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7-OH-DPAT, unlike quinpirole, does not prime a yawning response in rats

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Abstract

Repeated treatment in ontogeny with the dopamine (DA) D_2/D_3 receptor agonist quinpirole is associated with enhanced quinpirole-induced yawning and other behaviors such as vacuous chewing, vertical jumping, and antinociception. To determine if the reputedly DA D_3 agonist (±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (7-OH-DPAT) would prime for yawning in a manner analogous to that for quinpirole, rats were treated for the first 11 days after birth with an equimolar dose of either quinpirole or 7-OH-DPAT (195.4 nmol/kg/day) and tested for agonist-induced yawning in adulthood. While enhanced quinpirole-induced and 7-OH-DPAT-induced yawning was observed in quinpirole-primed rats, acute treatments with quinpirole and 7-OH-DPAT did not produce an enhanced yawing response in 7-OH-DPAT-"primed" rats. Our findings indicate that 7-OH-DPAT, unlike quinpirole, does not prime for quinpirole- or 7-OH-DPAT-induced yawning in rats. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Quinpirole; 7-OH-DPAT; Priming; Yawning; Supersensitization; Rats

1. Introduction

Quinpirole induces characteristic behaviors in rats, most notably oral activity and yawning. Oral activity is the type behavior described by Waddington [24] as spontaneous chewing movements that are not directed onto physical material (i.e., vacuous chewing). Quinpirole is thought to induce vacuous chewing via stimulation of the dopamine (DA) D_2 receptor class (i.e., D_2, D_3, and D_4 receptors), because its effect is blocked by spiperone. However, some interaction with D_1 receptors is evident, as the D_1 receptor antagonist *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) similarly attenuates the quinpirole effect [3]. A number of other behaviors are induced by DA D_2 agonists, including eating, vertical jumping, rearing, paw treading, and antinociception. Each of these behaviors has been shown to be enhanced by ontogenetic quinpirole priming [13–17]. Until now, there have been no published data concerning the ability of (±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (7-OH-DPAT) to prime receptors for subsequent enhanced effects by agonists.

Both quinpirole and 7-OH-DPAT reportedly induce yawning behavior in rats via stimulation of the DA D_2 receptor class [7,12,13,19]. In a series of studies involving the induction of DA receptor supersensitization, we found that ontogenetic treatments with quinpirole would produce long-lived sensitization of receptors mediating quinpirole-induced yawing response in adult rats [13]. In addition, it is evident that these DA receptors can be permanently sensitized by extraordinarily low doses of quinpirole, administered once a day for the first 11 days after birth [15].

The current study was conducted to determine if quinpirole and 7-OH-DPAT, applied in equimolar doses, would be equi-effective in inducing yawning in rats. Moreover, we sought to determine if repeated low equimolar doses of quinpirole and 7-OH-DPAT, administered during postnatal ontogeny, would sensitize receptors for

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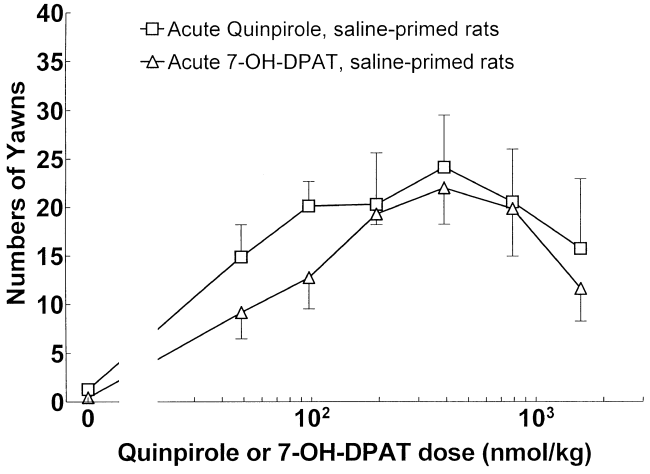

Fig. 1. Quinpirole- and 7-OH-DPAT-induced yawning in adult male Wistar rats. The abscissa indicates the acute dose of quinpirole or 7-OH-DPAT. The ordinate represents numbers of yawns counted in 1 h (±SEM) after injection of seven rats per group with either saline vehicle, quinpirole, or 7-OH-DPAT. The same group of rats received all doses of quinpirole or 7-OH-DPAT.

both quinpirole- and 7-OH-DPAT-induced yawning later in life.

2. Materials and methods

Wistar albino rats were bred in a home colony and housed at 22±1°C on a 12 L/12 D cycle (lights on at 07:00 hours), with free access to food (Murigran, Motycz, Poland) and water. Litters were reassigned at birth so that each reconstituted litter had only one or two of the original littermates.

In this experiment, male and female rat pups were treated daily for the first 11 days from birth, with either quinpirole HCl (195.4 nmol/kg/day, i.p.), 7-OH-DPAT HBr (195.4 nmol/kg/day, i.p.), or saline vehicle (1 ml/kg, control group). Between 6 and 8 weeks after birth, these rats were acutely challenged with quinpirole or 7-OH-DPAT and observed for yawning behavior (n=7 or 8 per group).

To assess yawning, adult male and female rats were placed in individual glass chambers (19×26×19 cm) with a steel grid floor, in a quiet well-ventilated and well-lighted room. After rats were acclimated to the new environment for at least 30 min, a single i.p. injection of saline vehicle was administered, and each rat was observed for 60 min, starting from the time of injection. Numbers of yawns were counted, recorded, and summarized for each rat. At the end of the session, each rat was injected i.p. with either quinpirole or 7-OH-DPAT (48 nmol/kg; i.e., 12.5 or 16.2 μg/kg of quinpirole HCl or 7-OH-DPAT HBr, salt forms, respectively) and observed for another 60 min. On the following 5 days, rats were challenged, day by day, with increasing doses of quinpirole or 7-OH-DPAT (97.7, 195.4, 390.9, 791.8, or 1583.6 nmol/kg; i.e., 25, 50, 100, 200, or 400 μg/kg, salt form, for quinpirole HCl; 32.5, 65, 130, 260, or 520 μg/kg, salt form for 7-OH-DPAT HBr) and observed for yawning. Because the experiment occurred over many weeks, and across seasons, we intentionally paired "saline-primed" rats with 7-OH-DPAT- and quinpirole-primed rats for all sessions. For this reason, each testing protocol is treated as an individual study. Testing occurred between 09:00 and 15:00 hours. Observations were made by an experienced observer who, because of markings on each rat, was aware of the treatment grouping of each rat during the test session. This procedure has been described in detail [13,15].

A one-way analysis of variance (ANOVA), followed by the post-ANOVA Newman–Keuls test was used to evaluate the significance of difference between groups, with an alpha of 0.05 taken as the level of significance.

3. Results

In "saline-prime" male rats (Fig. 1) and in "saline-primed" female rats (not shown) quinpirole and 7-OH-DPAT produced similar dose-related numbers of yawns. Responses to quinpirole and 7-OH-DPAT were greater in males, with a peak of 22 to 24 yawns vs. only 9.9±2.1 (7-OH-DPAT) (mean±SEM) or 14.9±3.1 (quinpirole) in females.

In male rats that had been primed in ontogeny with quinpirole, peak levels for a bell-shaped dose–effect curve for quinpirole were 30.2, $F(1, 14)=6.16$, $P=0.026$, and 35.0 yawns, $F(1, 14)=16.1$, $P=0.0013$ (Fig. 2).

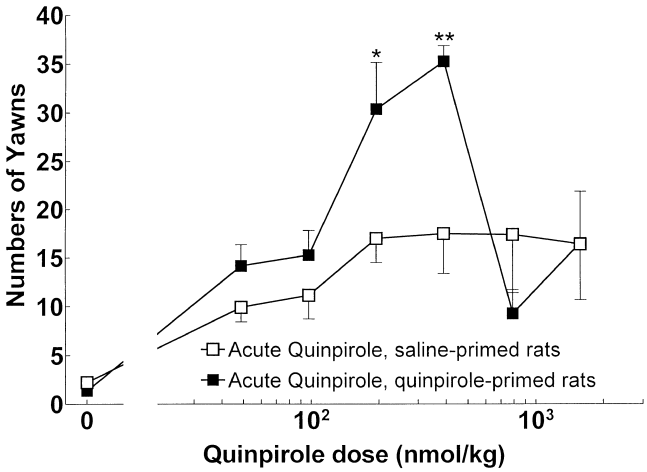

Fig. 2. Effect of ontogenetic quinpirole priming on quinpirole-induced yawning in male rats in adulthood. Rat pups were treated daily for the first 11 days from birth with vehicle or quinpirole (195.4 nmol/kg/day IP), and were tested in adulthood for their yawning response to quinpirole (abscissa). The ordinate represents numbers of yawns counted in 1 h (±SEM) after injection of eight rats per group with saline vehicle or quinpirole. *P<0.05 vs. response to an equimolar quinpirole dose in 'saline-primed' rats. The same group of rats received all doses of quinpirole.

Table 1
Quinpirole- and 7-OH-DPAT-induced yawning in quinpirole-primed, 7-OH-DPAT-primed, and saline-primed female rats

	Group				
Acute treatment (nmol/kg)	Saline-primed	Saline-primed	Quinpirole-primed	Saline-primed	7-OH-DPAT-primed
7-OH-DPAT					
0	2.13±0.52	2.37±0.89	1.12±0.40	0.75±0.31	0.63±0.18
49	4.88±1.33	4.38±1.25	5.50±2.05	1.13±0.35	3.75±0.92
98	5.63±1.40	12.13±2.52	10.75±2.97	8.50±1.66	5.75±1.33
195	7.75±3.54	8.37±1.91	8.87±2.12	8.25±1.68	5.50±0.65
391	9.88±2.25	15.63±2.71	15.12±2.12	10.13±2.27	13.00±3.16
792	9.25±1.81	13.25±3.35	18.87±2.59	16.13±2.87	16.88±3.51
1584	7.38±2.58	17.63±4.34	9.25±2.34	9.37±2.69	17.63±4.34
Quinpirole					
0	1.88±0.99	1.75±0.53	2.25±0.90	2.87±0.48	6.00±1.75
49	6.75±1.28	9.00±1.28	16.88±2.59*	8.12±2.90	8.63±1.79
98	7.38±1.68	13.25±0.80	22.00±2.28**	11.00±1.87	10.38±1.72
195	14.88±3.08	19.38±3.48	21.00±3.81	15.12±2.91	16.38±2.74
391	9.88±2.12	17.88±5.67	7.13±0.98	20.00±4.91	16.75±3.99
792	8.00±1.95	16.38±6.04	6.25±1.72	15.25±2.75	12.50±2.37
1584	5.13±2.05	14.13±4.36	10.50±2.80	7.50±1.87	7.75±0.41

* $P < 0.05$ vs. respective quinpirole treatment of saline-primed rats (e.g., in adjacent column to left).
** $P < 0.01$ vs. respective quinpirole treatment of saline-primed rats (e.g., in adjacent column to left).

Among female rats, there was significantly greater yawning in the quinpirole-primed group at quinpirole challenge doses of 48.8 nmol/kg, $F(1, 14)=7.44$, $P=0.016$, and 97.7 nmol/kg, $F(1, 14)=13.11$, $P=0.003$ (Table 1). These effects signify the effectiveness of quinpirole priming on acute quinpirole responses for both male and female rats. In quinpirole-primed male and female rats, 7-OH-DPAT, at any dose, failed to produce enhanced responses (Fig. 3; Table 1).

Among rats that were treated daily in early postnatal ontogeny with 7-OH-DPAT (195.4 nmol/kg/day × 11 days) and challenged in adulthood, there was no alteration in the 7-OH-DPAT dose–effect curve in these rats vs. "saline-primed" male rats (Fig. 4) and female rats (Table 1). Throughout the range of the dose–effect curve, there was no enhancement of the response to 7-OH-DPAT despite the attempt at priming in ontogeny with 7-OH-DPAT. These findings indicate that ontogenetic treatments with 7-OH-DPAT do not sensitize for 7-OH-DPAT-induced responses later in life.

Also shown for rats treated daily in early postnatal ontogeny with 7-OH-DPAT is the absence of an enhanced

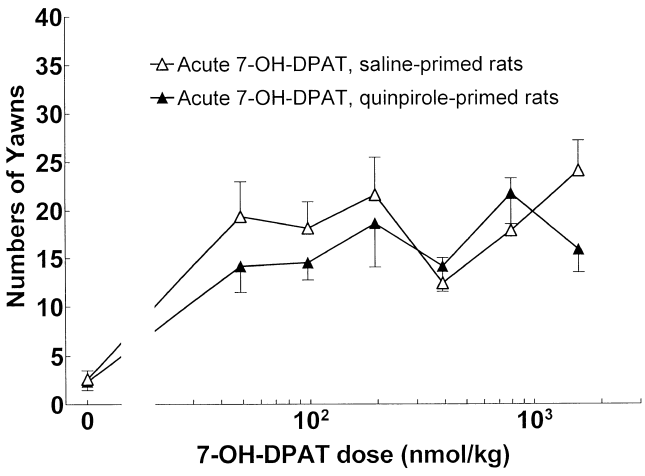

Fig. 3. Effect of ontogenetic quinpirole priming on 7-OH-DPAT-induced yawning in male rats in adulthood. Rat pups were treated daily for the first 11 days from birth with vehicle or quinpirole (195.4 nmol/kg/day, i.p.), and were tested in adulthood for their yawning response to 7-OH-DPAT (abscissa). The ordinate represents numbers of yawns counted in 1 h (±SEM) after injection of eight rats per group with saline vehicle or 7-OH-DPAT. The same group of rats received all doses of 7-OH-DPAT.

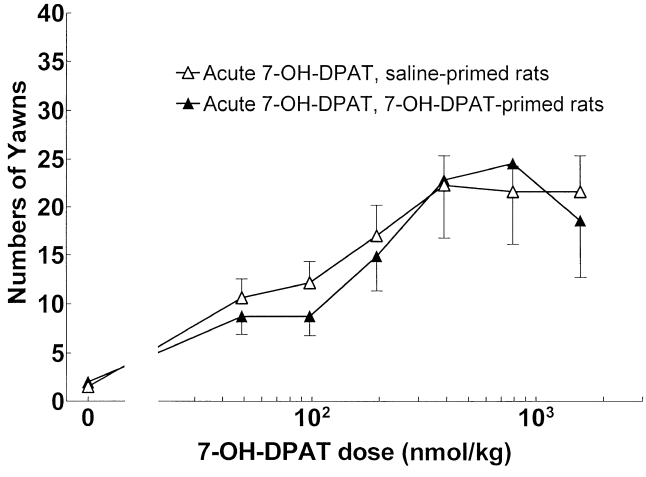

Fig. 4. Effect of ontogenetic 7-OH-DPAT attempted priming on 7-OH-DPAT-induced yawning in male rats in adulthood. Rat pups were treated daily for the first 11 days from birth with vehicle or 7-OH-DPAT (195.4 nmol/kg/day, i.p.) and were tested in adulthood for their yawning response to 7-OH-DPAT (abscissa). The ordinate represents numbers of yawns counted in 1 h (±SEM) after injection of eight rats with saline vehicle or 7-OH-DPAT. The same group of rats received all doses of 7-OH-DPAT.

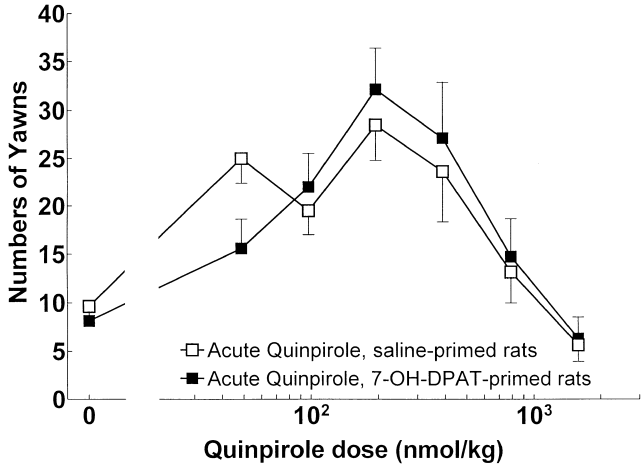

Fig. 5. Effect of ontogenetic 7-OH-DPAT attempted priming on quinpirole-induced yawning in male rats in adulthood. Rat pups were treated daily for the first 11 days from birth with vehicle or 7-OH-DPAT (195.4 nmol/kg/day, i.p.) and were tested in adulthood for their yawning response to quinpirole (abscissa). The ordinate represents numbers of yawns counted in 1 h (±SEM) after injection of eight rats per group with saline vehicle or quinpirole. The same group of rats received all doses of quinpirole.

yawning response to challenge doses of quinpirole in adulthood in both male rats (Fig. 5) and female rats (Table 1). Throughout the range of the dose–effect curve, there was no greater response to quinpirole vs. the response of "saline-primed" rats.

4. Discussion

In accordance with previous findings, repeated quinpirole treatments of rats in early postnatal ontogeny produced long-term enhancement of quinpirole-induced yawning in adulthood [4,13,15]. Other long-lived D_2 agonist-enhanced behaviors occurring in these rats include locomotor activity with rearing [5,6,17], age-related jumping with paw treading [16], eating [16], and antinociception [14]. The induction of long-lived sensitization of DA receptors, produced by repeated agonist treatments during ontogenetic development, is readily achieved in rats that are largely DA denervated [2], and this phenomenon has been designated as a "priming" process.

Szechtman et al. [21] have demonstrated that the number of injections of DA agonist, rather than the dosing interval between injections, is the predominant factor regulating development of long-lived quinpirole sensitization in rats. The dose of quinpirole within a defined range has additional impact on sensitization to later quinpirole enhancement of behaviors in these rodents with primed DA receptors. For example, Szechtman's group reported that repeated treatments of rats with a quinpirole dose of 0.025 mg/kg did not induce enhanced quinpirole effects, even after 10 consecutive daily treatments. However, higher doses (0.25 and 2.5 mg/kg) did sensitize this receptor complex. This same group further found that long-term intermittent treatments with quinpirole (0.5 mg/kg) induced pronounced sensitization to quinpirole-induced locomotor response (i.e., sixfold increase) [10].

As previously stated, 7-OH-DPAT was approximately equi-effective with quinpirole in inducing yawing episodes in male rats. It should be noted that quinpirole-induced yawning has been associated with reduced microdialysate levels of DA, presumably by action at DA D_3 receptors [7]. In addition, quinpirole and 7-OH-DPAT have similar affinities for DA D_3 receptors [18]. Therefore, it is not surprising that quinpirole and 7-OH-DPAT had similar effects on yawning number in "saline-primed" rats in the current study.

Presumed long-lived sensitization of DA "D_2 complex" receptors was observed as enhanced yawning responses to both quinpirole and 7-OH-DPAT in male rats; and as enhanced quinpirole responses in female rats. However, unlike quinpirole, ontogenetic treatments with 7-OH-DPAT did not appear to prime receptors. In rats in which there was attempted ontogenetic priming with 7-OH-DPAT, there was no later enhancement of yawning by acute quinpirole treatment or 7-OHDPAT treatment. Others have shown that repeated 7-OH-DPAT treatments (0.01 to 1.0 mg/kg) do not result in cross-sensitization to apomorphine- or cocaine-induced locomotor activity in rats [20]. Conversely, the 10-day treatment with a high dose of 7-OH-DPAT (1000 μg/kg) produced progressive increases in locomotor activity, demonstrating that 7-OH-DPAT is inherently capable of inducing behavioral sensitization [20]. In the current study, failure of 7-OH-DPAT to induce sensitivity to a later challenge dose of 7-OH-DPAT is therefore likely to be related to the purposeful low dose of 7-OH-DPAT that was used for priming. It is noteworthy, that quinpirole at an equimolar dose, did prime receptors to later challenges with quinpirole.

There is a question of whether quinpirole acts preferentially at a population of DA D_2 or D_3 receptors, different from those activated by 7-OH-DPAT; or whether each of these D_2/D_3 agonists acts with different efficacy on the same receptor population. Currently, this problem is not easily addressed. One might approach this, using the preferential DA D_3 agonist (+)-*trans*-3,4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-(1)benzopyrano(4,3*b*)-1,4-oxasin-9-ol [PD128907], which has been used in a behavioral model of D_3 receptor activation, namely hypothermia and prepulse inhibition [23], and failure to lower serum prolactin levels [9]. However, more recent findings clearly demonstrate, nonetheless, that PD128907 is also a partial agonist at DA D_3 receptors [22]. In addition, even the locomotor and hypothermic actions of reputed D_3 agonists now has been ascribed to DA D_2 receptor effects [1,8]. Therefore, even when more-selective D_3 agonists are developed, it will remain difficult to definitively ascribe DA receptor populations to the observed priming (behavioral) responses of quinpirole and 7-OH-DPAT.

From these behavioral experiments, we can conclude that 7-OH-DPAT is unable to prime receptors in the same way as a low equimolar dose of quinpirole, but that quinpirole-primed rats display greater responses to both quinpirole and 7-OH-DPAT. Differences between quinpirole and 7-OH-DPAT in effectively priming DA receptors, conceivably could be related to their respective effects on other neurochemical systems (see Ref. [11]), but this has not been systematically studied.

In summary, there is a major difference in the abilities of quinpirole and 7-OH-DPAT to prime rats for yawning responses to low doses of these respective DA agonists. It is premature to preferentially assign either specific D_2 or D_3 receptors to this effect, but the findings bring into question the generally assumed categorization of D_3 receptors with DA agonist-induced yawning.

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