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RAPID COMMUNICATION

Enhanced Quinpirole Response in Rats Lesioned Neonatally With 5,7-Dihydroxytryptamine

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BRUS, R., A. PLECH AND R. M. KOSTRZEWA. *Enhanced quinpirole response in rats lesioned neonatally with 5,7-dihydroxytryptamine.* PHARMACOL BIOCHEM BEHAV **50**(4) 649-653, 1995.—The ontogenic destruction of dopamine (DA) neurons in rat brain is associated with supersensitization of DA D_1 receptors. This effect is attenuated when rats are cotreated in ontogeny with the serotonin (5-HT) neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT). In an attempt to determine whether 5-HT fibers might have a similar modulatory role on the sensitivity of the DA D_2 receptor complex, we pretreated rats with desipramine HCl (20 mg/kg IP, base), 1 h before the DA neurotoxin, 6-hydroxydopamine (6-OHDA; 134 μg ICV, base) and/or 5,7-DHT (75 μg ICV) and/or vehicle. At about 3 months after birth dose-effect curves for quinpirole-induced oral activity were constructed for each group of rats. We found that quinpirole, an agonist for the DA D_2 receptor complex, produced a dose-related increase in oral activity in all groups of rats. After a 200 μg/kg dose of quinpirole HCl, however, neonatal 5,7-DHT-lesioned rats had a peak oral response of 54.4 ± 5.1 (mean and SEM) vs. 22.6 ± 4.8 for control rats ($p < 0.01$). In neonatal 6-OHDA-lesioned rats this dose of quinpirole increased oral activity to 36.8 ± 5.8 oral movements ($p < 0.05$ vs. control). In rats lesioned with both 5,7-DHT and 6-OHDA, the oral response was not different from control. The enhanced oral response to quinpirole in 5,7-DHT-lesioned rats was attenuated by spiperone, an antagonist for the DA D_2 receptor complex. These findings are believed to be the first to demonstrate that receptors of the DA D_2 complex become sensitized after ontogenic injury to 5-HT fibers. This effect is opposite to the attenuated sensitivity of DA D_1 receptors in rats with a similar 5-HT lesion.

Serotonin 5,7-Dihydroxytryptamine Supersensitivity Receptors Dopamine 6-Hydroxydopamine Oral activity Quinpirole

THE ONTOGENIC destruction of dopamine (DA) neurons in rat brain is associated with prominent DA D_1 receptor supersensitivity (2-4,15,22,23), as reflected by enhanced DA D_1 agonist-induced locomotor and stereotyped activities, including oral activity. Although not as pronounced, DA D_2 receptor supersensitivity is also observed in these lesioned rats (2-4,24).

As a consequence of the DA fiber denervation of neostriatum by 6-hydroxydopamine (6-OHDA), serotonin (5-HT) fibers sprout and hyperinnervate the neostriatum (1,7,26,29-31). Although the 5-HT receptor antagonist, mesulergine, does not attenuate apomorphine-induced (primarily D_2) activity and DA D_1 agonist-induced stereotyped responses (31), more recent studies indicate that 5-HT systems play an important role in mediating effects of DA systems. For example, the 5-HT receptor antagonist, mianserin, attenuates the enhanced DA D_1 agonist-induced oral activity in neonatal 6-OHDA-lesioned rats. By testing assorted 5-HT agonists and antagonists, it appears that 5-HT_{2C} receptors specifically play the critical role in mediating the actions of a DA D_1 agonist (13).

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[Nomenclature for 5-HT receptors follows the recommendation of the Serotonin Club Nomenclature Committee (16). The 5-HT_{2C} receptor was formerly classified as 5-HT_{1C}.] Also, 5-HT_{2C} receptors become supersensitized in neonatal 6-OHDA-lesioned rats, as reflected by enhanced oral activity responses to the 5-HT agonist, m-chlorophenylpiperazine (m-CPP) (11). In fact, by reducing the extent of DA neuronal damage by varing the dose of 6-OHDA and age of the rat at the time of lesioning, it is possible to sensitize 5-HT receptors, even when DA D_1 receptors are not sensitized (14,21). When 5-HT fibers are largely destroyed during postnatal ontogeny by 5,7-dihydroxytryptamine (5,7-DHT), enhanced oral activity responses to a DA D_1 agonist are no longer present (5). Moreover, when 5-HT fibers are partially destroyed in adult rats that were DA depleted neonatally with 6-OHDA, hyperlocomotor activity is produced (20).

Using quantitative autoradiography, Radja and co-workers have demonstrated that several 5-HT receptor subtypes increase in number by 30 to 60% in the neostriatum of neonatal 6-OHDA-lesioned rats. This includes 5-HT_{1B}, 5-$HT_{1nonA,B}$ and 5-HT_2 receptors. In fact, increased 5-HT_{1B} sites were observed in the substantia nigra and globus pallidum, presumed projection sites of neostriatal neurons (28). The changes may account, at least in part, for enhanced behavioral responses to 5-HT agonists in these rats.

The above series of findings demonstrate that there is as much as a doubling in the number of 5-HT fibers, an approximate 50% increase in the number of 5-HT receptors and a several-fold increase in the sensitivity level of 5-HT receptors in the neostriatum of 6-OHDA-lesioned rats. Because of the apparent modulatory role of these fibers and receptors on the process of DA D_1 receptor supersensitivity, it was of interest to study the effect of a 5-HT fiber lesion on the sensitivity of the DA D_2 receptor complex. The three recognized subtypes of this receptor have high affinity for quinpirole, in the order of $D_3 > D_4 > D_2$ [see (17)]. We will show that a neonatal 5,7-DHT lesion in rats produces enhanced quinpirole-induced oral activity, which is likely to be a reflection of supersensitization of the DA D_2 receptor complex.

METHOD

Timed-pregnant Sprague-Dawley albino rats (Charles River Labs, Research Triangle Park, NC) were housed at 22 ± 1°C under a 12 L : 12 D cycle (lights on at 0700 h) and given free access to food and water. At birth, rat pups from different litters were grouped, then randomly assigned among 8 to 10 different dams. Each reconstituted litter consisted of 10 pups, with approximately equal numbers of males and females.

At 3 days after birth pups were pretreated with desipramine HCl [20 mg/kg, base form, IP; Research Biochemicals Inc. (RBI), Natick, MA], 1 h before saline-ascorbic acid (0.1%) vehicle, 5,7-DHT creatinine sulfate monohydrate complex (75 μg, base form, half in each lateral ventricle; RBI) and/or 6-OHDA HBr (134 μg, base form, half in each lateral ventricle; RBI). This procedure has been described in detail (22). In this study, each litter was comprised of rats of a single treatment. From experience, we have found that this housing produces greater uniformity in body mass within groups and increased growth in lesioned rats. This latter fact is probably related to ease of access to the dam's nipples, since heavier control rats are not competing with the smaller lesioned rats. Rats were weaned at 28 days, then group housed in wire cages. Only males were used in this study.

Oral activity was determined in a quiet, well-ventilated and well-lighted room when rats were between 2 and 4 months of age. Each rat was first acclimated in a clear plastic cage (48 × 26 × 36 cm) with sawdust bedding, for a period > 1 h. A single IP injection of quinpirole HCl (50-400 μg/kg, salt

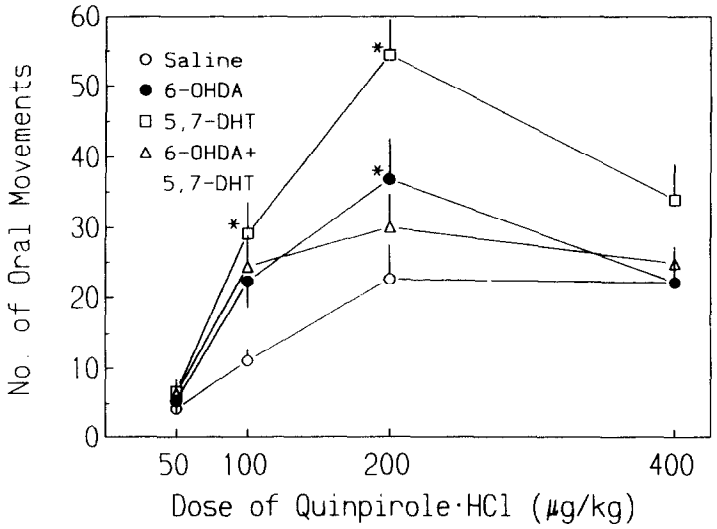

FIG. 1. Dose-effect curves for quinpirole-induced oral activity in adult rats. Rats were treated at 3 days after birth with bilateral ICV injections of vehicle, 6-OHDA (134 μg) and/or 5,7-DHT (75 μg), following desipramine pretreatment (20 mg/kg IP, 1 h). Each rat was observed for 1 min every 10 min over 60 min, starting 10 min after challenge with quinpirole HCl or saline. Numbers of oral movements were recorded (ordinate) for each dose of quinpirole HCl (abscissa). Each group is the mean of seven to nine rats. *$p < 0.05$, vs. same treatment in the saline group.

form; RBI) or saline vehicle was administered 10 min before observation. Numbers of oral movements were counted for 1 min every 10 min during a 60-min observation period. Oral activity represents the number of chewing movements occurring during the cumulative 6-min session. This procedure has been described in detail (22).

To assess whether DA D_2 and other receptors might be involved in the action of quinpirole, the oral response to quinpirole was determined 1 h after IP administration of a variety of antagonists, which included spiperone HCl (0.1 mg/kg) (DA D_2 complex), SCH 23390 HCl [R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine] (0.3 mg/kg) (DA D_1), mianserin HCl (1.0 mg/kg) (5-HT_2), and scopolamine HCl (0.1 mg/kg) (muscarinic). In one instance, the DA D_1 agonist SKF 38393 HCl [(±)-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol] (1.0 mg/kg) was administered simultaneously with quinpirole. Doses in the article refer to the salt form of agents, unless indicated otherwise. The same rats were used for constructing dose-effect curves and for testing the effects of the different agonists and antagonists on quinpirole-induced oral activity.

The initial effect of quinpirole was determined with the observer being blinded. However, because of markings and size differences between intact and lesioned rats, the main study was not able to be done in a blinded manner. The observer had extensive experience with observations of oral activity and stereotyped behaviors in rats. The results were subsequently verified by another experienced observer who was blinded at the initial test session. In this study, oral activity represented chewing sequences that were vacuous (not directed onto any physical matter) and nonvacuous (27).

An analysis of variance (ANOVA), followed by the post-ANOVA test of Bonferroni, was used to test for statistically significant effects of quinpirole in the different groups. A Dunnett's test was used to determine the ability of antagonists to attenuate quinpirole effects.

RESULTS AND DISCUSSION

In all groups of rats, quinpirole HCl produced a dose-related increase in oral activity. At the lowest quinpirole HCl dose, 50 μg/kg, the oral response in all groups was virtually identical, $F(3, 28) = 0.57$, $p = 0.64$, and similar in magnitude to the effect after acute saline treatment (not shown). The peak oral effect occurred at the dose of 200 μg/kg IP (Fig. 1). The major finding in this study is the marked increase in quinpirole effect in rats lesioned neonatally with 5,7-DHT. Oral activity in the 5,7-DHT-lesioned rats increased approximately 2.5-fold vs. controls after the 100 μg/kg, $F(3, 28) = 4.12$, $p = 0.015$, $p < 0.05$, Bonferroni test, and 200 μg/kg, $F(3, 28) = 6.37$, $p = 0.002$, $p < 0.01$, Bonferroni test, doses of quinpirole HCl. Although there was a 62% increase in oral activity in neonatal 6-OHDA-lesioned rats following the 200 μg/kg dose of quinpirole HCl ($p < 0.05$), this same quinpirole treatment did not produce an increased response in rats lesioned neonatally with both 5,7-DHT and 6-OHDA.

Spiperone HCl (0.1 mg/kg), an antagonist for the DA D_2 receptor complex, completely attenuated the action of quinpirole ($p < 0.001$) (Table 1). Similarly, the DA D_1 antagonist SCH 23390 HCl (0.3 mg/kg) and the muscarinic antagonist scopolamine HCl (0.1 mg/kg) attenuated the effect of quinpirole. The DA D_1 agonist SKF 38393 HCl (1.0 mg/kg) partially attenuated the action of quinpirole (26.0 ± 5.2 oral movements) in the 5,7-DHT group, but not in the control group of rats (not shown).

TABLE 1

EFFECT OF RECEPTOR ANTAGONISTS ON QUINPIROLE-INDUCED ORAL ACTIVITY IN INTACT AND 5,7-DHT-LESIONED RATS

	Neonatal Treatment	
Acute Treatment	Vehicle	5,7-DHT
Saline		
+ Saline	2.8 ± 0.8	3.6 ± 1.7
+ SCH 23390	1.9 ± 0.9	0.1 ± 0.1*
+ Spiperone	3.9 ± 1.6	1.1 ± 0.6
+ Mianserin	3.5 ± 1.3	1.6 ± 1.0
+ Scopolamine	3.0 ± 1.0	3.7 ± 2.4
Quinpirole		
+ Saline	28.5 ± 6.3	44.7 ± 4.7
+ SCH 23390	8.1 ± 1.4†	6.9 ± 1.3†
+ Spiperone	1.6 ± 1.0†	1.3 ± 0.3†
+ Mianserin	21.9 ± 5.4	40.3 ± 6.6
+ Scopolamine	27.3 ± 3.1	19.4 ± 4.7†

Each value for oral activity is the mean ± SEM of eight rats. Antagonists were administered 1 h before observation; quinpirole, 10 min before observation.

*$p < 0.05$, †$p < 0.001$ vs. saline + saline or quinpirole + saline group.

These findings suggest that the neonatal destruction of 5-HT fibers by 5,7-DHT produces supersensitization of the DA D_2 receptor complex. Quinpirole is an agonist for each of the subtypes of the D_2 complex in the sequence D_3 ($K_i = 5.1$ vs. [^{125}I]iodosulpride) > D_4 ($K_i = 46$) > D_2 ($K_i = 576$). When administered to rats in a dose of 200 μg/kg or less, quinpirole appears to have effects mainly at DA D_3 receptors, as reflected by yawning behavior (6,18,19) and associated reduction in neurally released DA (6). When used in a higher dose range, quinpirole would affect D_4 and, ultimately, D_2 receptors. Because of the dose range of quinpirole in the present study, it is possible that the oral activity responses are mediated by DA D_3 receptors. However, because of (a) the complexities inherent in pharmacokinetic aspects related to distribution of quinpirole in vivo and (b) known integration of multineural inputs for behavioral activities, it is possible that D_2 and D_4 receptors are involved in the actions of quinpirole. Spiperone, the DA receptor antagonist that attenuated the effect of quinpirole, has similar affinity for the D_2, D_3, and D_4 receptors (17).

Because the quinpirole effect was partially blocked by scopolamine, it is likely that the neural pathway via the DA D_2 receptor complex involves cholinergic neurons—as per DA D_1 agonist-induced oral activity (25). However, unlike the DA D_1 pathway, which is mediated via 5-HT systems (5,13), the DA D_2 pathway apparently does not utilize 5-HT fibers because mianserin did not attenuate the effect of quinpirole. A complex modulatory role of DA D_1 receptors on the DA D_2 effect is suggested by the attenuated responses to quinpirole after either SCH 23390 or SKF 38393.

In a parallel study, we found that this same dose of 5,7-DHT eliminated DA D_1 receptor supersensitivity and enhanced m-CPP-induced (5-HT_{2C}) oral activity while reducing neostriatal 5-HT content by 90% (5). Therefore, DA D_1 and D_2 receptors are seemingly modulated in opposite ways by 5-HT fibers.

Sensitization of the DA D_2 receptor complex, as found in

neonatal 6-OHDA-lesioned rats in this study, would coincide with sensitization of DA D_1 receptors, as found in similarly treated rats in earlier studies (22,23). Similarly, in rats lesioned neonatally with both 6-OHDA and 5,7-DHT, there is attenuation of DA D_1 (5) and DA D_2 receptors (present study). In all of our studies to date, the 134 μg ICV dose of 6-OHDA has consistently produced 98–99% depletion of DA in the neostriatum (5,12–14,21).

The mechanisms underlying the influence of 5-HT fibers on DA D_1 and D_2 receptor complexes are not known. In an earlier study, mianserin was found to attenuate DA D_1 agonist-induced oral activity. However, a DA D_1 antagonist did not attenuate the 5-HT oral activity effect (13). This implies that DA fibers acted in series with downstream 5-HT fibers. In a similar manner, using a series of agonists and antagonists, it was found that cholinergic systems appear to be downstream from 5-HT fibers that are involved in the genesis of oral activity (25). In this light, it is not unexpected that 5-HT fibers might have a powerful modulatory role on the sensitivity level of receptors of other neurochemical systems.

Gerfen and co-workers have shown that neostriatal neurons with DA D_1 receptors project predominately to the substantial nigra, while neostriatal neurons with DA D_2 receptors project predominately to the globus pallidum (8,9). Also, striatonigral neurons are predominately substance P- or dynorphin-containing neurons, while striatopallidal neurons are predominately enkephalin-containing neurons (9). This difference in the topographical distribution of neostriatal neurons with D_1 vs. D_2 receptors may relate to the subsensitizing of D_1 receptors and supersensitizing of D_2 receptors following 5-HT fiber lesions.

In summary, neonatal 5,7-DHT treatment of rats is associated with enhanced quinpirole-induced oral activity in adulthood. Coincident 6-OHDA treatment is associated with attenuation of the enhanced effect of quinpirole. We believe that these changes are indicative of a prominent modulatory role that 5-HT fibers exert on the sensitivity level of DA D_1 receptors (early studies) and D_2 receptors (this study).

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