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Alteration of striatal [^{11}C]raclopride and 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine uptake precedes development of methamphetamine-induced rotation following unilateral 6-hydroxydopamine lesions of medial forebrain bundle in rats

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Abstract

We studied the positron emission tomography (PET) tracer distributions of ligands for dopamine D_1 receptors ([^{11}C]SCH23390) and D_2 receptors ([^{11}C]raclopride) and of the dopamine precursor analog 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]FDOPA) in the brain after 6-hydroxydopamine (6-OHDA) lesions of the medial forebrain bundle in rats. The number of methamphetamine-induced rotation was higher at 14 days than at 3 days after the 6-OHDA lesions. The brains of 6-OHDA-treated rats were analyzed by tissue dissection following i.v. bolus of each tracer at 3 days (acute stage) or 3 weeks (chronic stage) postlesion. [^{11}C]Raclopride, but not [^{11}C]SCH23390, showed higher accumulation in the striatum on the lesion side than on the non-lesion (intact) side both at 3 days and 3 weeks postlesion. On the other hand, lower accumulation of [^{18}F]FDOPA was observed in the striatum on the lesion side at 3 days postlesion and in both the striatum and cerebral cortex on the lesion side at 3 weeks postlesion. Our studies demonstrate that an increase in [^{11}C]raclopride and a decrease in [^{18}F]FDOPA uptake in the denervated striatum is evident even at 3 days after the 6-OHDA lesions when the methamphetamine-induced rotational behavior is not established.

Keywords: 6-Hydroxydopamine; Striatum; [^{11}C]Raclopride; 6-[^{18}F]Fluoro-L-3,4-dihydroxyphenylalanine; Methamphetamine-induced rotation; Rat

Rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the medial forebrain bundle (MFB), through which the nigrostriatal pathway and mesocorticolimbic pathway project from the ventral midbrain [21], develop contralateral sensory neglect as well as postural and motor asymmetry, which are characterized by spontaneous and drug-induced rotation of the animal [29]. The 6-OHDA rat has been widely used as an animal model of Parkinson's disease, the clinical features of which are dominated by bradykinesia, rigidity, tremors, postural instability, and dementia [20]. In this model, there is an immediate and almost complete destruction of the dopamine

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neurons of the substantia nigra and ventral tegmental area, resulting in near total depletion (2% of normal) of dopamine in the ipsilateral striatum as a result of 6-OHDA injections [10]. An immunohistochemical study showed that after 6-OHDA injections there is no evident damage to dopaminergic neurons and fibers in the contralateral side of the brain [10,12]. There have been several reports on the enhanced effects of directly acting dopamine agonists, such as apomorphine in rotational behavior after the unilateral 6-OHDA lesions. The rotational behavior induced by dopamine agonists has been attributed to postsynaptic dopamine receptor supersensitivity in the striatum that occurs following the unilateral destruction of mesostriatal dopamine fibers [31]. Based on these observations, it is conceivable that the 6-OHDA-lesioned rat model may be useful for evaluating brain functions in Parkinson's disease.

6-[^{18}F]Fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]FDOPA) is a positron-emitting analog of the dopamine precursor L-DOPA and is one of the earliest [^{18}F]-labeled compounds, which is proposed as an imaging agent for external in vivo examination of the central nervous dopaminergic system [6]. Therefore, [^{18}F]FDOPA has been used as an imaging agent to investigate the activity of aromatic amino acid decarboxylase in the striatum and to assess the integrity of the dopaminergic system in the living brain by using positron emission tomography (PET) [7]. We previously demonstrated upregulation of dopamine D_2 receptors in the striatum and decrease in FDOPA uptake in both the striatum and cerebral cortex at 3 weeks after the 6-OHDA lesions in this model rat [11]. However, little information is available with regard to changes in dopamine receptors and FDOPA uptake in the brain, particularly, during the acute stage that follows the 6-OHDA lesions under the same experimental conditions.

Therefore, in the present study, we studied the tracer distributions of ligands for dopamine D_1 receptors ([^{11}C]SCH23390) and D_2 receptors ([^{11}C]raclopride), and of [^{18}F]FDOPA in the brain at 3 days and 3 weeks after the 6-OHDA lesions of the MFB in rats. Furthermore, to correlate the degree of motor symptoms with the tracer distributions at two different point of time, rotational behavior induced by methamphetamine challenge was sequentially evaluated 3 and 14 days after the 6-OHDA lesions.

The subjects were male Wistar rats (Kiwa Laboratory Animals, Kaisou, Japan), weighing 120–130 g at the beginning of the experiment. The experimental protocols used in this study were approved by the ethics committees for animal experimentation at Miyazaki Medical College and Kyoto University. Sixty rats were anesthetized using pentobarbital (40 mg/kg, i.p.), and unilateral lesions of the left MFB were created by injecting 12 μg 6-OHDA hydrobromide (Sigma, St. Louis, MO, USA) in 4 μl sterile saline containing 0.01% ascorbic acid. Stereotaxic coordinates for the lesions were as follows: AP 3.2 mm rostral to the interaural line, L 1.3 mm left of midline, and V 6.7 mm ventral to the dural surface, with the incisor bar set 2.4 mm below the level of the ear bars [14]. For analyzing tracer distributions in the brains of the 6-OHDA-treated rats, 30 rats were used at 3 days and the remaining 30 rats were used at 3 weeks 6-OHDA postlesion. Nine rats were randomly selected from the latter group of 30 rats, and the number of rotation following methamphetamine (3 mg/kg, i.p.) challenge was evaluated at 3 and 14 days after the 6-OHDA lesions [10,12]. In addition to the 60 6-OHDA-treated rats, seven rats were used as sham-lesioned animals for the behavioral experiment. Sham lesions were created by injecting the same amount (4 μl) of saline into the left MFB as described above.

[^{11}C]SCH23390 was synthesized by [^{11}C]methylation reaction of SCH24518 in an automated synthesis apparatus (CUPID C-100, Sumitomo Heavy Industries Co. Ltd., Tokyo, Japan), according to the method reported by Halldin et al. [9] with a slight modification. The radiochemical purity of [^{11}C]SCH23390 was >97.4%. The specific activity of the product was 38.5–81.4 GBq/μmol. [^{11}C]Raclopride was synthesized by [^{11}C]methylation reaction of *O*-desmethylraclopride in the CUPID C-100. The radiochemical purity of [^{11}C]raclopride was >98.4%. The specific activity of the product was 32.6–88.9 GBq/μmol. [^{18}F]FDOPA was synthesized in a multipurpose synthetic system [18], according to the method reported by Namavari et al. [22] with a slight modification. The radiochemical purity of [^{18}F]FDOPA was >98.5%. The specific activity of the product was 33.0–33.7 MBq/μmol.

The regional distribution of radioactivity in the rat brain was examined after i.v. injection of [^{11}C]SCH23390, [^{11}C]raclopride, or [^{18}F]FDOPA at 3 days and 3 weeks 6-OHDA postlesion. In previous studies, many investigators reported that degeneration of nigral dopaminergic neurons as well as dopamine receptor supersensitivity in the denervated striatum was established in 3 weeks 6-OHDA postlesion [19,32]. One hour (for [^{11}C]SCH23390 and [^{11}C]raclopride) or 1.5 h (for [^{18}F]FDOPA) after the i.v. injection, the rats were killed by decapitation, and each side of the brain was dissected into different brain regions (striatum, cerebral cortex, cerebellum, etc.) on ice as described by Glowinski and Iversen [8]. The brain samples were weighed and radioactivity accumulation of each tracer was determined for each brain region bilaterally. Radioactivity was measured using a scintillation counter (model 5003, Packard, USA). First, results were expressed as radioactivity per unit wet tissue weight (cpm/g). Next, the biodistribution of [^{11}C]SCH23390, [^{11}C]raclopride, and [^{18}F]FDOPA was computed as a ratio of lesion side to intact side for each brain region of the 6-OHDA rats.

Two-way ANOVA with repeated measures was used to statistically analyze the data for the methamphetamine-induced rotation. When significant differences were found between groups and/or time effects ($P < 0.05$), post-hoc comparisons were performed by the Newman–Keuls test. Data of the ratio of lesion side to intact side for each brain region were analyzed non-parametrically by the Wilcoxon signed rank test. Furthermore, the Mann–Whitney *U*-test was used to analyze

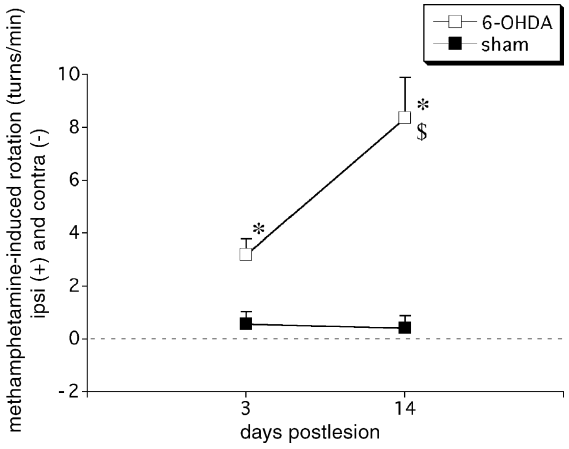

Fig. 1. The mean number of rotations (±S.E.M.) per min recorded over a 60-min test period in response to methamphetamine (3 mg/kg, i.p.) is shown for unilaterally 6-OHDA-lesioned ($n = 9$) and sham-lesioned rats ($n = 7$). "ipsi (+)" and "contra (−)" refer to the direction of rotation with respect to the lesion side. $^{*}P < 0.05$, compared to each corresponding value of the sham-lesioned animals (ANOVA followed by Newman–Keuls test). $^{\$}P < 0.05$, compared to the value at 3 weeks after 6-OHDA lesioning for each group (ANOVA followed by Newman–Keuls test).

the difference between the ratio at 3 days and 3 weeks postlesion for each tracer and each brain region. *P*-values of <0.05 were regarded as significant.

When compared with the sham-lesioned animals, methamphetamine induced significant elevated number of rotations ipsilateral to the 6-OHDA injections at both 3 and 14 days postlesion in the 6-OHDA rats (group effect, $F_{1,14} = 24.00$, $P < 0.01$; Newman–Keuls test, $P < 0.05$) (Fig. 1). Furthermore, the number of methamphetamine-induced rotation, in the 6-OHDA group, was significantly higher at 14 days than at 3 days after the 6-OHDA lesions (time effect, $F_{1,14} = 7.94$, $P < 0.05$; Newman–Keuls test, $P < 0.05$) (Fig. 1).

Table 1 shows the biodistribution of [^{11}C]SCH23390, [^{11}C]raclopride, and [^{18}F]FDOPA in the three brain regions (cerebral cortex, striatum, and cerebellum) on the lesion side of the 6-OHDA rats, which is represented as the radioactivity ratio in the lesion side relative to the intact side of the brain, at 3 days and 3 weeks after the 6-OHDA lesions. The biodistribution of [^{11}C]raclopride in the striatum was significantly higher (Wilcoxon signed rank test, $P < 0.01$) on the lesion side than on the intact side of the 6-OHDA rats both at 3 days and 3 weeks postlesion. On the other hand, the biodistribution of [^{18}F]FDOPA in the striatum was lower (Wilcoxon signed rank test, $P < 0.01$) on the lesion side than on the intact side at both 3 days and 3 weeks postlesion. The biodistribution of [^{18}F]FDOPA in the cerebral cortex was lower on the lesion side than on the intact side at 3 weeks after the 6-OHDA lesions (Wilcoxon signed rank test, $P < 0.05$). None of the three regions showed any significant difference in the biodistribution of [^{11}C]SCH23390 between the lesion and intact sides of the brain at 3 days and 3 weeks after the 6-OHDA lesions.

Table 1
Biodistribution of each tracer in three brain regions of the 6-OHDA rats

	Three days	Three weeks
[^{11}C]SCH23390 ($n = 10$)		
Cerebral cortex	1.00 ± 0.02	1.10 ± 0.05
Striatum	0.97 ± 0.03	1.10 ± 0.04
Cerebellum	1.03 ± 0.02	1.00 ± 0.01
[^{11}C]raclopride ($n = 10$)		
Cerebral cortex	1.06 ± 0.05	1.11 ± 0.06
Striatum	1.61 ± 0.09**	1.90 ± 0.10**
Cerebellum	1.07 ± 0.05	1.01 ± 0.02
[^{18}F]FDOPA ($n = 10$)		
Cerebral cortex	0.99 ± 0.04	0.90 ± 0.06*
Striatum	0.74 ± 0.05**	0.81 ± 0.03**
Cerebellum	0.95 ± 0.07	0.99 ± 0.01

Each value presents a ratio (mean ± S.E.M.) of lesion side to intact side of each brain region (cpm/g) of the 6-OHDA rats (lesion side/intact side). No difference was observed between the ratio at 3 days and at 3 weeks postlesion for any brain region with respect to the three tracers (Mann–Whitney *U*-test).
* $P < 0.05$.
** $P < 0.01$ vs. corresponding values of intact side (Wilcoxon signed rank tests).

No difference was observed between the ratio at 3 days and at 3 weeks postlesion for any brain region with respect to the three tracers (Mann–Whitney *U*-test).

This study showed that the unilateral MFB lesions produced with 6-OHDA caused methamphetamine-induced rotation ipsilateral to the lesions both at 3 and 14 days postlesion. However, the number of rotation was lower at 3 days than that at 14 days postlesion. Similar findings were also reported by Labandeira-Garcia et al. [15]. They showed that there is a marked and progressive loss of dopaminergic terminals for a few days after the 6-OHDA lesions. This loss is counteracted by factors acting at both presynaptic and postsynaptic levels. There is rapid development of dopamine receptor supersensitivity, detected within 24–48 h of lesions (indicated by rotational behavior and striatal Fos expression induced by apomorphine). Additionally, dopamine is more easily released in the lesion side by methamphetamine at the time of lesions; this response is possibly accompanied by decreased dopamine reuptake. This leads to stronger dopamine stimulation of the denervated striatum when methamphetamine is administered during the first week postlesion. These might be the possible explanations for the delayed alteration of methamphetamine-induced rotation when compared with the alteration in tracer distributions in the present study.

Here, the biodistribution of [^{11}C]SCH23390 did not change in any brain region of the 6-OHDA-treated animals within 3 weeks postlesion. An upregulation of dopamine D_1 receptors after the MFB lesions has been demonstrated in receptor autoradiographic studies [5,23]. Furthermore, supersensitivity of dopamine D_1 receptors has been reported in the striatal tissue homogenates after the MFB lesions with 6-OHDA [3,26]. In contrast, there are other contradicting results showing no change or decrease in density of striatal dopamine D_1 receptors after denervation of the nigrostri-

atal dopaminergic pathway [16,28]. The precise reason for these discrepancies is unknown, but the discrepancies may be related to the differences in the methods (e.g. radioligand binding assay, autoradiography) used and/or different time points considered after 6-OHDA lesioning in the earlier studies.

In previous studies, it was observed that denervation of the nigrostriatal pathway can cause supersensitivity of the postsynaptic population of dopamine D_2 receptors [5,23]. Furthermore, Araki et al. also observed that the upregulation of D_2 receptors was more pronounced than that of D_1 receptors in the striatum after 6-OHDA lesioning [1,2]. These observations are consistent with our present findings.

The present study also showed that [^{18}F]FDOPA uptake significantly decreased in the striatum 3 days postlesion, and in both the striatum and cerebral cortex 3 weeks postlesion. A lowered capacity of dopamine synthesis was observed not only in the striatum but also in the cerebral cortex on the lesion side during the chronic stage. The [^{18}F]FDOPA uptake in the cerebral cortex has been reported to increase [13] or decrease [27] in patients with Parkinson's disease. When this is considered along with the evidence that the degree of dopamine denervation in the 6-OHDA-treated animals was almost complete [10], the present findings suggest that the [^{18}F]FDOPA uptake in the cerebral cortex may decrease in parkinsonian patients in an advanced stage. Further studies on the tracer distributions in rats with partial 6-OHDA lesions may clarify the issue.

As reviewed by Laruelle, numerous independent laboratories have established that [^{11}C]raclopride behaves as predicted by the occupancy model, i.e., higher synaptic dopamine levels are associated with lower ligand binding and vice versa [17]. In view of the occupancy model, an increase in [^{11}C]raclopride and a decrease in [^{18}F]FDOPA uptake in the denervated striatum may, at least in part, be due to endogenous dopamine reduction.

As we previously reported, the present study demonstrated an increase in [^{11}C]raclopride uptake in the striatum and a decrease in FDOPA uptake in both the striatum and cerebral cortex ipsilateral to the 6-OHDA lesions at 3 weeks postlesion [11]. Furthermore, this study revealed that the similar findings, such as an increase in [^{11}C]raclopride and a decrease in FDOPA uptake in the denervated striatum, are already evident at 3 days postlesion. Although contradicting results have also been obtained previously [4,30], other studies using in vivo binding methods have reported proliferation of D_2 receptors as early as 4 days after 6-OHDA injections [24,25], and these results may be related to our findings.

In conclusion, the present study demonstrates an increase in [^{11}C]raclopride and a decrease in FDOPA uptake in the denervated striatum both 3 days and 3 weeks following the 6-OHDA lesions. Therefore, the combination of a D_2 antagonist and FDOPA may provide a potentially useful method for assessing the effects of dopamine depletion in Parkinson's disease.

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