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Upregulation of Postsynaptic Dopamine Receptors in the Striatum Does Not Influence Haloperidol-Induced Catalepsy in Mice

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IWATA, S., K. IZUMI AND M. NOMOTO. *Upregulation of postsynaptic dopamine receptors in the striatum does not influence haloperidol-induced catalepsy in mice.* PHARMACOL BIOCHEM BEHAV 42(4) 803-808, 1992.—The incidence of haloperidol-induced catalepsy was investigated in mice whose postsynaptic dopamine (DA) receptors in the striatum had been upregulated by denervation with 6-hydroxydopamine (6-OHDA). In nonupregulated mice, which were injected with 6-OHDA 4 days before, DA in the striatum fell to 21% of the level found in vehicle-injected mice but [^{3}H]spiperone binding to the membrane of the striatum did not increase. In upregulated mice, which were injected with 6-OHDA 28 days before, DA was at 24% and [^{3}H]spiperone binding increased by 15%.

The ED_{50} values (with 95% confidence limits) for haloperidol-induced catalepsy in nonupregulated mice and that in upregulated mice was 0.40 mg/kg (0.25–0.65 mg/kg) and 0.29 mg/kg (0.16–0.51 mg/kg), respectively. There was no significant difference in the incidence of catalepsy between the two groups of mice. This suggests that the intensity of catalepsy produced by the DA receptor blockade may be unaltered even when the density of receptors increases.

Catalepsy Haloperidol Spiperone binding 6-Hydroxydopamine Dopamine receptor

THE increase of postsynaptic dopamine (DA) receptors induces supersensitivity to the DA agonist. For example, locomotion or stereotyped behavior that are produced by the stimulation of postsynaptic DA receptors is enhanced by the upregulation of postsynaptic DA receptors (9,24).

The blockade of postsynaptic DA receptors produces catalepsy, which is characterized by the inability to initiate movements in an abnormal position (30), or hypoactivity and the failure to correct various abnormal postures imposed by the observer without failure of the righting reflex (1). Catalepsy induced by neuroleptics is attributed to the blockade of striatal DA receptors (4,5,8,14,25,26,29).

The effect of the DA receptor antagonist on the state of upregulation of postsynaptic DA receptors has not been clear. A few studies about this problem have been presented (3,22), but in those studies receptor binding assay was not performed. Furthermore, no researcher focused on this subject. We first studied the effect of the DA receptor antagonist in cases where the number of postsynaptic DA receptors increases.

In this experiment, we examined haloperidol-induced catalepsy in mice whose postsynaptic DA receptors were upregulated by 6-hydroxydopamine (6-OHDA) treatment.

METHOD

Animals

Male ddY mice (Kuroda Junkei Dohbutu Ltd., Kumamoto, Japan), weighing 35–50 g, were used. Animals were housed with free access to standard food (Clea Japan, Inc., Ohsaka, Japan) in an air-conditioned room under a constant 12 L : 12 D cycle (light on 7:00 a.m.) at a temperature of 22–24°C and 60–70% relative humidity.

6-OHDA Treatment

6-OHDA was administered into the lateral ventricles to destroy the dopaminergic nerve terminals. Mice were anesthetized with ether. 6-OHDA hydrobromide (100 μg as free base) purchased from Sigma Chemical Co. (St. Louis, MO) dissolved in 5 μl vehicle (0.1% ascorbic acid in 0.9% saline) was delivered through a stainless steel cannula (0.4 mm external diameter) with an infusion pump (Natume, Seisakujo, Tokyo, Japan) at a rate of 0.125 μl/s. The cannula was inserted vertically through a small hole in the skull 1 mm lateral and 1 mm caudal to the bregma and 3 mm into the surface of the skull. Twenty minutes before delivery, mice were injected with diazepam (10 mg/kg, IP) to reduce the mortality from 6-OHDA-induced convulsion. An additional dose of 6-OHDA (100 μg) was administered to mice 1 week later. Sham-operated animals were given a vehicle solution instead of 6-OHDA but otherwise treated similarly. This procedure eliminated the effect of ascorbic acid (31) and handling influence on the results.

Catalepsy Measurement

Catalepsy was assessed by placing the forelimbs on a horizontal steel bar 2 mm in diameter at a height of 5 cm. Cata-

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lepsy was defined as positive when animals sustained the posture for more than 30 s as described previously (12). Haloperidol (Yoshitomi Pharmaceutical Co., Ohsaka, Japan) was dissolved in 0.9% saline and administered intraperitoneally in a volume of 0.1 ml/10 g. Mice were individually placed in a clear, acrylic box (30 × 45 × 25 cm). Mice were left in the box for 30 min to allow for adaptation to the new environment before drugs were injected. All experiments were performed in the box between 10:00 a.m. and 5:00 p.m. Haloperidol-induced catalepsy was measured 4 days after the last treatment with 6-OHDA or vehicle, when the density of DA receptors in the striatum had not yet increased (nonupregulated) and 28 days after the last treatment, when it had already increased (upregulated). The ED_{50} and 95% confidence limits were obtained by the graphic method (16) in which the percentage of animals that showed catalepsy 30 min after haloperidol administration was plotted on a probability scale graph.

Membrane Preparation

Mice were decapitated at 4 or 37 days after treatment with 6-OHDA or vehicle solution. Striatal tissues were rapidly removed on an ice-cold glass plate by the method of Schubert and Sedvall (27) and immediately homogenized using a Polytron (Kinematica Co., Switzerland) at 6 on the dial for 30 s in 1 ml 50 mM Tris-buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl. Fifty microliters of the homogenate was used for monoamine assay. The remains were further centrifuged at 20,000 × *g* for 10 min at 4°C, washed twice with 1 ml cold buffer, and resuspended in 1.5 ml cold buffer. This resuspended membrane solution was used for spiperone binding study and protein assay.

Binding Assay

[^{3}H]Spiperone (specific activity 1198.8 GBq/mmol, New England Nuclear, Newton, MA) was employed as a ligand for the DA D_2 receptor in the striatum. Membranes, which contained 0.05–0.175 mg protein per tube (protein concentration: 0.05–0.175 mg/ml), were incubated with various concentrations (0.025–0.5 nM) of [^{3}H]spiperone at 37°C for 20 min. The reaction was started by adding membrane into the tube containing [^{3}H]spiperone. After incubation of the samples, the reaction was stopped by the addition of 4 ml ice-cold 50 mM Tris-HCl buffer (pH 7.4, with 120 mM NaCl and 5 mM KCl) and rapid filtration through Whatman (Maidstone, England) GF/B glass-fiber filters. The filters were washed three times with 4 ml ice-cold buffer, dried, and counted for radioactivity by liquid scintillation spectrometry (Aloka, LSC-900, Tokyo, Japan) at 40% efficacy. Specific [^{3}H]spiperone binding was defined as that displaced by coincubation with 1 μM (+)-butaclamol (Research Biochemicals, Inc., Wayland, MA).

Monoamine Assay

Monoamine contents of the striatal tissue were measured as follows. The sample was homogenized using an ultrasonic cell disrupter (Model 185, 40% pulsed power for 30 s, Branson, Danbury, CT) in a polypropylene tube with 200 vol cold 0.1 M perchloric acid containing 5 mM EDTA and DHBA as an internal standard. Following centrifugation at 28,000 × *g* (Kubota 20000T) for 20 min at 4°C, supernatant was filtered through a 0.45-μm filter (Gelman Sciences Japan Ltd., Tokyo, Japan) and a 20-μl aliquot of filtrated solution was injected into a high-pressure liquid chromatographer. The HPLC system was composed of a delivery pump (Model 510, Waters Associates, Inc., Milford, MA), sample injectors (WISP 710B, Waters Associates), and a reverse-phase column (Eicopak, Eicom, Kyoto, Japan, MA-ODS; length 250 mm, internal diameter 4.6 mm) and an electrochemical detector (LC-4B, amperometric detector) set at a potential +0.80 V. The analytical column temperature was controlled at 40°C. The mobile phase consisted of 7.35 g citric acid, 6.80 g sodium acetate, 0.003 g EDTA, and 0.215 g sodium octylsulfate in 850 ml distilled water; to this mixture methanol (130 ml) was added. The pH of this final solution was 3.90. The flow rate of the mobile phase was adjusted to 1 ml per min.

To investigate the regional changes of monoamines by 6-OHDA, we dissected the mouse brain by the method of Heffner et al. (10). Monoamines were measured in the same way as mentioned above.

Protein Assay

Fifty microliters of the homogenate was used for protein measurement. The protein concentration was determined by the modified method of Lowry et al. (17).

Statistics

For statistical analysis of the monoamine contents and B_{max} and K_d values, Student's *t*-test was applied.

RESULTS

Catalepsy Evaluation

The value of ED_{50} (95% confidence limits) for catalepsy in nonupregulated and upregulated mice were 0.40 mg/kg (0.25–0.65 mg/kg) and 0.29 mg/kg (0.16–0.51 mg/kg), respectively. The calculated potency ratio (PR) was 1.40 and the factor for PR (f_{PR}) was 2.10, indicating that catalepsy induced by haloperidol had not changed in DA-receptor-upregulated mice (Fig. 1).

6-OHDA-Treated mice showed marked irritability and hyperreactivity to manipulation. Vehicle-treated mice were prone to display increasing catalepsy with successive trials. On the other hand, 6-OHDA-treated animals showed less catalepsy as the trials progressed. The PR between mice treated with 6-OHDA and vehicle in the nonupregulated group was 2.0 and the f_{PR} was 1.95, indicating that 6-OHDA treatment

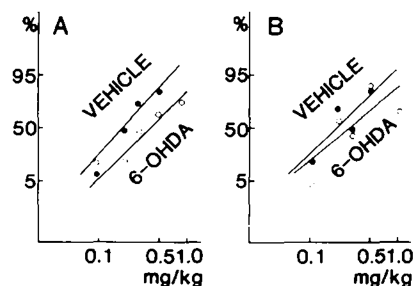

FIG. 1. Catalepsy measured in (A) nonupregulated and (B) upregulated mice. Catalepsy was evaluated with the forelimbs at 30 min following administration of haloperidol. Each point represents a percentage of five to eight animals per dose. Closed and open circles represent incidence of catalepsy in vehicle- and 6-OHDA-treated mice, respectively. The abscissa is dose of haloperidol and ordinate is the incidence of catalepsy.

TABLE 1

EFFECT OF 6-OHDA ON BRAIN MONOAMINES IN THE STRIATUM

	Nonupregulated		Upregulated	
	Vehicle	6-OHDA	Vehicle	6-OHDA
n	7	23	9	20
DA	9,684 ± 313	2,047 ± 268*	11,903 ± 748	2,914 ± 419*
DOPAC	2,541 ± 219	576 ± 64*	1,423 ± 101	654 ± 79*
HVA	1,573 ± 87	639 ± 48*	1,725 ± 218	1,160 ± 84
NAd	77 ± 4	72 ± 7	269 ± 64	350 ± 61
MOPEG	17 ± 8	nd	359 ± 115	321 ± 72
5-HT	577 ± 50	550 ± 22	805 ± 73	955 ± 121
5-HIAA	596 ± 27	776 ± 44*	450 ± 98	602 ± 66

6-OHDA (100 μg) was injected into both lateral ventricles and additional doses of 6-OHDA (100 μg) were given 1 week later. Haloperidol-induced catalepsy was evaluated 4 (nonupregulated) (A) and 28 (upregulated) (B) days after the second injection of 6-OHDA, and mice were decapitated 7 to 9 days after haloperidol injection. Values represent the mean nanogram per gram of wet tissue ± SE. *n* represents the number of mice; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; NAd, noradrenaline; MOPEG, 3-methoxy-4-hydroxyphenylethyleneglycol; 5-HT, 5-hydroxytryptamine; and 5-HIAA, 5-hydroxyindoleacetic acid.

*Significant decrease in the denervated striatum after 6-OHDA compared to the vehicle control using Student's *t*-test ($p < 0.01$).

significantly attenuated the incidence of catalepsy ($p < 0.05$). But, the PR between mice treated with 6-OHDA and vehicle in the upregulated group was 1.14 and the f_{PR} was 1.23, indicating that the incidence of haloperidol-induced catalepsy did not significantly change after 6-OHDA treatment.

Mice in which DA in the striatum did not fall to below 50% of the control value were not used in the catalepsy measurement.

Effect of 6-OHDA Treatment on Brain Monoamines

Treatment with 6-OHDA resulted in a 79% reduction of DA in the striatum in nonupregulated mice, while the same treatment caused a 76% decrease in upregulated animals (Table 1). There were no significant changes in the noradrenaline (NAd) contents by 6-OHDA but the NAd contents in upregulated mice was much greater than those in nonupregulated animals. The amount of 5-hydroxyindoleacetic acid (5-HIAA) in nonupregulated mice was increased, but there was no significant change in 5-hydroxytryptamine (5-HT) concentration.

DA concentration in the homogenate used for the binding assay decreased to 84% in nonupregulated mice and 89% in upregulated ones compared to each vehicle control (Table 2).

Regional monoamine changes are shown in Table 2. DA in the striatum and in the nucleus accumbens was 47 and 24% of control values, respectively. NAd in the striatum was 55% of control, but it was much reduced in the cortex, hippocampus, and cerebellum.

[^{3}H]Spiperone Binding

[^{3}H]Spiperone binding to the membrane of the striatum was saturable and the data can be represented accurately by a monophasic binding curve (Fig. 2). In nonupregulated mice, [^{3}H]spiperone binding (B_{max} 485 fmol/mg protein) was found to be almost identical to that in animals treated with vehicle (B_{max} 473 fmol/mg protein) (Table 3). However, in upregulated mice [^{3}H]spiperone binding (B_{max} 578 fmol/mg protein) in 6-OHDA-treated mice was 15% more than in vehicle-treated animals (B_{max} 501 fmol/mg protein) (Table 3). This

TABLE 2

REGIONAL MONOAMINE CONTENTS AFTER 6-OHDA TREATMENT

	DA		NAd	
	Vehicle	6-OHDA	Vehicle	6-OHDA
Striatum	8,159 ± 442	3,818 ± 816*	252 ± 14	138 ± 7*
Nucleus accumbens	6,091 ± 85	1,483 ± 258*	953 ± 77	117 ± 22*
Frontal cortex	nd	nd	512 ± 26	5 ± 5*
Hippocampus	18 ± 1	4 ± 2*	624 ± 37	7 ± 4*
Midbrain	144 ± 13	212 ± 15*	698 ± 15	183 ± 13*
Cerebellum	6 ± 1	3 ± 1	323 ± 16	9 ± 2*
Brainstem	28 ± 2	32 ± 5	649 ± 25	457 ± 12*

Mice were decapitated 4 days after the second injection of 6-OHDA, which was administered as in Table 1. Brains were dissected according to the method of Heffner et al. (10). Values represent the mean nanogram per gram of wet tissue ± SE. All abbreviations as in Table 1.

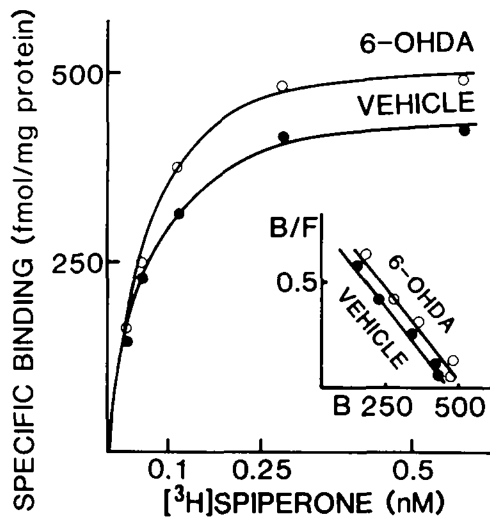

FIG. 2. Specific binding of [^{3}H]spiperone to membrane of striatum in one of the upregulated mice. Data is shown as representative from vehicle (●)- and 6-OHDA (○)-treated animal. The sections were incubated in the presence of 0.025–0.5 nM [^{3}H]spiperone, and specific binding was determined by subtracting the binding incubated in the presence of 1 μM (+)-butaclamol (nonspecific binding) from the total binding. Inset: Scatchard analysis revealed a single class of sites. The abscissa is the specific binding of [^{3}H]spiperone and the ordinate is the ratio of bound [^{3}H]spiperone to the concentration of free [^{3}H]spiperone.

indicates that postsynaptic DA receptors in the striatum were upregulated by denervation with 6-OHDA. The K_d value did not significantly change in either group of mice.

DISCUSSION

These results suggested that the incidence of haloperidol-induced catalepsy did not change in mice whose postsynaptic DA receptors in the striatum had been upregulated by denervation with 6-OHDA.

Morelli et al. (20) reported that the cataleptic effect of haloperidol increased in rats whose striatal DA had been reduced to 20% of control value 15 days after stereotaxic injection of 6-OHDA in the medial forebrain bundle. However, they neither performed receptor binding assays not discussed the state of the postsynaptic DA receptors. Sanberg (25) showed that bilateral injections of kainic acid into the striatum attenuated the haloperidol-induced catalepsy and ascribed this phenomenon to the loss of DA receptors. Nahorski (22) reported that intraventricularly 6-OHDA-treated mice were considerably less susceptible to the cataleptic activity of pimozide. And, he attributed the result to increased numbers or availability of DA receptors following dopaminergic denervation with 6-OHDA. However, it was not confirmed whether DA receptors were or were not upregulated by receptor assay. Even though he performed the experiment 5–14 days after 6-OHDA treatment and even though DA content decreases to one quarter of the control level, we thought that both the duration and the degree of DA depletion were insufficient for the upregulation of DA receptors. We considered the possible reasons why the incidence of catalepsy did not change in DA-receptor-upregulated mice. First, it may be that a mere 15% increase in postsynaptic DA receptors is not sufficient to change haloperidol-induced catalepsy. Second, it may be that the measurement of depressed behavior such as catalepsy is not as sensitive as an evaluation of active behavior such as rotation or circling. Third, even if neuroleptic-induced catalepsy is produced by the blocking of postsynaptic DA receptors newly synthesized DA receptors by denervation might play no role in catalepsy.

There are two ways to increase postsynaptic DA receptors. One is to impair the dopaminergic terminals by 6-OHDA (6); the other is to administer neuroleptics chronically (7). We employed the former method since the latter is prone to produce tolerance in haloperidol-induced catalepsy (21).

Dopaminergic nerve terminals in other brain regions were destroyed together with those in the striatum because 6-OHDA was administered intraventricularly in our experiment (Table 2). We tried to inject the drug into striatum or medial forebrain bundle to destroy striatal dopamine terminals selectively, but direct injections of a sufficient dose of 6-OHDA into the striatum killed most mice and injections into medial forebrain bundle failed to destroy the striatal DA terminals sufficiently. Therefore, 6-OHDA was administered to the lateral ventricles. 6-OHDA was administered twice every seventh day because mortality of drug-treated mice increased dramati-

TABLE 3

[^{3}H]SPIPERONE BINDING IN THE STRIATUM IN NONUPREGULATED AND UPREGULATED MICE

	n	B_{max} (fmol/mg prot)	K_d (pM)	DA (ng/g)
Nonupregulated				
Vehicle	4	473 ± 9	47 ± 1.8	12,137 ± 1614
6-OHDA	4	485 ± 45	51 ± 2.6	1,947 ± 459*
Upregulated				
Vehicle	7	501 ± 20	47 ± 3.8	11,578 ± 905
6-OHDA	7	578 ± 14*	47 ± 3.4	1,245 ± 265*

Mean ± SE for four and seven nonupregulated and upregulated mice. B_{max} and K_d were calculated by Scatchard analysis.

*Significant increase in B_{max} in upregulated mice compared to vehicle control using Student's t-test ($p < 0.01$).

cally when the whole dose (200 μg/mouse) was injected at once.

Staunton et al. (28) and Mishra et al. (19) studied the time course of the effect of 6-OHDA treatment on striatal DA levels and showed that DA levels decreased until the second day and the content of the DA was stable from at that time. We experienced nonupregulated studies at the fourth day after 6-OHDA treatment, when destruction of the DA terminals had already been accomplished.

We did not use desipramine, which preserves NAd terminals, because desipramine treatment mixed with diazepam (10 mg/kg) dramatically increased mortality and desipramine could not prevent the destruction of NAd terminals sufficiently. In Table 2, NAd contents in various regions were reduced. But, in Table 1 NAd contents in the striatum did not alter significantly. This might be due to the different method of brain dissection or HPLC condition. Although there was the possibility that the destruction of NAd terminals might have an effect on haloperidol-induced catalepsy, there is little problem comparing the 6-OHDA-treated nonupregulated mice and 6-OHDA-treated upregulated ones because NAd terminals in the two groups were destroyed equally. We could not exclude the possibility that NAd receptors in "upregulated mice" were upregulated because we did not examine the receptor assay of NAd receptors.

Receptor binding assays were performed by [^{3}H]spiperone in the striatum because neuroleptic-induced catalepsy is attributed to the blockade of striatal DA receptors (4,5,8,14, 25,26,29). We could obtain only five data points in Scatchard plots because we conducted receptor binding assays with the brain of one mouse to find the relationship between the degree of DA receptor upregulation and that of DA depletion. However, we could depict Scatchard plots because [^{3}H]spiperone binding in the striatum has been established and proved to be a single binding site and saturable.

Figure 1A showed that the value of ED_{50} for haloperidol-induced catalepsy in 6-OHDA-treated mice was significantly higher than that in vehicle-treated mice of the nonupregulated group. It was difficult, therefore, to induce catalepsy in 6-OHDA-treated mice. We considered that this phenomenon might be due to an increased "irritability" or "reactivity" to exogenous nociceptive (nonpainful) stimuli (15). Without irritability, there would had been no significant difference in ED_{50} between the 6-OHDA- and vehicle-treated mice because PR (2.0) only just exceeded f_{PR} (1.95).

Denervation causes an increase in the number of postsynaptic receptors (upregulation). An animal whose postsynaptic receptors are upregulated shows supersensitive behavior to receptor-stimulating drugs, but the relationship between the density of receptors and the intensity of behaviors is not clear. Highly positive correlations were found between amphetamine- and lergotrill-induced rotation and specific binding of [^{3}H]spiperone in rats lesioned in unilateral substantia nigra with 6-OHDA (13). Apomorphine-induced stereotyped behavior in rats that were daily administered haloperidol for 30 days increased when [^{3}H]spiperone binding in the striatum increased (9). Differences of intensity in apomorphine-induced stereotyped behavior between different strains of rats were also attributed to the density of DA D_2 receptors in the striatum (11,18). On the contrary, circling behavior led by apomorphine was maximal within 3 days following the destruction of dopaminergic afferent neurons, although a gradual increase in the density of binding sites for [^{3}H]spiperone occurred during a 2- to 3-week period after the destruction (28). There are some reports in which [^{3}H]spiperone binding to the striatum was not altered in denervation-supersensitive animals (2). Conversely, the density of postsynaptic DA receptors never increases without causing supersensitive behavior.

Onn et al. (23) proved the sprouting of DA terminals in the striatum by using regional histochemical and biochemical analysis 4 months after intraventricular administration of 6-OHDA. Furthermore, Zhang et al. (32) biochemically showed the sprouting of DA terminals in the striatum. They suggested the increase of DA content paralleled homovanillic acid (HVA) content, indicated by the increased number of DA terminals. In our study, DA content in nonupregulated mice and that in upregulated mice was 2.047 ng/mg and 2.914 ng/mg, respectively. Dihydroxyphenylacetic acid + HVA/DA ratio in the former group and that in the latter were 0.51 and 0.54, respectively. Although we could not evaluate sprouting from these data, it did not seem that marked sprouting took place.

In conclusion, haloperidol-induced catalepsy was unaltered even though the density of postsynaptic DA receptors increased.

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