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Supersensitized D1 Receptors Mediate Enhanced Oral Activity After Neonatal 6-OHDA

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KOSTRZEWA, R. M. AND L. GONG. *Supersensitized D1 receptors mediate enhanced oral activity after neonatal 6-OHDA.* PHARMACOL BIOCHEM BEHAV **39**(3) 677–682, 1991.—Enhanced oral responses have been observed in rats that are treated shortly after birth with 6-hydroxydopamine (6-OHDA). A series of studies was conducted to characterize this effect. A dose-response curve demonstrated that the dopamine D1 receptor agonist, SKF 38393, produced a maximal response in 6-OHDA-treated rats at a dose of 0.10 mg/kg (IP). With the D2 receptor antagonist, spiperone, a bell-shaped dose-response curve was seen, with a maximal effect in the 6-OHDA group occurring at 80 μg/kg. There were only slight increases in oral activity with different SKF 38393 or spiperone doses in the saline group, indicating that there was an overt supersensitization of D1 receptors in the 6-OHDA-treated rats. The D1 antagonist SCH 23390 (0.30 mg/kg, IP) attenuated the response to both SKF 38393 and spiperone. The oral response to the D2 agonist, quinpirole (0.10 mg/kg, IP) was not preferentially increased in the 6-OHDA group of rats. These findings indicate that the enhanced oral response in neonatal 6-OHDA-treated rats is mediated by supersensitive dopamine D1 receptors. The persistence of the enhanced oral response in 6-OHDA-treated rats at 8 months demonstrates that this sensitization of D1 receptors is a long-lived phenomenon.

Oral dyskinesia D1 receptor D2 receptor 6-Hydroxydopamine Dopamine Supersensitivity

RODENTS treated with repeated doses of neuroleptics that act primarily on dopamine (DA) D2 receptors become sensitized to the induction of orofacial dyskinesias by DA receptor agonists (5, 7, 8, 20). The enhanced induction of oral activity in these rats represents a short-lived event, disappearing gradually after withdrawal from the neuroleptic (18). A functional interaction between D1 and D2 receptors is involved in this phenomenon (1, 21, 22). It is now known that intact rats treated acutely with a D1 receptor agonist or D2 receptor antagonist display an increase in the incidence of oral activity (9, 13–16).

In a recent report, we found that neonatal treatment of rats with 6-hydroxydopamine (6-OHDA) produced destruction of central DA-containing neurons and was accompanied by enhanced induction of oral activity by a DA D1 agonist and D2 antagonist (10). This occurred despite the lack of a change in the B_{max} and K_d for striatal D1 and D2 receptors.

The present series of studies was conducted to determine whether neonatal 6-OHDA treatment produced a) a shift in dose-effect curves for agents that induced oral activity, or b) a true supersensitization of DA receptors that mediates oral activity. The time-course of D1 receptor agonist- and D2 receptor antagonist-induced changes in oral activity was studied in both the intact and DA-depleted rats to verify that sampling times were suitable for the observation periods. By using combinations of D1 and D2 receptor agonists and antagonists, the interaction of the receptor types in lesioned vs. control rats was determined. Finally, by studying these phenomena in rats more than 6 months of age, a long-lived sensitization of D1 receptors was found. The findings demonstrate that supersensitized D1 receptors are involved in the induction of enhanced oral activity in 6-OHDA-lesioned rats.

METHOD

Subjects

Timed pregnant Sprague-Dawley albino rats were obtained from Charles River Laboratories (Research Triangle, NC). Animals were housed at 22 ± 1°C under a 12-h/12-h light-dark cycle (on at 0700 h) and were allowed free access to food and water. At birth, litters were reassigned, so that each dam had rats from several litters.

Treatment

At 3 days after birth, rats were individually removed from the litter and were placed on a flat surface under a bright light. In this manner, the sagittal and transverse sinuses overlying the cranium, as well as bregma and lambda, could be seen through the transparent intact dermis. A microliter syringe was equipped with a 26-gauge needle having a polyethylene sleeve up to 2 mm from the tip. The needle was positioned 1.5 mm anterior to lambda and 2 mm lateral to the sagittal plane. After the needle was lowered into one lateral ventricle, and 5 μl of 6-OHDA so-

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lution or vehicle was injected, the needle was left in place for about 30 s. Immediately afterward, an injection was made in the same manner into the other lateral ventricle. Rats received a bilateral intracerebroventricular (ICV) injection of 6-OHDA HBr (100 μg, salt form, on each side; Sigma Chemical Co., St. Louis, MO) or the vehicle, saline-ascorbic acid (0.1%). Rats were weaned at 28 days and were then group-housed by sex in wire cages. In this paper, the dose of 6-OHDA and test agents are for the salt form.

Behavioral Observation

General. Rats were observed for oral responses to test agents between 4 and 8 months of age. For each test session, rats were placed in individual clear plastic cages (48 × 26 × 18 cm or 48 × 26 × 36 cm, depending on the size of the rat) in a quiet, well-ventilated and well-lighted room, and were allowed to accommodate to the new environment for at least 2 h. Cages of the same height were used for any single test session.

Testing. Between 1100 and 1600 h, each rat was given a single intraperitoneal (IP) challenge dose of vehicle, spiperone HCl (Research Biochemicals, Inc., Natick, MA) or ±SKF 38393 HCl [1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride] (Research Biochemicals Inc.). Each rat was then observed one at a time, for one minute every ten minutes, over a 30- or 60-minute period, beginning 60 minutes after spiperone or 10 minutes after SKF 38393. Numbers of rapid jaw movements were counted.

The initial determinations of oral activity after SKF 38393, spiperone, and saline were obtained with the observer being unaware of the treatment group for each rat. Later studies were not able to be done in a blind manner because of markings and size differences between control and 6-OHDA groups of rats.

Phenomenology of oral activity. Oral activity in these studies is of the type described in the paper by Waddington (19), as "vacuous (or abortive or spontaneous) chewing, whereby what appear to be robust chewing sequences are manifested, but are not directed onto any evident physical material." No differentiation between lateral and vertical jaw movement was made. Also, there was occasional tongue thrusting noted in these rats. Oral activity that occurred in eating, grooming, yawning or taffy pulling (coordinated movement of the forepaws toward the mouth and then away from the body) was not counted.

The phenomenology of oral activity after quinpirole was similar to that described above. However, after quinpirole treatment, there was much eating or chewing of the wood-chip bedding.

Effect of quinpirole. Oral activity was determined for 60 minutes, starting 10 minutes after treatment with the dopamine D2 agonist, quinpirole HCl (Research Biochemicals, Inc.; 0.10 mg/kg, IP).

Effect of SCH 23390. The effect of the DA D1 receptor antagonist, SCH 23390, was determined in rats that were challenged with SKF 38393 HCl (0.30 mg/kg, IP) or spiperone HCl (80 μg/kg, IP). Rats received SCH 23390 HCl (0.30 mg/kg, IP) and/or spiperone 60 minutes before observation. SKF 38393 was administered 10 minutes before observation.

Statistics

A one-way or two-way analysis of variance (ANOVA), followed by the post-ANOVA test of Newman-Keuls, was used to determine statistically significant differences between groups.

RESULTS

Effect of Neonatal 6-OHDA Treatment on Induction of Oral Activity in Rats

Spontaneous oral activity in control and 6-OHDA-lesioned rats was low. Following saline treatment, rats of either group had less than 5 oral movements during a 1-h observation period (Fig. 1). After a challenge dose of SKF 38393 HCl (3.0 mg/kg, IP, 10 min), however, the number of oral movements was increased to 14.3 ± 1.9 in the saline group, and to 43.4 ± 10.5 in the 6-OHDA group of rats ($p<0.005$). Spiperone HCl (80 μg/kg, IP, 60 min) had a similar effect, increasing the number of oral movements to 11.8 ± 2.9 and 55.0 ± 7.7 in the control and 6-OHDA groups, respectively ($p<0.005$). These findings replicate the recent observation that oral responses to a D1 receptor agonist and D2 receptor antagonist are potentiated in rats treated neonatally with 6-OHDA (10).

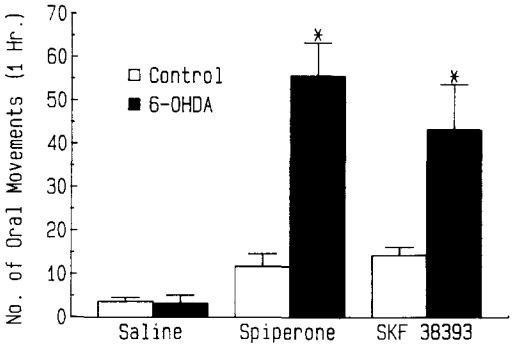

FIG. 1. Effect of neonatal 6-OHDA HBr treatment (200 μg ICV, 3 days after birth) on SKF-38393- and spiperone-induced oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes over a 60-minute period, beginning 10 minutes after SKF 38393 hydrochloride (3.0 mg/kg, IP) or 60 minutes after spiperone hydrochloride (80 μg/kg, IP). Each group is the mean of 4 to 8 rats. *Indicates $p<0.005$ vs. respective vehicle control groups.

Time Course of Spiperone-Induced Oral Activity in Rats

To determine the appropriate time interval for observing rats, a time-course curve of oral activity was plotted at 10-min intervals, beginning 60 min after spiperone HCl (80 μg/kg, IP). The number of oral movements in the control group was reasonably constant for the first 5 sessions (60 to 100 min). In the 6-OHDA group, there was a marked decline in oral activity, starting after the 90-min observation time (Fig. 2). Although not shown, a similar progressive decline in oral activity was observed at the other doses of spiperone.

The overall incidence of oral activity after spiperone was greater in the 6-OHDA vs. saline group of rats ($p<0.001$). At each of the individual times, except at 100 min after spiperone, the incidence of oral activity was greater in the neonatal 6-OHDA vs. saline group ($p<0.005$ at 60–90 min; $p<0.05$ at 110 min).

Dose-Response Study of Spiperone-Induced Oral Activity

In order to determine the optimal dose of spiperone for induction of the oral response, a series of doses of spiperone was administered to rats. As shown in Fig. 3, the oral response to spiperone was elevated at the 80 and 160 μg/kg doses in the 6-OHDA vs. the control group of rats ($p<0.05$). The greatest incidence of oral activity occurred at the 80 μg/kg dose of spiperone HCl in the 6-OHDA group of rats, 46 ± 5.5 oral movements in a 30-min period (i.e., 4 observation times). Doubling this dose resulted in a decline in oral activity to about half that level. Only the 80 μg/kg dose of spiperone HCl increased the

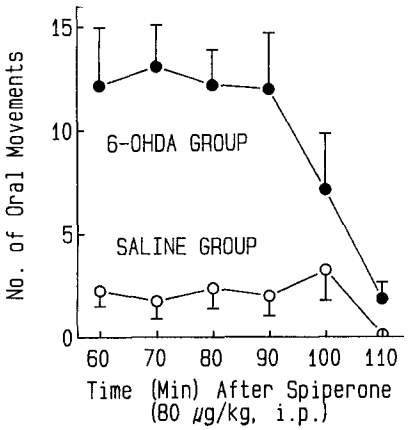

FIG. 2. Time course of spiperone-induced oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, starting 60 minutes after spiperone hydrochloride (80 µg/kg, IP). Each group is the mean of 7 or 8 rats. The number of oral movements in 6-OHDA-treated vs. control rats is different from 60 to 90 min, inclusive ($p<0.005$) and at 110 min ($p<0.05$).

incidence of oral activity in the saline control group of rats ($p<0.05$).

Time Course of SKF 38393-Induced Oral Activity in Rats

To determine the appropriate time for observing SKF 38393-induced oral activity, a time-course needed to be constructed. It was found, for both the control and 6-OHDA groups of rats, that oral activity did not subside during the 1-hour observation period following SKF 38393 HCl treatment (1.0 mg/kg, IP, 10 min before 1st observation; Fig. 4). At the other doses of SKF 38393 HCl, the findings were similar. In subsequent studies, a 1-hour observation period was used.

Dose-Response Study of SKF 38393-Induced Oral Activity

To determine the optimal doses of SKF 38393 for inducing oral activity, a dose-response curve was constructed. In the saline control group, SKF 38393 HCl at a dose of 0.10 mg/kg and higher resulted in only a slight increase in oral activity, as many as 14.3 oral movements in 1 h at the 0.10 and 3.0 mg/kg doses, and these increases were statistically significant ($p<0.01$; Fig. 5). In the 6-OHDA group, the threshold dose of SKF 38393 HCl was 0.03 mg/kg, with oral activity increasing to 15 ± 2.9 movements ($p<0.01$). At higher doses of SKF 38393, there were about 40 oral movements during the session ($p<0.005$). In subsequent studies, a 1.0 mg/kg dose of SKF 38393 HCl was used.

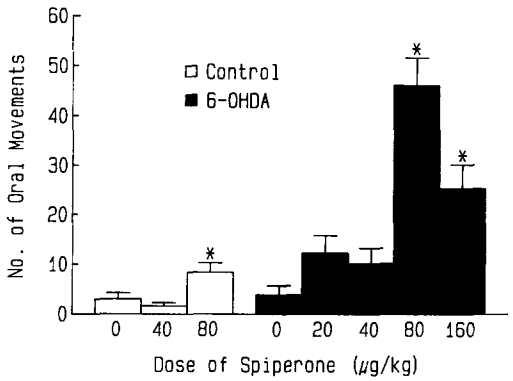

FIG. 3. Dose-response relationship for spiperone-induced oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, in the interval 60 to 90 minutes after spiperone hydrochloride (20 to 160 µg/kg, IP; total of 4 observations). Each group is the mean of 5 to 8 rats. *Indicates $p<0.05$ vs. control rats.

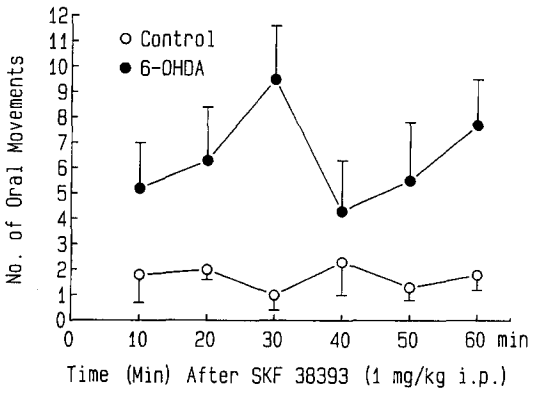

FIG. 4. Time course of SKF-38393-induced oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, starting 10 minutes after SKF 38393 hydrochloride treatment (1.0 mg/kg, IP). Each group is the mean of 4 to 6 rats. The number of oral movements in 6-OHDA vs. control rats is different ($p<0.001$, ANOVA; at 30 and 60 min, $p<0.005$, Newman-Keuls).

Effect of Combined D1 Receptor Agonist and D2 Receptor Antagonist Treatments

This study was conducted to determine whether combined treatments with a DA D1 receptor agonist and D2 receptor antagonist would produce a potentiated oral response. Rats were injected with spiperone HCl (80 µg/kg, IP, 60 min) and SKF 38393 HCl (1.0 mg/kg, IP, 10 min) and were then observed for

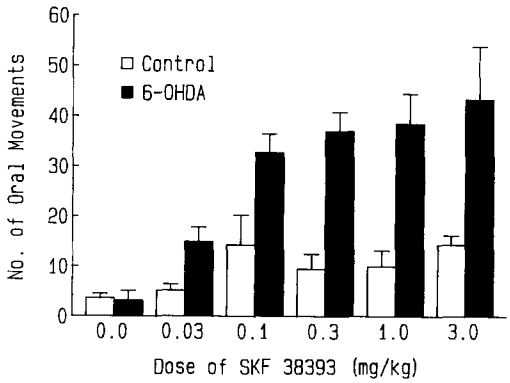

FIG. 5. Dose-response relationship for SKF-38393-induced oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, starting 10 minutes after SKF 38393 hydrochloride (0.03 to 3.0 mg/kg, IP). Each group is the mean of 4 or 6 rats. The number of oral movements in 6-OHDA vs. control rats is different at each respective dose of SKF 38393 ($p<0.01$).

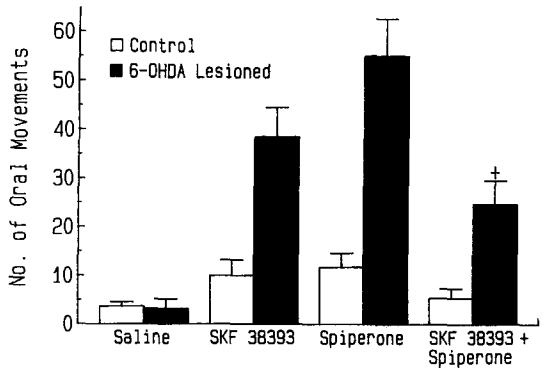

FIG. 6. Effect of combined SKF 38393 and spiperone treatments on induction of oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, for 60 minutes, beginning 10 minutes after SKF 38393 hydrochloride (1.0 mg/kg, IP) and 60 minutes after spiperone hydrochloride (80 μg/kg, IP). Each group is the mean of 4 to 11 rats. SKF 38393 and spiperone, alone or in combination, induced a greater number of oral movements in 6-OHDA vs. respective control rats ($p<0.005$). +Indicates $p<0.01$ vs. the group treated with spiperone alone.

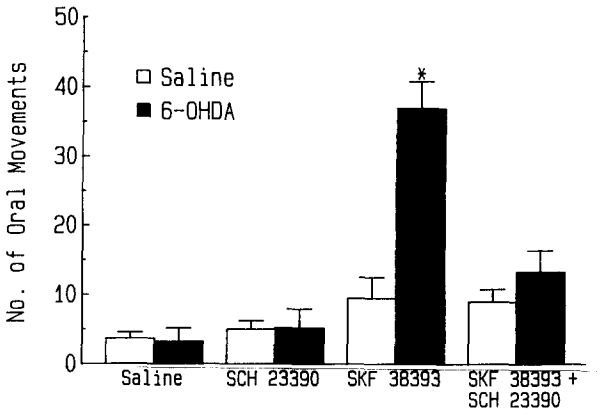

FIG. 8. Attenuation of SKF-38393-induced oral activity in rats by SCH 23390. Numbers of oral movements were determined for one minute every 10 minutes, for 60 minutes, starting 10 minutes after SKF 38393 hydrochloride (0.30 mg/kg, IP) and 60 minutes after SCH 23390 hydrochloride (0.30 mg/kg, IP). Each group is the mean of 4 to 6 rats. *Indicates $p<0.005$ vs. other 6-OHDA groups.

60 min (Fig. 6). In the 6-OHDA group of rats that were treated with SKF 38393 alone, there were 38.5 ± 6.0 oral movements in the session ($p<0.005$ vs. saline treatment). In this same group, when treated with spiperone alone, there were 55.0 ± 7.7 oral movements ($p<0.005$ vs. saline treatment). A combination of these agents resulted in a decline in the incidence of oral activity in the 6-OHDA group of rats to 24.7 ± 4.9 oral movements ($p<0.01$ vs. SKF 38393 or spiperone treatments). Thus an attenuation of oral activity was produced by combining the D1 receptor agonist and D2 receptor antagonist treatments. A similar trend with the combined treatments was also seen in the control group of rats.

Effect of Quinpirole, a D2 Receptor Agonist, on Oral Activity

In an attempt to determine how sensitivity of different types of DA receptors might be altered by neonatal 6-OHDA treatment, induction of oral activity by the DA D2 receptor agonist, quinpirole, was studied. Rats were treated with quinpirole HCl (0.10 mg/kg, IP, 10 min before first observation) and were then observed for 60 min (Fig. 7). It was found that quinpirole increased the incidence of oral activity in both the control and 6-OHDA groups of rats ($p<0.005$), but that there was no difference in the numbers of oral movements between control and 6-OHDA groups. Determination of the number of oral movements was confounded by quinpirole-induced eating in both intact and 6-OHDA-lesioned rats. Eating occurred, on average, about once in each 1-minute observation period for both the intact and 6-OHDA-lesioned rats.

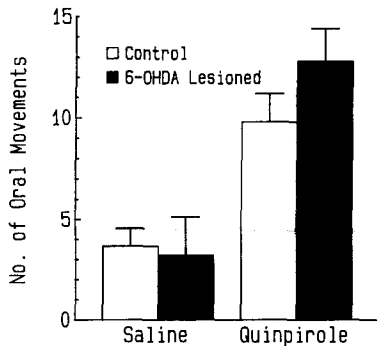

FIG. 7. Effect of quinpirole on induction of oral activity in rats. Numbers of oral movements were determined for one minute every 10 minutes, for 60 minutes, starting 10 minutes after treatment with quinpirole hydrochloride (0.10 mg/kg, IP). Each group is the mean of 5 to 11 rats. Quinpirole increased the incidence of oral activity in control and 6-OHDA groups, respectively ($p<0.05$, $p<0.005$, respectively), but there was no difference in 6-OHDA vs. control group following quinpirole.

Effect of Combined D1 Receptor Agonist and D1 Receptor Antagonist Treatments

To determine whether a DA D1 receptor antagonist would attenuate the oral response of rats to a D1 receptor agonist, rats

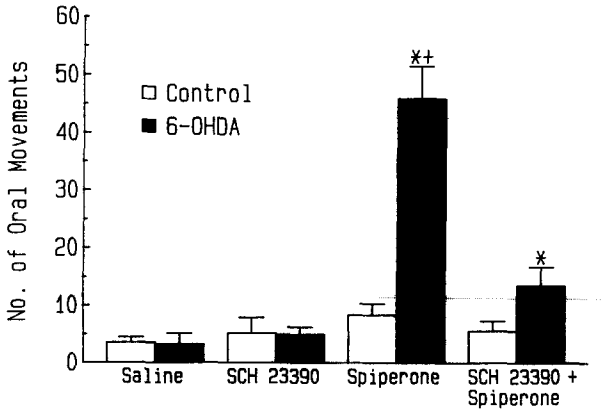

FIG. 9. Attenuation of spiperone-induced oral activity in rats by SCH 23390. Numbers of oral movements were determined for one minute every 10 minutes, for 30 minutes, starting 60 minutes after spiperone hydrochloride (80 μg/kg, IP) or SCH 23390 hydrochloride (0.30 mg/kg, IP). Each group is the mean of 5 to 11 rats. *Indicates $p<0.001$ vs. respective saline control group. +Indicates $p<0.005$ vs. 6-OHDA groups treated with SCH 23390 alone or with SCH 23390 plus spiperone.

were treated with SCH 23390 HCl (0.30 mg/kg, IP) 1 h before SKF 38393 HCl (0.30 mg/kg, IP). As shown in Fig. 8, SCH 23390 attenuated the action of SKF 38393 ($p<0.005$), indicating that SKF-38393-induced oral activity is a D1-receptor-mediated event.

Effect of Combined D1 and D2 Receptor Antagonist Treatments

To determine whether the markedly enhanced oral response to spiperone in the 6-OHDA group of rats might be due to an indirect effect on D1 receptors, rats were given combined treatments with spiperone HCl (80 μg/kg, IP) and SCH 23390 HCl (0.30 mg/kg, IP) 1 h before observation. As shown in Fig. 9, SCH 23390 attenuated the action of spiperone ($p<0.005$), indicating that the spiperone action is mediated through D1 receptors.

DISCUSSION

In a previous study, it was observed that rats treated neonatally with 6-OHDA were more sensitized to D1 receptor agonist- and D2 receptor antagonist-induction of oral activity (10). Those findings were confirmed and expanded in the present study.

An increase in oral activity is observed after a dose of only 0.03 mg/kg of SKF 38393, indicating a true supersensitization of the oral response of neonatal 6-OHDA-treated rats. A plateau was found for the dose-response effect of SKF 38393, with maximal oral activity being produced by doses of SKF 38393 of 0.10 to 3.0 mg/kg.

The dose-response curve to spiperone was bell-shaped, with the optimal dose being 80 μg/kg. The difference in incidence of oral movements after spiperone in the 6-OHDA-treated vs. control rats indicates that supersensitization occurs to this agent in the lesioned rats.

The D1 receptor antagonist, SCH 23390, attenuated the response of neonatal 6-OHDA-treated rats to either SKF 38393 or spiperone. This finding indicates that enhanced oral responses in the lesioned rats is due primarily to supersensitization of D1 receptors. That the spiperone effect is mediated through activation of D1 receptors in intact rats was shown by Rosengarten and coworkers (16). The doses of SCH 23390 in this study are similar or identical to those used in other studies to specifically attenuate oral activity responses to a D1 agonist (12,16); to attenuate D1 agonist-induced behaviors (3, 4, 6); and to impair the development of striatal D1 receptors (11,17).

In our studies, the combined treatment with spiperone and SKF 38393 did not increase the oral response. In contrast, there was a lessening of the response. In effect, since there was an optimal dose for spiperone, the combination appears to have shifted the response to the right on the bell-shaped dose-response curve for spiperone, thereby resulting in an attenuated effect.

Supersensitization appears to be restricted to D1 receptors in the neonatal 6-OHDA group of rats, since the response to a low dose of quinpirole was similar to that of the control group of rats.

Because much of the enhanced stereotypic and locomotor activity of neonatal 6-OHDA-treated rats occurs only after L-dihydroxyphenylalanine (L-dopa) treatment and/or SKF 38393 treatments (2–4), the exaggerated behaviors are known to be the consequence of "priming." That is, subsequent treatments with an agonist produce increasingly greater behavioral effects. Moreover, it has been found that these neonatal 6-OHDA-treated rats may be homologously or heterologously primed. That is, treatments with a D1 or D2 agonist, respectively, will increase subsequent responses to a D1 agonist (6). However, the increased oral activity in the neonatal 6-OHDA-treated rats does not appear to represent a primed event, since these rats displayed an increased oral response on their first exposure to SKF 38393. Also, the repeated treatments with SKF 38393, which were incurred during construction of the dose-response curve, did not increase a later response to a given dose of SKF 38393. Therefore, the enhanced oral activity of neonatally lesioned rats apparently represents a supersensitization that resides in the D1 receptor after the lesion, independent of priming phenomena.

In the earlier report on enhanced oral activity after the neonatal 6-OHDA lesion, rats were studied at about 2½ months of age (10). In the present study, rats are observed up to 8 months of age. The enhanced oral response seen in rats of this age indicates that the receptor-associated supersensitization is a long-lived event.

It is felt that simple supersensitization of the D1 receptor may not be the singular event to account for the enhanced induction of oral activity in the 6-OHDA-lesioned rats. First, the interactive nature of D1 and D2 receptors in oral activity is well documented (1, 15, 21, 22). There is a question as to whether acute oral dyskinesias in rats are associated with D1 receptor hyperfunction during a concurrent D2 receptor hypofunction (18). Second, in rats that are exquisitely sensitive to D1 agonists, following neonatal 6-OHDA treatment plus daily SKF 38393 treatments during postnatal development, the D1 agonist challenge in adulthood does not increase the number of oral movements (unpublished observation).

The biochemical change responsible for the altered oral response in 6-OHDA-lesioned rats has not been determined. In the previous study, however, it was shown that the number and affinity of D1 and D2 receptors were not altered, even though endogenous DA content was markedly reduced. The present series of studies helps to identify the altered DA receptor responses that occur in those rats with greatly increased oral activity following neonatal destruction of brain DA-containing fibers. This animal model may be useful in the discovery process of agents that modulate dyskinetic oral activity in assorted human clinical disorders.

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