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RAPID COMMUNICATION

Ontogenic Homologous Supersensitization of Quinpirole-Induced Yawning in Rats

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KOSTRZEWA, R. M. AND R. BRUS. *Ontogenic homologous supersensitization of quinpirole-induced yawning in rats.* PHARMACOL BIOCHEM BEHAV **39**(2) 517–519, 1991.—Yawning in male rats is a behavior that may be induced by a group of dopamine receptors when low doses of dopamine-receptor agonists are administered. To determine whether agonist treatments during postnatal development could produce a long-lived supersensitization of these dopamine receptors, rats were treated daily for the first 28 days from birth with quinpirole HCl (3.0 mg/kg/day, IP), an agonist that acts at D2 and D3 receptors. At 8 to 10 weeks from birth the dose-effect curve for quinpirole-induced yawning demonstrated that a supersensitization of dopamine receptors for yawning behavior had occurred. Yawning at the optimal dose of quinpirole HCl (100 μg/kg, IP) was increased 2-fold. The B_{max} and K_d for D2 receptor binding in rat striatum were unaltered in this group of rats. These findings indicate that dopamine receptors can be ontogenically "primed" or supersensitized, and that the phenomenon apparently is not related to changes in striatal D2 receptor binding characteristics.

Yawning Dopamine receptors Homologous priming Quinpirole Receptor supersensitization Ontogeny

YAWNING is a behavior that can be induced by a variety of substances, including dopamine D2 receptor agonists and mixed D1:D2 agonists (5, 10, 16, 18, 20). Generally, as the dose of agonist increases, yawning response rate decreases so that a bell-shaped dose-effect curve for the yawning response is typically observed. At least part of the explanation for this effect is that higher doses of agonists induce competing behaviors, including the stereotyped actions that are commonly associated with such agonists. Since there are few competing behaviors with low doses of dopamine receptor agonists, yawning represents a behavior that offers advantages over others when studying the phenomenon of receptor supersensitization.

In rats with lesions of brain dopamine-containing neurons, prolonged dopamine receptor supersensitization can result (2,19). However, other treatments and procedures are associated with temporary changes in dopamine receptor sensitization (1, 6, 7, 11).

Because of the finding that neonatal treatments with dopamine D1 and D2 receptor antagonists produced an impaired development of striatal D1 and D2 receptors respectively (8,15), it was expected that postnatal treatments with a dopamine receptor agonist would increase receptor number and/or alter the sensitivity of the receptor. Also, such an effect was expected to be long-lived, as per those after D1 and D2 antagonist treatments. Yawning was the candidate behavior for demonstrating this effect, because of the reasons described above.

This paper describes the production of a long-lived supersensitization of dopamine receptors that mediate yawning behavior. Although the exact class of dopamine receptor involved with the behavioral event is not known with certainty, it is shown that the binding characteristics of dopamine D2 receptors in the striatum are not altered by these treatments.

METHOD

Timed pregnant Sprague-Dawley albino rats (Charles River Labs, Research Triangle, NC) 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. Starting at birth, rat pups were injected intraperitoneally (IP) daily, for the first 28 days from birth, with quinpirole HCl (3.0 mg/kg/day; salt form) or the saline (0.9%) vehicle. After the last treatment, rats were weaned and group housed by sex in wire cages. At about 8 weeks from birth, rats were placed in individual clear Perspex cages (48 × 26 × 18 cm) in a quiet, well-ventilated and well-lighted room, and were given 30 min to acclimate. Afterwards, each of 4 rats was injected IP with saline vehicle and observed for 60 min, beginning immediately after the injection. At the end of this session, each rat was injected IP with a challenge dose of quinpirole HCl (25, 50, 100 or 200 μg/kg, salt form) and observed for 60 min. Because of markings on the rats the observer was aware of the treatment group of each rat during the test session.

Another group of rats was used to determine the binding status of dopamine D2 receptors in the striatum (3) using teflon on glass homogenization of tissue, to prevent destruction of receptors during this procedure [see (14)]. Eight different concentrations of [^{3}H]spiperone, 25 to 1500 pM, were used for the binding study. Ketanserin (20 nmol) was present in the incubation solution to inhibit binding of the [^{3}H]spiperone ligand to serotonin S2 receptors (9).

An analysis of variance (ANOVA) was used to compare behavioral and biochemical data from treated and control groups of rats. Dunnett's test was subsequently used to compare the effects of each quinpirole dose on yawning behavior, while the post-ANOVA test of Newman-Keuls was used to compare B_{max} and K_d values for striatal D2 receptor binding.

RESULTS AND DISCUSSION

In 8- to 10-week-old male rats that were treated with quinpirole HCl for the first 28 days from birth, the number of yawns was not different from that of the vehicle group during the 60-min interval after an injection of saline. Each group had a mean incidence of yawning in this instance of less than 1 (Fig. 1). A challenge dose of quinpirole increased yawning behavior in both groups of rats. The maximal incidence of yawning in both groups occurred at a dose of quinpirole HCl of 100 μg/kg. However, quinpirole-induced yawning was increased to a much greater extent in the group of rats that was ontogenically primed ($p<0.05$). For this group yawning was greater at each different challenge dose of quinpirole HCl (25 to 200 μg/kg, IP), vs. the vehicle group ($p<0.05$, Fig. 1). The 200 μg/kg dose of quinpirole HCl produced less yawning than the 100 μg/kg dose, indicating the bell-shaped curve previously noted by others for quinpirole-induced yawning in control rats. The total number of yawns induced by the optimal dose of quinpirole (100 μg/kg) in the quinpirole-primed rats (this report) is greater than that observed previously after dopamine agonist treatment of rats (4, 10, 12, 20). In the present study, as in the above cited reports, more than 90% of yawns occurred during the first 30 min after agonist treatment (data not shown). These findings demonstrate that the absolute maximal score for yawning behavior can be enhanced in a specified time frame, thereby providing further evidence for supersensitization of those dopamine receptors that mediate the yawning response.

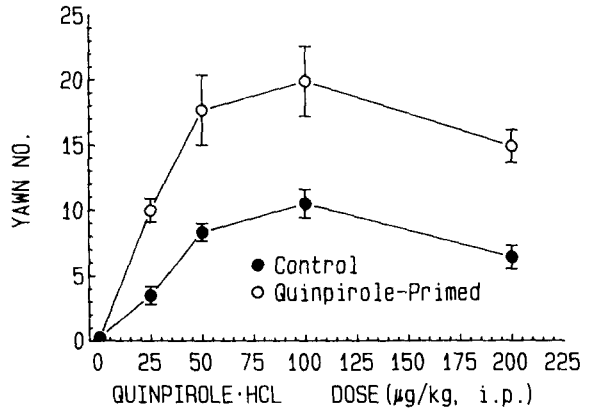

FIG. 1. Quinpirole-induced yawning in rats that were ontogenically primed with quinpirole. Male rats were treated daily for the first 28 days from birth with either quinpirole HCl (3.0 mg/kg/day, IP) or saline (0.9%) vehicle and were studied at 8 to 10 weeks from birth. Each rat was observed for 60 min starting immediately after a single challenge dose of quinpirole. Ordinate indicates numbers of yawns; abscissa indicates challenge dose of quinpirole HCl. Each point is the mean of 6 to 10 rats.

TABLE 1

EFFECT OF ONTOGENIC QUINPIROLE TREATMENTS ON DOPAMINE D2 RECEPTOR BINDING IN RAT STRIATUM*

	D2 Receptor Binding	
Group	B_{max} (fmol/mg tissue)	K_d (pM)
Vehicle	40.8 ± 1.9	93.5 ± 4.2
Quinpirole†	43.2 ± 2.9	98.8 ± 14.3

*Each group is the mean of 5 or 6 rats.

†Quinpirole HCl (3.0 mg/kg/day, IP) was administered to male rats once a day for the first 28 days from birth. Rats received no other treatments and were sacrificed at 2 months of age.

Despite the increased sensitivity of ontogenically primed rats for quinpirole induction of yawning, there was no change in either the B_{max} or K_d for binding to the D2 receptor in rat striatum (Table 1). Therefore, sensitization appears to be a phenomenon not related to the number or affinity of D2 receptors. It is likely that mechanisms associated with generation of second messengers are more relevant in mediating the supersensitive phenomenon (13). However, it is possible that a different class of receptors, namely the D3 subgroup, may be involved in mediating yawning behavior per se, and the supersensitization of this behavior. This view is supported by the fact that quinpirole is 100 times more selective for D3 than D2 receptors (17). Specific agonists and antagonists for the D3 receptor are not yet available to resolve this hypothesis.

In summary, we have produced a rat model with a long-lived supersensitization of dopamine receptors that is associated with yawning behavior. This model may be of value in the study of both behavioral and biochemical processes related to supersensitization of receptors.

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REFERENCES

1. Barone, P.; Tucci, I; Parashos, S. A.; Chase, T. N. Supersensitivity to a D-1 dopamine receptor agonist and subsensitivity to a D-2 receptor agonist following chronic D-1 receptor blockade. Eur. J. Pharmacol. 149:225–232; 1988.
2. Breese, G. R.; Baumeister, A. A.; McCown, T. J.; Emerick, S. G.; Frye, G. D.; Crotty, K.; Mueller, R. A. Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: Relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J. Pharmacol. Exp. Ther. 231:343–354; 1984.

3. Creese, I.; Snyder, S. H. Nigrostriatal lesions enhance striatal ^{3}H-apomorphine and ^{3}H-spiroperidol binding. Eur. J. Pharmacol. 56: 277–281; 1979.
4. Delini-Stula, A.; Hunn, C. Effects of single and repeated treatment with antidepressants on apomorphine-induced yawning in the rat: the implication of α-1 adrenergic mechanisms in the D-2 receptor function. Psychopharmacology (Berlin) 101:62–66; 1990.
5. Gower, A. J.; Berendsen, H. H. G.; Princen, M. M.; Broekkamp, C. L. E. The yawning-penile erection syndrome as a model for putative dopamine autoreceptor activity. Eur. J. Pharmacol. 103:81–89; 1984.
6. Hess, E. J.; Albers, L. J.; Le, H.; Creese, I. Effects of chronic SCH23390 treatment on the biochemical and behavioral properties of D_1 and D_2 dopamine receptors: Potentiated behavioral responses to a D_2 dopamine agonist after selective D_1 dopamine receptor up-regulation. J. Pharmacol. Exp. Ther. 238:846–854; 1986.
7. Hu, X.-T.; Wang, R. Y. Haloperidol and clozapine: differential effects on the sensitivity of caudate-putamen neurons to dopamine agonists and cholecystokinin following one month continuous treatment. Brain Res. 486:325–333; 1989.
8. Kostrzewa, R. M.; Saleh, M. I. Impaired ontogeny of striatal dopamine D_1 and D_2 binding sites after postnatal treatment of rats with SCH-23390 and spiroperidol. Dev. Brain Res. 45:95–101; 1989.
9. Leysen, J. E.; Niemmegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. [^{3}H]Ketanserin (R 41 468), a selective ^{3}H-ligand for serotonin$_2$ receptor binding sites. Mol. Pharmacol. 21:301–314; 1982.
10. Longoni, R.; Spina, L.; Di Chiara, G. Permissive role of D-1 receptor stimulation by endogenous dopamine for the expression of postsynaptic D-2-mediated behavioral responses. Yawning in rats. Eur. J. Pharmacol. 134:163–173; 1987.
11. Missale, C.; Nisoli, E.; Liberini, P.; Rizzonelli, P.; Memo, M.; Buonamici, M.; Rossi, A.; Spano, P. Repeated reserpine administration up-regulates the transduction mechanisms of D_1 receptors without changing the density of [^{3}H]SCH23390 binding. Brain Res. 483:117–122; 1989.
12. Mogilnicka, E.; Klimek, V. Drugs affecting dopamine neurons and yawning behavior. Pharmacol. Biochem. Behav. 7:303–305; 1977.
13. Morelli, M.; De Montis, G.; Di Chiara, G. Changes in the D_1 receptor-adenylate cyclase complex after priming. Eur. J. Pharmacol. 180:365–367; 1990.
14. Norman, A. B.; Borchers, M. T.; Wachendorf, T. J.; Price, A. L.; Sanberg, P. R. Loss of D_1 and D_2 dopamine receptors and muscarinic cholinergic receptors in rat brain following in vitro polytron homogenization. Brain Res. Bull. 22:633–636; 1989.
15. Saleh, M. I.; Kostrzewa, R. M. Impaired striatal dopamine receptor development: differential D-1 regulation in adults. Eur. J. Pharmacol. 154:305–311; 1988.
16. Serra, G.; Collu, M.; Gessa, G. L. Yawning is elicited by D_2 dopamine agonists but is blocked by the D1 antagonist, SCH 23390. Psychopharmacology (Berlin) 91:330–333; 1987.
17. Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. Nature 347:146–151; 1990.
18. Stoessl, A. J.; Dourish, C. T.; Iversen, S. D. Apomorphine-induced yawning in rats is abolished by bilateral 6-hydroxydopamine lesions of the substantia nigra. Psychopharmacology (Berlin) 93:336–342; 1987.
19. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol. Scand. Suppl. 367:69–93; 1971.
20. Yamada, K.; Nagashima, M.; Kimura, H.; Matsumoto, S.; Furukawa, T. Possible involvement of differing classes of dopamine D-2 receptors in yawning and stereotypy in rats. Psychopharmacology (Berlin) 100:141–144; 1990.