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RAPID COMMUNICATION

Supersensitized Oral Responses to a Serotonin Agonist in Neonatal 6-OHDA-Treated Rats

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GONG, L. AND R. M. KOSTRZEWA. *Supersensitized oral responses to a serotonin agonist in neonatal 6-OHDA-treated rats.* PHARMACOL BIOCHEM BEHAV 41(3) 621-623, 1992.—Neonatal 6-hydroxydopamine (6-OHDA) treatment of rats is associated with supersensitization of the dopamine D_1 agonist induction of oral activity. The present study was conducted to determine whether induced oral responses to serotonin (5-HT) agonists would be similarly altered in this rat model. At 3 days after birth, rats received desipramine HCl (20 mg/kg, IP) 1 h before 6-OHDA HBr (100 μg in each lateral ventricle) or saline-ascorbic acid (0.1%) vehicle. At approximately 9 mo, rats were challenged with the mixed 5-HT_{1C} and 5-HT_2 receptor agonist, *m*-chlorophenylpiperazine diHCl (*m*-CPP 2HCl; 0.30–6.0 mg/kg, IP) and were then observed for 1 min every 10 min over a 60-min period. *m*-CPP induced oral activity in both the vehicle and 6-OHDA groups, with the responses of the 6-OHDA group being much greater. An *m*-CPP dose of 3.0 mg/kg produced a maximal response of 63.6 ± 3.2 oral movements in the 6-OHDA group. A bell-shaped response curve was obtained, with lower and higher doses of *m*-CPP producing less of an effect. Attenuation of the *m*-CPP-induced response by the 5-HT receptor antagonist, mianserin HCl (1.0 mg/kg, IP, 30 min before *m*-CPP), indicates that the *m*-CPP effect is receptor mediated. These findings demonstrate that neonatal 6-OHDA treatment produces ontogenic long-lived supersensitization of a 5-HT receptor system in rats.

6-Hydroxydopamine 5-HT receptor Oral dyskinesia *m*-Chlorophenylpiperazine Supersensitization Ontogeny

IT was recently reported that a dopamine D_1 receptor agonist (SK&F 38393) and D_2 receptor antagonist (spiperone) produced enhanced oral activity in rats treated neonatally with the neurotoxin 6-hydroxydopamine (6-OHDA) (8). This enhanced induction of oral activity occurred in the absence of a change in B_{max} and K_d of both D_1 and D_2 receptors in the striatum despite a reduction in striatal DA content of >95%. It was additionally found that there was an overt supersensitization of D_1 receptors that mediated the behavioral response to SK&F 38393 and that a D_1 receptor antagonist would attenuate the response to both SK&F 38393 and spiperone (7).

It is well known that D_1 receptors mediate a variety of enhanced stereotyped and locomotor responses to dopamine agonists in rats lesioned as neonates with 6-OHDA (2–5). However, despite an increase in striatal serotonin (5-HT) content (2,12) attendant with 5-HT fiber hyperinnervation of the striatum of the neonatal 6-OHDA-lesioned rats (1,11), there has been no distinct behavioral change attributable to the 5-HT system in these rats (14).

Since the 5-HT agonist, *m*-chlorophenylpiperazine (*m*-CPP), was recently reported to affect oral activity in rats (13), we felt that this agent would represent a reasonable means of testing whether 5-HT receptor-mediated responses might be sensitized in neonatal 6-OHDA-treated rats. We report that there is an enhanced oral response to *m*-CPP in those rats treated neonatally with 6-OHDA.

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 allowed free access to food and water. Pups were pretreated at 3 days after

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birth with desipramine HCl (20 mg/kg, IP, base form, 1 h; Sigma Chemical Co., St. Louis, MO), followed by 6-OHDA HBr (100 μg in each lateral ventricle; Regis Chemical Co., Chicago, IL) or saline-ascorbic acid (0.1%) vehicle. This procedure has been described in detail (7). Rats were weaned at 28 days and group housed by sex in wire cages. In this study, only females were used. It was subsequently determined that there is no sex difference in the oral activity response to *m*-CPP.

At about 9 months from birth, each rat was challenged with a single dose of *m*-CPP 2HCl (0.30–6.0 mg/kg, IP; Sigma) or vehicle. Animals were observed once a min every 10 min over a 60-min period. Numbers of oral movements were counted. This procedure has been described in detail (7). To test for 5-HT receptor involvement in the *m*-CPP action, some rats were pretreated with mianserin HCl (1.0 mg/kg, IP, 30 min; Sigma). Oral activity counts were obtained by a single experienced observer aware of the treatment grouping of rats. It was previously established that the same effect of the agonist is obtained when the study is "blinded."

An analysis of variance (ANOVA) was used to test for differences between groups, followed by the posthoc ANOVA test of Student Newman-Keuls.

RESULTS AND DISCUSSION

When adult rats were treated with *m*-CPP, a mixed 5-HT_{1C} and 5-HT_2 receptor agonist (10), there was a dose-related increase in oral activity in both control and neonatal 6-OHDA-treated rats (Fig. 1). In the control group, a maximal response of 18.3 ± 2.5 (mean ± SEM) oral movements was produced by an *m*-CPP 2HCl dose of 1.0 mg/kg. In the 6-OHDA group, however, the maximal response was 63.6 ± 3.2 oral movements, occurring with an *m*-CPP 2HCl dose of 3.0 mg/kg. At a 6.0 mg/kg dose of *m*-CPP, there were only 29.6 ± 4.8 oral movements in the 6-OHDA group, indicating the bell-shaped dose-effect curve. The basal level of oral activity after a saline injection was greater in the 6-OHDA group,

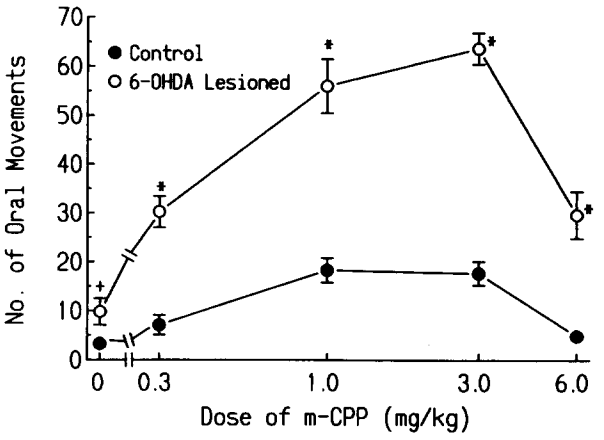

FIG. 1. Dose-response curve to *m*-CPP-induced oral activity in adult rats. Rats were treated at 3 days after birth with vehicle or 6-OHDA HBr (100 μg, salt form, in each lateral ventricle). Each rat was observed for 1 min every 10 min over 60 min, starting 10 min after challenge with *m*-CPP or saline. Numbers of oral movements were recorded (ordinate) for each dose of *m*-CPP 2HCl (abscissa). Each group is the mean of six or seven rats. *$p < 0.001$ vs. vehicle group challenged with the same dose of *m*-CPP; +$p = 0.024$ vs. saline group.

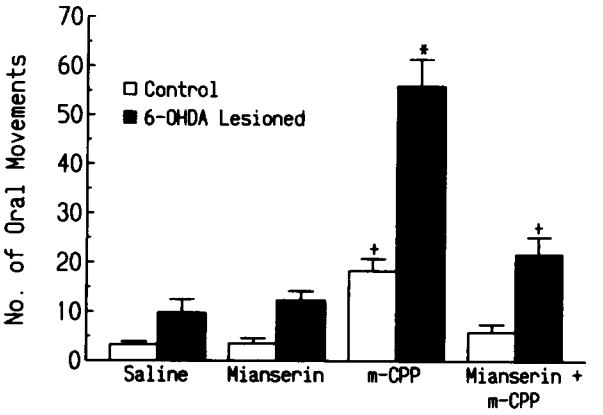

FIG. 2. Attenuation of *m*-CPP-induced oral activity in adult rats by mianserin. Rats were treated neonatally with 6-OHDA or vehicle at 3 days after birth and were observed as in Fig. 1. Half the rats were pretreated with mianserin HCl (1.0 mg/kg, IP) 30 min before a challenge dose of *m*-CPP 2HCl (3.0 mg/kg, IP) or vehicle. Each group is the mean of six or seven rats. *$p < 0.001$ vs. other groups; +$p < 0.05$ vs. respective control group treated with both mianserin HCl and *m*-CPP 2HCl.

$F(1,11) = 6.79, p = 0.024$. At each dose of *m*-CPP, the oral activity response of the 6-OHDA group of rats was greater than that of the vehicle control group: for *m*-CPP 2HCl, 0.3 mg/kg, $F(1,11) = 40.3$, $p < 0.001$; for *m*-CPP 2HCl, 1.0 mg/kg, $F(1,11) = 42.8$, $p < 0.001$; for *m*-CPP 2HCl, 3.0 mg/kg, $F(1,12) = 131.6$, $p < 0.001$; for *m*-CPP 2HCl, 6.0 mg/kg, $F(1,12) = 26.2, p < 0.001$.

Mianserin HCl (1.0 mg/kg, IP), an antagonist with mixed 5-HT_{1C} and 5-HT_2 receptor affinity, attenuated the response to *m*-CPP in both the control group, $F(3,24) = 19.55$, $p < 0.001$, and 6-OHDA group, $F(3,21) = 32.82$, $p < 0.001$ (Fig.2). In separate studies, it was determined that ketanserin, a 5-HT_2 receptor antagonist, did not attenuate the response to *m*-CPP. Nevertheless, at this time there is no specific agonist or antagonist for 5-HT_{1C} receptors (10) so it cannot be stated with certainty that this is the receptor responsible for the effect of *m*-CPP.

In previous studies of the 5-HT system in neonatal 6-OHDA-treated rats, it was found that 5-HT fibers apparently were not responsible for altered locomotor and stereotyped responses to dopamine agonists (14). Also, the sprouted 5-HT fibers did not seem to retain an inhibitory control on striatal acetylcholine-containing fibers (6). The important finding in this report is that there is a 5-HT receptor system that becomes sensitized in the neonatal 6-OHDA-treated rats. At this time, it cannot be stated that this is related to sprouted 5-HT fibers that hyperinnervate rostral striatum of the neonatal 6-OHDA-lesioned rats (1,9,12,14). However, the identification of a 5-HT neurochemical system in dyskinetic oral activity signals the possibility that antagonists for one or more subtypes of 5-HT receptors might represent another approach to treat tardive dyskinesia or other dyskinetic movement disorders in humans.

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