Pharmacology Biochemistry and Behavior, Vol. 44, pp. 487–489, 1993

0091-3057/93 $6.00 + .00

BRIEF COMMUNICATION

Low-Dose Quinpirole Ontogenically Sensitizes to Quinpirole-Induced Yawning in Rats

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Received 24 April 1992

KOSTRZEWA, R. M., R. BRUS, M. RYKACZEWSKA AND A. PLECH. *Low-dose quinpirole ontogenically sensitizes to quinpirole-induced yawning in rats.* PHARMACOL BIOCHEM BEHAV **44**(2) 487–489, 1993.—It is known that dopamine (DA) receptors can be sensitized by repeated treatments with quinpirole during postnatal development. This study was undertaken to determine whether low-dose quinpirole treatments might sensitize receptors to quinpirole-induced yawning behavior. Rats were treated with quinpirole HCl (50 μg/kg per day) or saline at four different periods of ontogeny: a) the 10th day of gestation to day of birth; b) 1st–11th days after birth; c) 12th–22nd days from birth; or d) 23rd–33rd days from birth. The numbers of yawns occurring in 1 h after a challenge dose of quinpirole HCl (50 μg/kg, IP) was determined at 6 weeks. Rats exposed prenatally to quinpirole demonstrated increased numbers of yawns following the third dose of quinpirole (2-day interval between doses). In rats exposed postnatally to quinpirole, there was a 70–300% increase in the yawning response, with the greatest response occurring in the group treated with quinpirole from birth to 11 days from birth. The findings demonstrate that quinpirole receptors are sensitized by a low dose of quinpirole, 60-fold lower than previously shown. It is suggested that sensitized receptors are of the DA D_3 subclass.

Quinpirole Dopamine D_2 receptor D_3 receptor Yawning Supersensitization

DOPAMINE (DA) agonists are known to induce yawning behavior in male rats (4,7,8,10,11). Because D_3 receptors have 113-fold greater affinity for quinpirole (9), and because low doses of quinpirole induce yawning behavior, it has been postulated that D_3 receptors are responsible for DA agonist-induced yawning behavior (5).

Recently, we found that ontogenic treatments with the DA agonist quinpirole would sensitize receptors to quinpirole-induced yawning responses in adulthood (6). The current study was conducted to determine whether low doses of quinpirole during ontogeny would sensitize receptors to quinpirole-induced yawning behavior later in life.

METHOD

Wistar albino rats were bred in a home colony and housed at 22 ± 1°C on a 12 L : 12 D cycle (light on at 0700 h) and allowed free access to food and water. To study the ontogenic effects of quinpirole, prenatal and postnatal periods of development were chosen.

In the first part of the study, pregnant rats were treated daily with a low dose of quinpirole HCl (50μg/kg, SC) or saline (0.9%) from the 10th day of gestation until delivery. Male offspring were not directly treated but were tested for quinpirole-induced yawning behavior at 6 weeks.

In the second part of the study, dams went untreated. However, litters were treated daily IP with quinpirole HCl (50 μg/kg) or saline for 11 consecutive days from a) the 1st–11th days after birth, b) 12th–22nd days from birth, or c) 23rd–33rd days from birth. These rats were also tested, as above.

Yawning behavior was observed in a quiet, well-ventilated, and well-lighted room. Each rat was placed in a single clear plastic cage and allowed at least 30 min for acclimation. Afterward, each of four rats was injected IP with saline vehicle and observed for 60 min, beginning immediately after injection. At the end of this session, each rat was injected IP with a challenge dose of quinpirole HCl (50 μg/kg) and observed for another 60 min. Because of markings on rats, the observer was aware of the treatment group of each rat during the test session.

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Behavioral data from treated and control groups of rats were compared by an analysis of variance (ANOVA), followed by the post-ANOVA test of Newman-Keuls.

RESULTS

At 6 weeks from birth, litters of quinpirole-treated dams (50 μg/kg per day, from gestation day 10 until the day of birth) were tested. A single challenge dose of quinpirole HCl (50 μg/kg) increased yawning responses to the same extent in control and prenatally treated male rats, about 10 yawns during the hour of observation (Fig. 1). Two days later, a second challenge dose of quinpirole HCl increased yawning responses to a mean (±SEM) of 20.1 ± 2.3 yawns in the group of male rats exposed prenatally to quinpirole vs. a mean of 14.5 ± 2.5 yawns in the saline control group. This difference was not statistically different. However, when the same rats were tested a third time, 2 days later, there was a significant increase in the response of the group exposed prenatally to quinpirole, 25.2 ± 2.7 vs. 15.8 ± 3.1 yawns ($p < 0.01$). These findings suggest that prenatal exposure to low-dose quinpirole predisposes receptors to sensitization by subsequent doses of quinpirole. In female rats, quinpirole did not produce a greater yawning response in the group prenatally exposed to quinpirole (data not shown).

In male rats treated postnatally for the first 10 days from birth with quinpirole HCl (50 μg/kg per day), there was a three-fold increase in the yawning response at 6 weeks ($p < 0.001$) vs. the saline control (Fig. 2). In male rats that received daily quinpirole treatments (50 μg/kg per day) from the 12th-22nd days from birth, there was a twofold increase in the yawning response ($p < 0.001$). In the group of male rats that received the same dose of quinpirole from the 23rd-33rd days from birth, there was a 70% increase in the yawning response ($p < 0.01$). In female rats, quinpirole treatments during the different postnatal periods did not produce a greater yawning response at 6 weeks (data not shown).

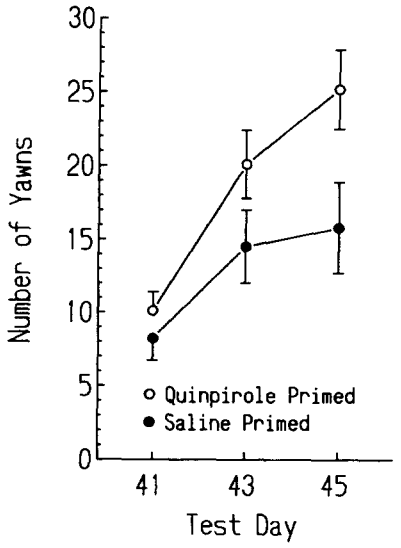

FIG. 1. Quinpirole-induced yawning behavior in male rats exposed to quinpirole during prenatal development. Pregnant rats were treated SC with low dose quinpirole HCl (50 μg/kg) or saline from the 10th day of gestation until birth of litters. On days 41, 43, and 45, rats were challenged with saline (not shown) and quinpirole HCl (50 μg/kg, IP). Numbers of yawns were counted during the following hour. Each value is the mean ± SEM of 10 (saline-primed group) or 16 (quinpirole-primed group) rats.

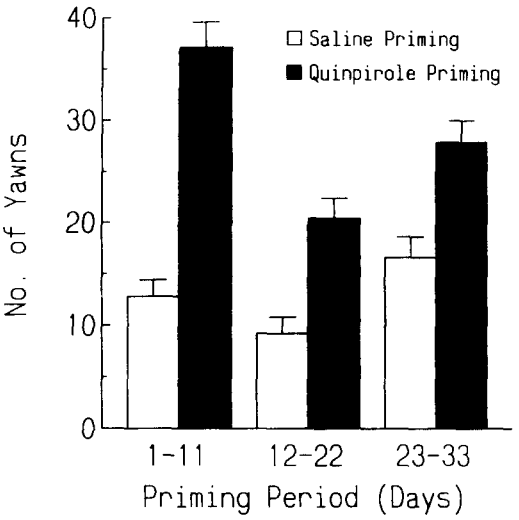

FIG. 2. Quinpirole-induced yawning behavior in male rats exposed to quinpirole during different periods of postnatal development. Male rats were treated daily IP with low-dose quinpirole HCl (50 μg/kg) or saline from a) the 1st-11th days from birth, b) the 12th-22nd days from birth, or c) the 23rd-33rd days from birth. At 6 weeks, rats were challenged with saline (not shown) and quinpirole HCl (50 μg/kg, IP). Numbers of yawns were counted during the following hour. Each value is the mean ± SEM of 14-24 rats.

In each of the above studies, a single injection of saline at 6 weeks produced a yawning response of less than 2/h in all instances (data not shown).

DISCUSSION

These findings demonstrate several features relevant to DA receptors of the D_2 class (i.e., D_2, D_3, and D_4 receptors). First, DA receptors of the D_2 class can be sensitized during development by treatments with quinpirole. This is in accord with previous demonstration of this phenomenon (6). A second, and the most important, feature is that low doses of quinpirole can produce this effect. The dose used in this study is 60 times lower than that used in our previous study. This also is in accord with the suggestion that the yawning response may be a DA D_3-mediated event because D_3 receptors have an affinity for quinpirole that is 113 times greater than shown specifically for D_2 receptors (9).

Another aspect is that quinpirole treatments will sensitize to yawning responses when low doses of this substance are administered for only 11 consecutive days, even as late as 33 days from birth. However, the greatest effect is produced when quinpirole is administered during the first 11 days from birth.

Finally, the effects of quinpirole may be latent, as shown for prenatally exposed rats. Only after several treatments with quinpirole at 6 weeks did sensitivity occur. The phenomenon whereby repeated exposure to an agonist induces receptor sensitivity is known as priming (3). It is well described for DA D_1 receptors (1,2). Because quinpirole is able to cross the blood-brain barrier, it was assumed that this agonist would cross the

placental barrier. We have no direct measure of this, but the findings give credence to this likelihood.

The present findings demonstrate that quinpirole receptors can be primed or sensitized by low-dose quinpirole treatments and the type and magnitude of the effect is dependent upon the period of exposure to quinpirole during pre- or postnatal development of male rats.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Scottish Rite Schizophrenia Research Program, N.M.J. The study was developed subsequent to a grant to R.M.K. from the John E. Fogarty International Center Health Scientist Exchange Program with Poland. The authors thank David Neely for statistical analyses and Lottie Winters for preparing the manuscript.

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