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The locomotor effects of a putative dopamine D_3 receptor agonist in developing rats

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Abstract

Dopamine receptors have been categorized into subfamilies D_1 and D_2, each with separate roles in dopamine-mediated behaviors. Of the D_2 subfamily, the dopamine D_3 receptor has been cloned, but the behavioral effects of selectively stimulating the D_3 receptor are largely unknown. The purpose of this study was to quantify the locomotor responses of developing rats to the putative dopamine D_3 receptor agonist, 7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT). One of three doses of 7-OH-DPAT (0.01, 0.10, 1.00 mg/kg) or saline was injected subcutaneously into rats at the age of 10, 20, 30, or 60 days. Five minutes after the injection, rats were placed in automated activity monitors which recorded locomotor behavior at 5 min intervals for 2 h. The high dose of 7-OH-DPAT increased locomotor activity in rats of all ages. The medium and low doses increased activity in 10- and 20-day-old rats but not in 30- or 60-day-old rats. The level of drug-induced activation peaked at 20 days of age. In 30- and 60-day-old rats, but not 10- and 20-day-old rats, a period of locomotor suppression preceded the activation in response to the high dose of 7-OH-DPAT. In rats aged 20 days and older, the middle and low doses decreased locomotion early in the test session, but activation did not ensue. This dose-response pattern across ontogeny closely resembles that induced by quinpirole, an agonist at the dopamine D_2 receptor subfamily.

Keywords: Dopamine; Dopamine D_3 receptor; 7-OH-DPAT (7-hydroxy-*N,N*-2-(di-*n*-propylamino)tetralin); Locomotion; (Rat)

1. Introduction

The dopamine receptor agonist, 7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT), has been introduced as a ligand specific for the dopamine D_3 receptor (Lévesque et al., 1992; Damsma et al., 1993). It binds to dopamine D_3 receptors with originally reported K_i values 100 times lower than values for binding to D_2 receptors in cell lines (Lévesque et al., 1992). The locomotor effects of 7-OH-DPAT have recently been investigated. Low doses of 7-OH-DPAT decrease activity in adult rats (Ahlenius and Salmi, 1994; Daly and Waddington, 1993; Feenstra et al., 1983; Mulder et al., 1987); higher doses increase locomotion or sniffing (Daly and Waddington, 1993; Van den Buuse, 1993). Despite extensive theorizing about the function of dopamine D_3 receptors based on the use of 7-OH-DPAT, the selectivity of this drug for D_3 receptors has been questioned (Ahlenius and Salmi, 1994; Freedman et al., 1994a).

Other agents that show some selectivity toward dopamine D_3 receptors have also been investigated. The dopamine receptor agonist, quinpirole (LY171555), decreases locomotion when low doses are injected peripherally in adult rats. High doses of quinpirole induce a response that is biphasic across time; they decrease activity initially after drug injection and then increase activity later in a single test session (Eilam and Szechtman, 1989; Van Hartesveldt et al., 1992). The receptor antagonists, AJ76 and UH232, are the most selective antagonists for dopamine D_3 receptors (Sokoloff et al., 1990). These agents increase locomotion (Svensson et al., 1986), as does another putative dopamine D_3 receptor antagonist, U99194A (Waters et al., 1993).

These behavioral studies, along with the pharmacological and anatomical profiles of the dopamine D_3 receptor, have prompted several hypotheses regarding the function of this receptor subtype (see Schwartz et al., 1993, for review). It has been postulated that activation of the dopamine D_3 receptor inhibits locomotion (Daly and

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Waddington, 1993; Waters et al., 1993), that at least some dopamine D_3 receptors function as autoreceptors (Ahlenius and Salmi, 1994; Feenstra et al., 1983; Sokoloff et al., 1980; Sokoloff et al., 1992; Van Oene et al., 1984), and that these receptors may be targets for treatment of disorders involving excessive dopamine transmission in mesolimbic circuits (Bouthenet et al., 1991; Landwehrmeyer et al., 1993; Sokoloff et al., 1990). The role of dopamine D_3 receptors in neural and behavioral function probably depends on such factors as location of receptor subsets and developmental stage of the organism. However, further clarifying the role of this receptor subtype depends largely on drug selectivity, which itself is still not clear for the putative dopamine D_3 receptor ligands.

Investigating locomotor effects of dopaminergic drugs across developmental stages may reveal information about the characteristics of mature dopamine receptor systems. Until the third or fourth postnatal week, locomotor activity is not suppressed by dopamine receptor agonists such as quinpirole (Van Hartesveldt et al., 1994), apomorphine (Shalaby et al., 1981; Spear and Brake, 1983), 3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride (3-PPP; Arnt, 1983; Hedner and Lundborg, 1985; Lin and Walters, 1994), SND919 and PD128483 (Lin and Walters, 1994). The late ontological onset of locomotor suppression in response to dopamine receptor agonists indicates that this behavioral response requires a neural mechanism that does not mature until later in development. Given the recent hypothesis that dopamine D_3 receptors are inhibitory with respect to locomotion (Daly and Waddington, 1993; Waters et al., 1993), the onset of locomotor suppression as a response to dopamine receptor agonists may correlate with the functional maturation of a subset of D_3 receptors. The purpose of the present study was to examine the effects of the putative dopamine D_3 receptor agonist, 7-OH-DPAT, on locomotion in developing rats.

2. Materials and methods

2.1. Subjects

Sprague-Dawley dams and sires were obtained from Charles River. Female rats, in breeding cages with males, were given daily vaginal lavage to check for sperm. Once shown to be sperm positive, females were housed individually until giving birth. Pregnant females were checked twice daily for litters, so that the time of birth was recorded within 12 h. The day of birth was recorded as day 0. On day 1, litters were culled to 10 pups with approximately equal numbers of males and females. On day 25, rats were weaned and separated by sex. Colony rooms were maintained at 21°C on a 13 : 11 h light : dark cycle with lights on at 07:00 h. Rats were tested at 10, 20, 30, and 60 days of age. Only males were tested at 60 days of age; both males and females were tested at other ages. Each animal was tested only once. Ten rats of 10, 20, and 30 days of age or 8 rats of 60 days of age were randomly assigned to each dose group, with approximately equal numbers of males and females in each group. Testing took place between 09:00 and 17:00 h.

2.2. Drug procedure

The putative dopamine D_3 receptor agonist, (±) 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT, Research Biochemicals, International, MA, USA), was dissolved in saline, which was also used as the vehicle. Subcutaneous injections were administered at the nape of the neck in doses of 0 mg/kg (vehicle injection), 0.01 mg/kg, 0.10 mg/kg, or 1.00 mg/kg. Injection volumes were 2.50 ml/kg for 10-, 20-, and 30-day-old rats and 1.00 ml/kg for 60-day-old rats.

2.3. Behavioral procedure

Five minutes after the injection, each animal was placed in the center of a randomly assigned Omnitech Digiscan Animal Activity Monitor. Each monitor is a 41.91 cm × 41.91 cm × 30.48 cm Plexiglas cage with a wire mesh floor. Photocell beams cross the arena. They are spaced 2.54 cm apart such that 16 beams cross side to side and 16 beams front to back, all 3 cm above the mesh floor. Solid flooring was added for the 10- and 20-day-old rats, so that beams crossed 1.5 cm above this floor board. The interruption of photocell beams was translated into various measures of locomotor activity by the Digiscan analyzer. Total distance travelled in cm was analyzed. Data were collected in 5 min intervals over a period of 2 h.

2.4. Statistics

In order to analyze the total distance travelled in 5 min intervals, a two-way analysis of variance (ANOVA) was carried out for each age group with drug dose and time as main factors. If a significant interaction was revealed, then a one-way ANOVA was carried out to test the effect of drug dose at each time interval. Duncan's New Multiple Range Test was used for subsequent analysis of significance at the $P = 0.05$ or $P = 0.01$ level. There were no significant differences between males and females at the ages in which both genders were tested (10, 20, and 30 days). Therefore, males and females were analyzed as one group.

3. Results

3.1. 10-day-old rats

In 10-day-old rat pups, the high (1.00 mg/kg) and middle (0.10 mg/kg) doses of 7-OH-DPAT increased

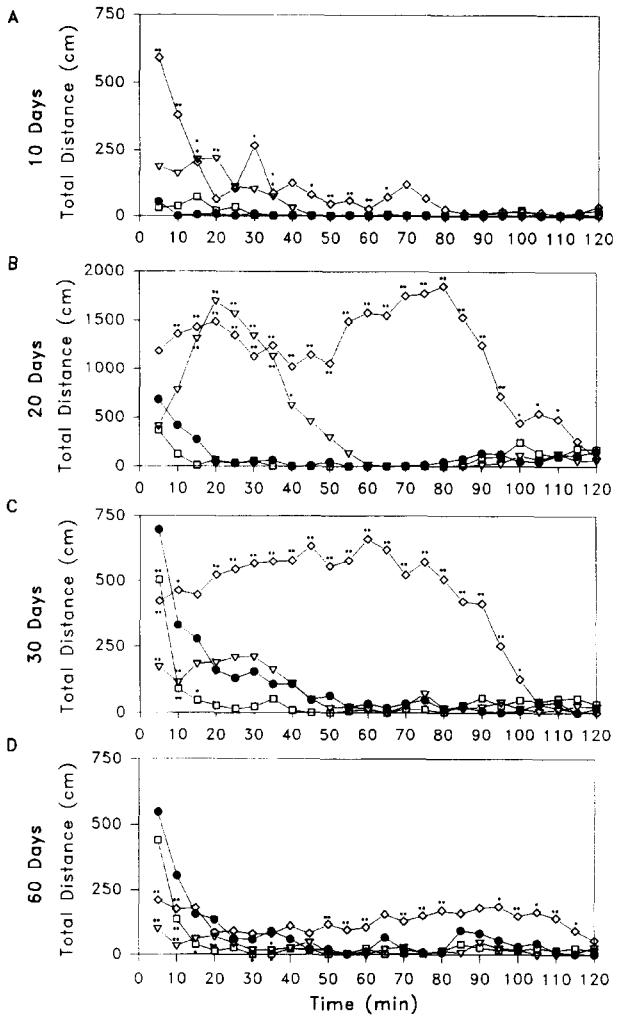

Fig. 1. The total distance travelled (cm) by rats after injection with various doses of 7-OH-DPAT at 10 (A), 20 (B), 30 (C), or 60 (D) days of age. Doses administered were 0.0 (●), 0.01 (□), 0.1 (▽), or 1.0 (◇) mg/kg s.c. Significant differences from control (0.0 mg/kg) are shown: * $P < 0.05$, ** $P < 0.01$.

locomotor activity, whereas the low dose (0.01 mg/kg) did not affect activity (Fig. 1A). A significant dose × time interaction [$F(69,828) = 3.92$, $P < 0.001$] as well as significant dose effects [$F(3,36) = 3.92$, $P = 0.016$] and time effects [$F(23,828) = 10.09$, $P < 0.01$] occurred in rats at 10 days of age.

The 1.00 mg/kg dose increased the total distance travelled for 75 min. Activity levels were significantly different from the vehicle-injected control group at the $P < 0.01$ level during the 5, 10, 50, 55, and 60 min intervals and at the $P < 0.05$ level during the 15, 30, 35, 45, and 65 min intervals. The 0.10 mg/kg dose increased activity significantly only at the 15 ($P < 0.05$), 20 ($P < 0.01$), and 35 ($P < 0.05$) min intervals.

3.2. 20-day-old rats

In 20-day-old rat pups, the high and middle (0.10 mg/kg) doses of 7-OH-DPAT increased locomotor activity, but again the low dose did not affect activity (Fig. 1B). A significant dose × time interaction [$F(69,828) = 9.20$, $P < 0.001$] as well as significant dose [$F(3,36) = 24.70$] and time [$F(23,828) = 10.32$, $P < 0.001$] effects occurred in rats at 20 days of age.

Injection of 1.00 mg/kg 7-OH-DPAT increased locomotor activity in comparison to the control group for 110 min. Although the total distance travelled during the first 5 min was not significantly increased, P values were < 0.01 through the 95 min interval and were < 0.05 at the 100–110 min intervals. The 0.10 mg/kg dose of 7-OH-DPAT increased activity at the $P < 0.01$ level from 15 to 35 min and at $P < 0.05$ in the 40 min interval.

3.3. 30-day-old rats

In 30-day-old rats, all three doses of 7-OH-DPAT decreased locomotor activity early in the test session (Fig. 1C). The high dose also increased activity later in the session. Thus, the high dose induced a biphasic locomotor response by initially decreasing and later increasing activity. A significant dose × time interaction [$F(69,828) = 11.00$, $P < 0.001$] as well as significant dose [$F(3,36) = 25.07$, $P < 0.001$] and time [$F(23,828) = 24.92$, $P < 0.001$] effects occurred in rats at 30 days of age.

During the first 5 min of testing, significant inhibition of total distance travelled ($P < 0.01$) occurred with all dose groups of 7-OH-DPAT in comparison with the vehicle-injected control group. The 0.10 mg/kg dose decreased activity also at the 10 min interval ($P < 0.01$). The 0.01 mg/kg dose decreased activity also at the 10 ($P < 0.01$) and the 15 ($P < 0.05$) min intervals. Animals injected with the 1.00 mg/kg dose of 7-OH-DPAT were more active than control animals already at the 10 min interval and they remained significantly more active through the 100 min interval ($P < 0.05$ at 10 min, $P < 0.01$ from 20 to 95 min, $P < 0.05$ at 100 min).

3.4. 60-day-old rats

In 60-day-old rats, all three doses of 7-OH-DPAT decreased locomotor activity early in the test session (Fig. 1D). The high dose also increased activity later in the session, thereby inducing the biphasic locomotor response. A significant dose × time interaction [$F(69,644) = 5.21$, $P < 0.001$] as well as significant dose [$F(3,28) = 10.37$, $P < 0.001$] and time [$F(23,644) = 25.12$, $P < 0.001$] effects occurred in rats at 60 days of age.

The high and middle doses induced significant inhibition for the first 10 min of testing ($P < 0.01$), but the low-dose inhibition was not significant at the 5 min interval. The middle and low doses continued to decrease activity through the 15 min interval (P values < 0.05), and the low dose also inhibited activity significantly at the 30 and 35 min intervals ($P < 0.05$). The highest dose of 7-OH-DPAT induced locomotor activation which was sig-

nificant only from 50 to 60 min ($P < 0.01$), from 70 to 80 min ($P < 0.01$), and from 95 to 115 min ($P < 0.05$ at the 95, 105, and 115 min intervals and $P < 0.01$ at the 100 and 110 min intervals).

4. Discussion

The locomotor responses of rats to 7-OH-DPAT administered peripherally in the present study were similar in several respects to the responses of rats to the dopamine D_2 receptor subfamily agonist, quinpirole, administered peripherally in previous studies by Eilam and Szechtman (1989), Van Hartesveldt et al. (1992) and Van Hartesveldt et al. (1994). First, the quality of behavior induced by 7-OH-DPAT and quinpirole was similar. Locomotor activation was characterized by a 'stiff-legged' exploration of the test chamber and did not involve stereotypy. Locomotor suppression was characterized by a frozen stance. Second, the adult dose-response patterns of activity to these drugs were similar. In 60-day-old animals, high doses of 7-OH-DPAT induced the biphasic locomotor response, as did higher doses of quinpirole given to adult rats. Low doses of either drug only decreased locomotor activity in older rats. These behaviors are similar to those elicited by 7-OH-DPAT in other studies (Ahlenius and Salmi, 1994; Daly and Waddington, 1993; Feenstra et al., 1983, Mulder et al., 1987).

The third similarity in responses to 7-OH-DPAT and to quinpirole is the ontogenetic sequence of the dose-response patterns induced by the two drugs. The developmental progression included: (1) only activation at 10 days of age, induced by a wide dose range of 7-OH-DPAT or quinpirole; (2) high magnitude of activation induced by high doses of either agonist at 20 days of age; (3) appearance of the biphasic response at 30 days of age, including the onset of significantly suppressed locomotor activity in response to these dopamine receptor agonists; and (4) relatively low magnitude of activation induced by high doses of the agonists at 60 days of age or later in adulthood. It should be noted that the activity level of 10-day-old rats in the control group was so low that detection of locomotor suppression would have been nearly impossible at this age in this paradigm. Manipulations that increase the activity of normal rats, such as the presence of milk or testing in the dark, may offer situations in which agonist-induced suppression of activity could be more easily observed.

Not only are the behavioral effects of 7-OH-DPAT and quinpirole parallel, but also the receptor binding characteristics of these drugs are similar. Originally, 7-OH-DPAT was reported to bind with approximately 100–200 times higher affinity at the dopamine D_3 receptor than at the dopamine D_2 receptor (Lévesque et al., 1992; Damsma et al., 1993). Quinpirole reportedly binds with similar relative affinities (Sokoloff et al., 1990). On the other hand, studies of dopamine D_3 receptor function in many different cell lines, show K_i values for 7-OH-DPAT and quinpirole to be only 20–40-fold lower for these drugs' displacement of binding to dopamine D_3 receptors compared with dopamine D_2 receptors (Freedman et al., 1994b; MacKenzie et al., 1994; McAllister et al., 1993; Schwartz et al., 1992; Seabrook et al., 1992). Yet these two ligands remain the most selective for D_3 receptors compared with many other ligands tested in these studies. Using the measure of pigment granule cell aggregation in cultured melanophores, Potenza et al. (1994) found similar EC_{50} values for 7-OH-DPAT and quinpirole in cells transfected with either dopamine D_2 or D_3 receptors, indicating in yet another paradigm that these drugs are not substantially more selective for dopamine D_3 receptors than for D_2 receptors. While 7-OH-DPAT binds to dopamine D_4 receptors with affinity three orders of magnitude lower than binding to dopamine D_2 or D_3 receptors (Lévesque et al., 1992), quinpirole binds to all three D_2-like receptors with similar affinity (Schwartz et al., 1992).

Therefore, it is not clear that experiments using 7-OH-DPAT in vivo provide specific information about dopamine D_3 receptor function. Rather, both quinpirole and 7-OH-DPAT activate both dopamine D_2 and D_3 receptors and perhaps even D_4 receptors. Ahlenius and Salmi (1994) have drawn a similar conclusion because they found that 7-OH-DPAT evokes the same locomotor effects as the well-known, non-specific dopamine receptor agonists, (+)3-PPP and apomorphine. In addition, they found that 7-OH-DPAT did not differentially affect dihydroxyphenylalanine (DOPA) accumulation in various regions of the striatum, despite the varied distribution of dopamine D_2 and D_3 receptors across this structure. Other investigators concur with this conclusion because they could not differentiate the effects of 7-OH-DPAT on neuronal firing rates (Freedman et al., 1994a) or K^+ channel activation (Liu et al., 1994) in the nigrostriatal pathway from effects in the mesolimbic circuit, despite the higher concentration of dopamine D_3 receptor mRNA in mesolimbic regions. Procedures that enhance the selectivity of binding of 7-OH-DPAT, (*R*)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-(3'-iodo-2'-propenyl)amino]tetralin (7-OH-PiPAT), or the 5-hydroxy analogue, 5-OH-PiPAT, to dopamine D_3 receptors have been developed for use in autoradiographic labeling (Burris et al., 1994), but the in vivo selectivity of 7-OH-DPAT is still questionable.

Although the behavioral studies discussed above do not differentiate which of several possible neural mechanisms mediate the behavioral effects of 7-OH-DPAT and quinpirole, there are two hypotheses that could account for the data. First, dopamine D_3 receptor occupation by agonists may decrease locomotor activity, whereas dopamine D_2 receptor occupation may increase activity (Daly and Waddington, 1993). Because the drugs have slightly higher affinities for dopamine D_3 receptors, the agonists may occupy D_3 receptors initially after injection, resulting in

locomotor suppression. After a high proportion of D_3 receptors was occupied, D_2 receptors would be occupied, resulting in locomotor activation. This sequence of events accounts for the biphasic locomotor response, early locomotor suppression followed by activation, within a single test session. Thus, portions of the response to 7-OH-DPAT would be mediated by non-specific binding to dopamine D_2 receptors (Daly and Waddington, 1993). According to this hypothesis, the low doses of 7-OH-DPAT or quinpirole induce early suppression but not later activation because only dopamine D_3 receptors are occupied by the drugs in low concentration. Because younger rats, 10 and perhaps 20 days of age, do not exhibit decreased locomotor activity in response to peripherally injected dopamine receptor agonists, it may be postulated that they do not have a sufficient number of functional dopamine D_3 receptors in relevant brain regions. However, strong D_3 receptor mRNA labeling has been demonstrated in rat brain tissue already at prenatal day 15 (Cadoret et al., 1993), but still neither the function nor the anatomical location of D_3 receptors has been thoroughly investigated in developing rats.

A second possible explanation for these results is the classic 'autoreceptor hypothesis' which states that dopamine autoreceptor occupation by agonists decreases locomotor activity, whereas postsynaptic receptor occupation increases activity (Ståhle, 1992; see Wolf and Roth, 1987, for review). This hypothesis entails a similar sequence of events as the first hypothesis except that the drug effects are said to be due to differential activation of pre- vs. postsynaptic receptors rather than dopamine D_2 vs. D_3 receptors. Dopamine autoreceptors, be they D_2 or D_3 receptor subtypes, would be occupied first by the agonists because autoreceptors may be more sensitive to dopamine receptor agonists (Skirboll et al., 1979). Autoreceptor occupation would decrease locomotor activity (Strömbom, 1976). Postsynaptic receptors would subsequently be occupied by the drug as it reached higher concentrations and the locomotor activation phase of the biphasic response would thus commence. This hypothesis has been used extensively to explain how low doses of dopamine receptor agonists decrease activity but high doses increase activity (Di Chiara et al., 1976; Strömbom, 1976). Ahlenius and Salmi (1994) have shown that indeed at low doses, 7-OH-DPAT may preferentially stimulate dopamine autoreceptors. However, the autoreceptor hypothesis in general has met with skepticism for several reasons, including time course of neuronal events (see Ståhle, 1992, for review), differential sensitivity of pre- versus postsynaptic receptors (Kendler et al., 1983), and developmental progression of so-called autoreceptor-mediated behaviors (Frantz and Van Hartesveldt, manuscript in preparation). Addressing 7-OH-DPAT specifically, Svensson et al. (1994) reported that doses of 7-OH-DPAT, which decrease locomotion, do not decrease limbic or striatal levels of dopamine or its metabolites. In addition, autoreceptors have been shown biochemically to be functional in the striatum by embryonic day 17 (De Vries et al., 1992) and in the nucleus accumbens by postnatal day 10 (Andersen and Teicher, manuscript submitted). Therefore, the autoreceptor hypothesis does not provide an explanation for the lack of locomotor suppression in response to dopamine receptor agonists in animals 20 days of age and younger.

If 7-OH-DPAT does activate both dopamine D_2 and D_3 receptors in rats, then the present study confirms that the developmental progression of locomotor responses to dopamine D_2 receptor subfamily agonists includes the characteristics listed above. This study thus provides a behavioral demonstration of what has also been quantified in cell lines transfected with dopamine receptors, namely that quinpirole and 7-OH-DPAT display very similar binding patterns and that neither of these agonists is likely to bind selectively to dopamine D_3 receptors in vivo. In the absence of a more selective dopamine D_3 receptor ligand, further research on D_3 receptor function must involve different methods.

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