schoots et al., 1995; Tarazi et al.,1997a,c), these results indicate that D_4 receptors can be upregulated by at least two conditions that decrease availability of endogenous DA. Also in accord with previous studies (Creese et al., 1977; Heikkila et al., 1981; Qin et al., 1994), the lesions resulted in moderate increase in D_2-like receptor binding in denervated CPu.

The magnitude of both D_4 and D_2-like receptors increases was significantly smaller in rats exposed to apomorphine and other DA agonists prior to sacrifice than otherwise untreated lesioned rats. These differences were not due to differences in the lesion extent, as assessed by assays of DA transporter density. Considering that only rotators were included in the comparison to untreated lesioned rats, the actual effect of exposure to DA agonists on upregulation of D_4 receptors might be even larger than what was observed. These findings suggest that D_4 receptor

upregulation is more sensitive to DA agonist exposure than the steady level of D_4 receptors.

The extent of D_2-like and D_4 receptor increases in CPu was significantly greater in rotators than in non-rotators, suggesting that rotational behavior provoked by DA agonists is dependent on the degree of upregulation of D_2-like receptors, and perhaps also D_4 receptors. To further investigate the potential functional role of upregulated D_4 receptors, we examined the behavioral effects of the highly D_4 selective agonist CP-226,269 and antagonist CP-293,019 on rotational behavior in these rats. Both compounds exhibit >1000-fold selectivity for D_4 than D_2 receptors (Kebabian et al., 1997; Kula et al., 1999b; Sanner, 1998; Tarazi and Baldessarini, 1999b) and have negligible affinity for non-dopaminergic receptors. When given alone, neither drug induced rotation or postural deviation at parenteral doses as high as 30 mg/kg. In addition, pretreatment with the D_4 antagonist CP-293,019 failed to alter rotational responses to either SKF-38393, which is active at D_1 sites, or quinpirole, which is active at both D_2 and D_4 receptors (Van Tol et al., 1991).

The absence of behavioral effects of D_4 receptor selective ligands in spite of increased radioligand binding in denervated CPu raises the concern that binding of [^{3}H]nemonapride in the presence of raclopride at a concentration used in the present study may not be exclusive to D_4 receptors. However, earlier findings (Tarazi et al., 1997b) indicate that 70–80% of the D_4 receptor binding can be blocked by highly D_4 receptor-selective antagonists L-745,870 and RBI-257 at concentrations that did not alter [^{3}H]nemonapride binding in the absence of raclopride, suggesting that most of the reported binding represents D_4 receptors. More direct evidence comes from observations that knock-out mice lacking D_4 receptors lack detectable binding using similar assay conditions (Defagot et al., 2000).

In summary, unilateral 6-OHDA lesions of the nigrostriatal DA pathway increased D_4 receptor binding in CPu, especially in rats that displayed contralateral rotation upon challenge with DA agonists. Despite the differential effects of 6-OHDA lesions on expression of D_4 receptors in rotators vs. non-rotators, D_4-selective agents were void of behavioral effects in this model. These findings suggest that D_4 receptors are unlikely to play a critical role in rotational behavior, and tend to support the view that D_2 receptors are the main subtype involved in lesion-induced behavioral supersensitivity.

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