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Ontogeny of Biphasic Locomotor Effects of Quinpirole

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VAN HARTESVELDT, C., M. E. MEYER AND T. J. POTTER. *Ontogeny of biphasic locomotor effects of quinpirole.* PHARMACOL BIOCHEM BEHAV **48**(3) 781–786, 1994.—The effects of the dopamine D_2/D_3 receptor agonist quinpirole (LY171555) on locomotor activity were tested on rats of 10, 15, 20, 30, and 60 days of age. In two separate experiments, doses of 0 (vehicle), 0.02, 0.2, or 2.0 mg/kg quinpirole were injected SC into rats at each age, and their effects measured either for 2 h at 15-min intervals, or 30 min at 5-min intervals. At 10, 15, and 20 days of age, quinpirole significantly increased distance travelled in a dose-dependent manner. At 30 and 60 days of age, quinpirole significantly decreased distance travelled early in the session and increased it later. These results suggest that a dopamine autoreceptor begins to function between 20 and 30 days of age. Concomitant with the appearance of quinpirole-induced locomotor suppression early in the session, the amount of quinpirole-induced activation late in the session declined.

Dopamine Locomotion Dopamine D_2 receptors Quinpirole Ontogeny Rat

PREVIOUS research has shown that direct and indirect catecholamine agonists can activate locomotor behaviors in the early postnatal period in the rat. These agonists include *l*-DOPA (2,7,23), amphetamine (3,8), clonidine (7,14,19), and cocaine (19). Agonists more specific to dopamine receptors also elicit locomotor activity in preweanling rats. Apomorphine (2,7,8,13,17), (+) 3-PPP ([3-(3-hydroxyphenyl)-*N*-n-propylpiperidine]; 1) and quinpirole (9,10,12) all increase locomotion in the preweanling rat.

In addition to locomotor activation, many dopamine agonists also decrease locomotion at low doses in the adult rat. For example, apomorphine decreases locomotion at low doses [e.g., (11)] in the adult rat. This suppressive effect has been interpreted as the behavioral consequence of activation of a dopamine autoreceptor, which results in a decrease in dopamine synthesis and/or release [see (21) for a review). In developing rats, locomotor suppression induced by apomorphine is not apparent until 28 days after birth (17); the suppressant effect of another dopamine agonist, 3-PPP, is not seen until 28–30 days postnatal (1,6). Both sets of results suggest that dopamine autoreceptors mature relatively late postnatal.

All dopamine autoreceptors identified to date have the characteristics of the dopamine D_2 (21) or D_3 (15) receptor subtype. Quinpirole is a dopamine D_2/D_3 agonist (18), and would, thus, be expected to show behavioral effects consistent with autoreceptor activation at low doses. In adult rats, quinpirole has biphasic effects: it suppresses locomotor activity at low doses, and first suppresses and later in the session activates locomotion at higher doses (5,22). Although it has been reported that the activities elicited by quinpirole are qualitatively the same in the 21-day-old rat as in the adult (12), there has been no report concerning the appearance of quinpirole-elicited suppression of locomotor activity. The purpose of the present study was to determine at what age quinpirole could suppress locomotor activity in developing rats.

METHOD

Subjects

Sprague–Dawley rats bred in this laboratory were tested at 10, 15, 20, and 30 days of age. Dams and sires were obtained from Charles River Farms, Wilmington, MA. Pregnant females were housed in breeding cages in the colony room on a 12 L : 12 D cycle. Breeding cages were checked for litters twice daily, and time of birth was noted within 12 h. Day of birth was recorded as day 0. Litters were culled by day 3 to 10 pups with equal numbers of males and females. Pups were housed with their dams until day of testing or 25 days, whichever occurred first. Pups tested at 30 days were removed from their dam at 25 days, separated by sex, and gang housed with their same-sex litter mates.

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Drugs

The dopamine D_2/D_3 agonist quinpirole (LY171555; Research Biochemicals International) was administered peripherally at doses of 0.02, 0.2, and 2.0 mg/kg. The quinpirole was dissolved in distilled water that was used alone as the vehicle control. Injections were administered subcutaneously (SC) in either the right or left flank at a volume of 0.1 ml/40 g of body weight.

Procedure

Immediately following SC drug injection, each rat pup was placed in the center of an Omnitech Digiscan Animal Activity Monitor and data were collected. Litters were tested on either 10, 15, 20, 30, or 60 days after birth. Each animal was tested only once. Animals from each age and dose group were tested for 2 h with data collection every 15 min. Because the results showed no initial suppression of activity until 20–30 days of

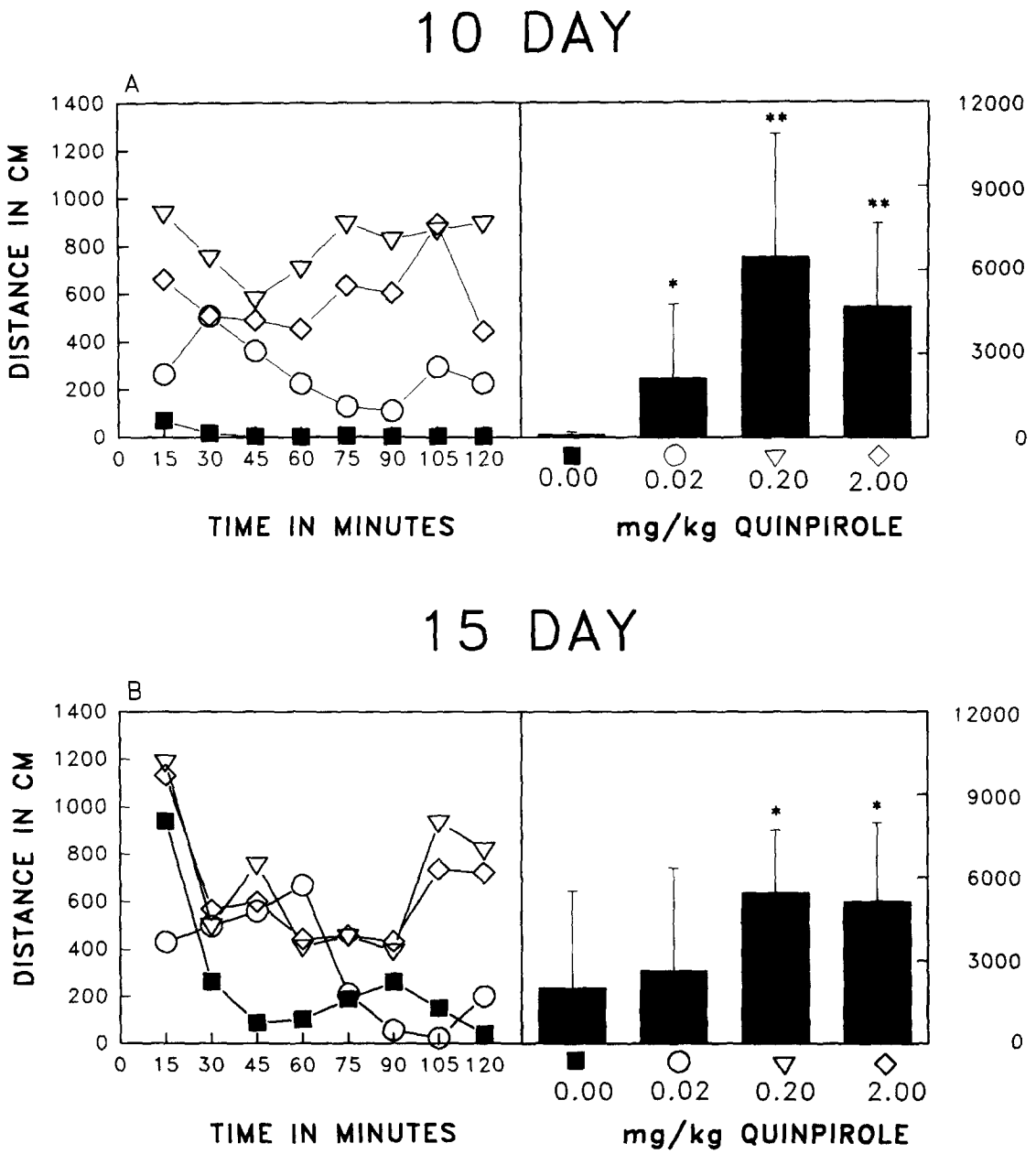

FIG. 1. The effects of quinpirole on distance travelled in rat pups of 10 (top) and 15 (bottom) days of age. Left panel, effect of quinpirole plotted by 15-min intervals; right panel, distance travelled for the entire 2-h session. Error bars represent the mean + 1 SD. Relative to controls (0.00 mg/kg), $*p < 0.05$; $**p < 0.01$.

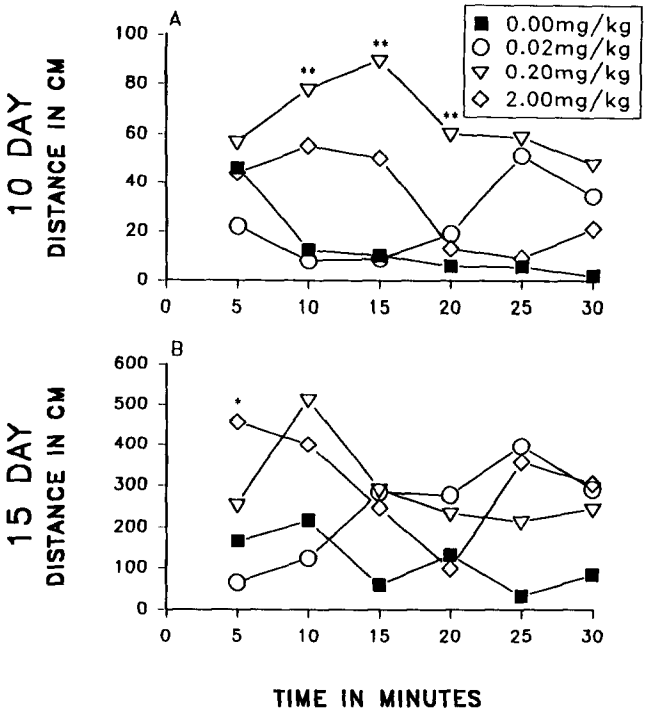

FIG. 2. The effects of quinpirole on distance travelled in rats of 10 (top) and 15 (bottom) days of age for 30 min. Error bars are omitted for clarity. Relative to controls (0.00 mg/kg), $*p < 0.05$; $**p < 0.01$. Note the difference in the × axis for the two age groups.

age, a second experiment was carried out in which animals from each age and dose group were tested for 30 min with data collection every 5 min. Approximately equal numbers of males and females were tested in each experiment, at each dose and age. $N = 10$ pups for each dose at each age in both experiments.

Apparatus

The acrylic cage within the monitor measured 41.91 cm wide × 41.91 cm long × 30.48 cm tall. The monitor was equipped with 16 beams 2.54 cm apart from side to side and 16 beams from front to back on the lower level, as well as 16 beams 2.54 cm apart from side to side on the upper level. A 41.91 × 41.91 × 2.2 cm solid insert was installed in the monitors prior to testing the 10-, 15-, and 20-day-old subjects so that the photocell beams were approximately 1.5 cm above the floor. The older animals were tested on a wire grid floor 3.0 cm below the photocell beams. The Digiscan analyzer converted the patterns of the beams broken into 18 different measures of locomotor activity. Data from one of these measures, distance, was analyzed. Total distance is defined as the distance travelled measured in centimeters.

Statistics

Data for each experiment (two experiments for each age group) were analyzed using an analysis of variance with repeated measures (eight for the first experiment, six for the second) and four drug doses. Subsequent analyses were made using one-way ANOVAs; comparisons between groups were made using Duncan's multiple range test. Because the emphasis of this research was on the appearance of locomotor suppression, data for males and females were analyzed separately only in the second experiment (30-min duration, 5-min intervals). No significant differences between sexes were found at any age; the data for the two sexes were, thus, collapsed.

RESULTS

At 10 days after birth, SC injection of quinpirole followed by a 2 h test resulted in significant differences in distance travelled (see Fig. 1A) as a function of dose, $F(3, 36) = 8.93$, $p < 0.001$. The 0.2 and 2.0 mg/kg groups travelled significantly farther than the vehicle control group ($p < 0.01$), as did the 0.02 mg/kg group ($p < 0.05$). Subcutaneous injection

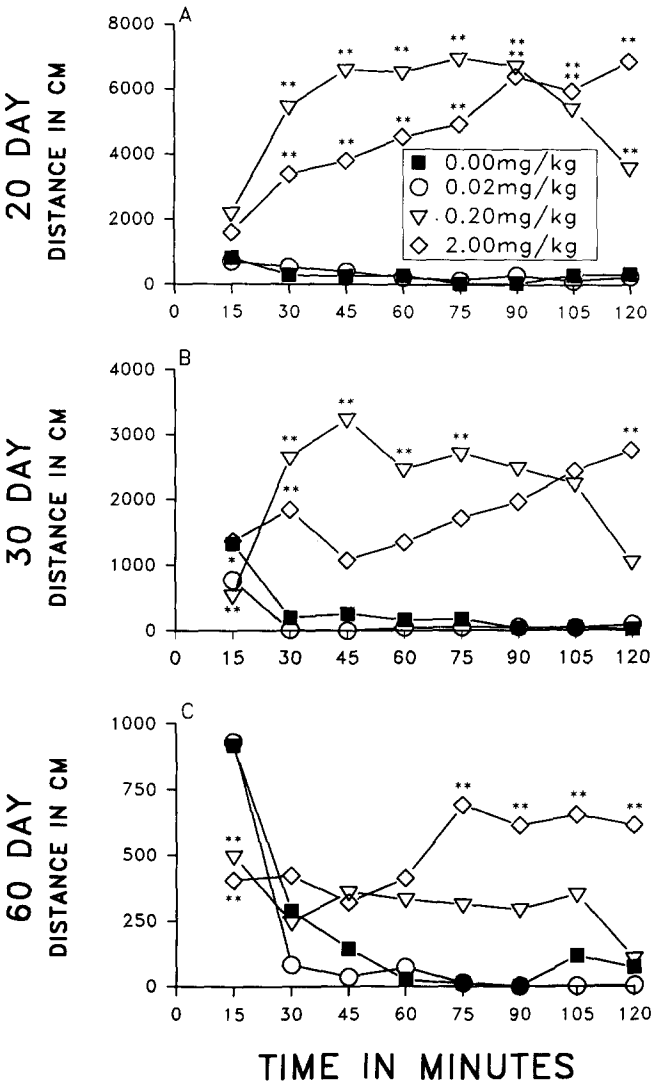

FIG. 3. The effects of quinpirole on distance travelled in rats of 20 (top), 30 (middle), and 60 (bottom) days of age for 2 h. Error bars are omitted for clarity. Relative to controls (0.00 mg/kg), $*p < 0.05$; $**p < 0.01$. Note the differences in the × axis for the three age groups.

of quinpirole followed by a 30-min test with readings every 5 min resulted in no evidence of drug-induced locomotor suppression; in fact, at several time points, rats in the 0.2 mg/kg group travelled significantly farther than the vehicle control group ($p < 0.01$). These data are shown in Fig. 2A.

At 15 days after birth, SC injection of quinpirole followed by a 2-h test resulted in differences in distance travelled (see Fig. 1B) which were significant as a function of dose, $F(3, 36) = 3.071$, $p = 0.039$, and time, $F(7, 252) = 4.70$, $p < 0.001$. Animals given the two highest doses travelled significantly farther than those given the low dose or the vehicle ($p < 0.05$); there were no significant differences between the two highest dose groups or between the lowest dose and the vehicle. Subcutaneous injection of quinpirole followed by a 30-min test with readings every 5 min resulted in no evidence of early drug-induced suppression of locomotion (Fig. 2B).

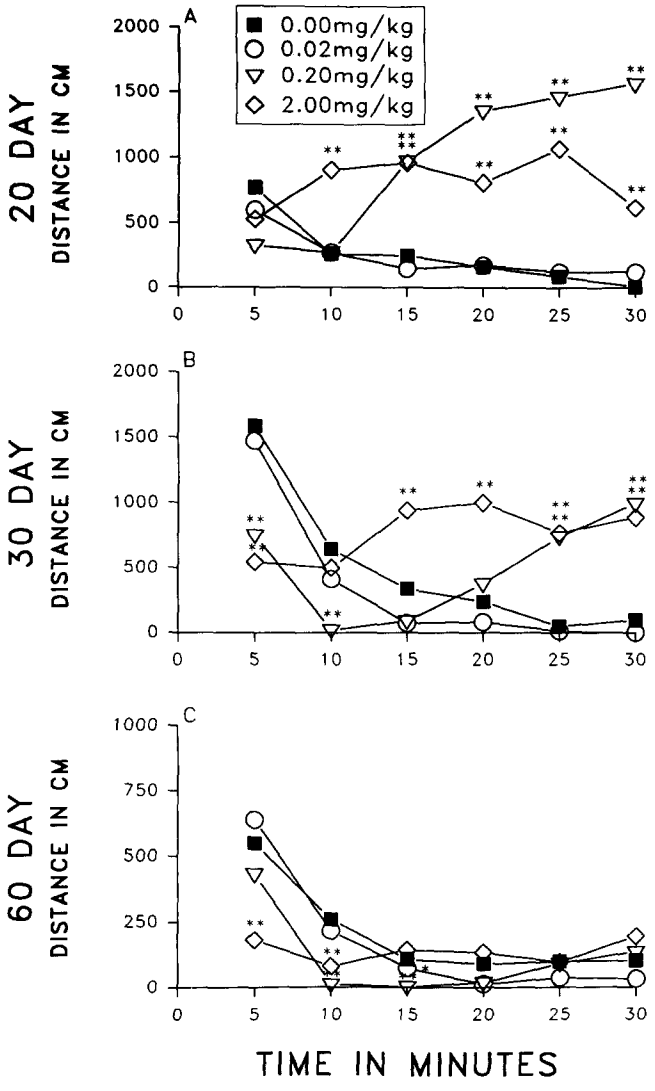

FIG. 4. The effects of quinpirole on distance travelled in rats of 20 (top), 30 (middle), and 60 (bottom) days of age for 30 min. Error bars are omitted for clarity. Relative to controls, $*p < 0.05$; $**p < 0.01$. Note that the × axis for the 60-day-old group is different from that for the other two age groups.

At 20 days after birth, SC injection of quinpirole followed by a 2-h test resulted in differences in distance travelled (see Fig. 3A) which were significant as a function of dose, $F(3, 36) = 42.914$, $p < 0.001$, and time, $F(7, 252) = 15.460$, $p < 0.001$, as well as a dose × time interaction, $F(21, 252) = 15.78$, $p < 0.001$. All dose groups differed significantly from one another ($p < 0.01$) except the lowest dose and the vehicle, and the two highest doses. After SC injection of either 2.0 mg/kg or 0.2 mg/kg quinpirole, distance travelled was significantly increased relative to the vehicle ($p < 0.01$) at all intervals from 30 through 120 min for both doses. Subcutaneous injection of quinpirole followed by a 30-min trial with 5 min intervals (see Fig. 4A) resulted in differences in distance travelled as a function of dose, $F(3, 36) = 17.706$, $p < 0.001$, and time, $F(5, 180) = 2.75$, $p = 0.02$, as well as a dose × time interaction, $F(15, 180) = 13.796$, $p < 0.001$. The 0.2 mg/kg dose resulted in an increase in distance travelled relative to the vehicle ($p < 0.01$) at the 15-, 20-, 25-, and 30-min intervals. The 2.0 mg/kg dose resulted in an increase in distance travelled relative to the vehicle ($p < 0.01$) at the 10-, 15-, 20-, 25-, and 30-min intervals. Although both the 0.2 and 2.0 mg/kg doses elicited less distance travelled than the vehicle control during the first 5 min, this difference was not statistically significant.

At 30 days after birth, SC injection of quinpirole followed by a 2-h test resulted in differences in distance travelled (see Fig. 3B) that were significant as a function of dose, $F(3, 36) = 6.485$, $p = 0.001$, as well as the dose × time interaction, $F(21, 252) = 5.177$, $p < 0.001$. The two highest dose groups did not differ significantly from one another, nor did the lowest dose group and the vehicle; all other comparisons were significant ($p < 0.01$). Both the 0.2 mg/kg and the 0.02 mg/kg doses resulted in a decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 15 min interval followed by an increase in distance travelled relative to the vehicle. The 0.2 mg/kg dose had significantly higher scores than the vehicle ($p < 0.01$) at the 30-, 45-, 60-, and 75-min intervals. The 2.0 mg/kg dose resulted in an increase in distance travelled relative to the vehicle ($p < 0.01$) at the 30- and 120-min intervals. Subcutaneous injection of quinpirole followed by a 30-min test with 5-min intervals (see Fig. 4B) resulted in significant differences in distance travelled as a function of dose, $F(3, 36) = 7.102$, $p < 0.001$, and time, $F(5, 180) = 29.982$, $p < 0.001$, as well as the dose × time interaction, $F(15, 180) = 17.797$, $p < 0.001$. The 0.2 mg/kg dose resulted in a decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 5- and 10-min intervals followed by a increase in distance travelled relative to the vehicle ($p < 0.01$) at the 25- and 30-min intervals. The 2.0 mg/kg dose resulted in a decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 5-min interval followed by an increase in distance travelled relative to the vehicle ($p < 0.01$) at the 15-, 20-, 25-, and 30-min intervals.

At 60 days after birth, SC injection of quinpirole followed by a 2-h test resulted in differences in distance travelled (see Fig. 3C) that were significant as a function of dose, $F(3, 36) = 4.839$, $p = 0.006$, time, $F(7, 252) = 20.642$, $p < 0.001$, and the dose × time interaction, $F(21, 252) = 8.04$, $p < 0.001$. Overall, the 2.0 mg/kg dose group differed significantly from the vehicle and 0.02 mg/kg dose groups ($p < 0.01$); no other differences were significant. Both the 2.0 mg/kg and the 0.2 mg/kg dose resulted in a significant decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 15-min interval. The 2.0 mg/kg dose also resulted in an increase in distance travelled relative to the vehicle ($p < 0.01$) at the

75-, 90-, 105-, and 120-min intervals. Subcutaneous injection of quinpirole followed by a 30-min test with 5-min intervals (see Fig. 4C) resulted in marginally significant differences in distance travelled as a function of dose, $F(3, 36) = 2.995$, $p < 0.042$, and significant differences as a function of time, $F(5, 180) = 83.72$, $p < 0.001$, as well as a dose × time interaction, $F(15, 180) = 10.97$, $p < 0.001$. The 0.2 mg/kg dose resulted in a decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 10- and 15-min intervals. The 2.0 mg/kg dose resulted in a decrease in distance travelled relative to the vehicle ($p < 0.01$) at the 5- and 10-min intervals.

DISCUSSION

The present experiments have shown for the first time that quinpirole begins to suppress locomotor activity in the developing rat between 20 and 30 days of age. At 30 days of age a low dose of quinpirole (0.02 mg/kg) decreases distance travelled and does not later increase it. We have also shown for the first time the ontogeny of the within-session biphasic effect of a dopamine agonist. At 30 days of age, the higher doses (0.2 and 2.0 mg/kg) of quinpirole suppress locomotion early in the session, and later activate it. The age at which low-dose locomotor suppression first appears is, thus, quite consistent for the dopamine agonists quinpirole, apomorphine, and 3-PPP. These results support the interpretation that the functional maturation of the dopamine autoreceptor occurs relatively late in postnatal life. However, it should be noted that the hypothesis that the decrease of dopamine released as a consequence of autoreceptor stimulation is responsible for suppression of locomotion is not universally accepted (20). Therefore, it might be more conservative to state that a separate receptor mechanism, autoreceptor or otherwise, that relates to locomotor suppression matures between 20–30 days of age.

The interpretation that a dopamine autoreceptor matures relatively late is supported by neurochemical research on the effects of both apomorphine and 3-PPP. After blocking dopamine transmission with gamma butyrolactone, apomorphine was found to attenuate the GBL-induced increase in dopamine levels by 14 days postnatal in the striatum, and 35 days postnatal in the olfactory tubercle (16). 3-PPP inhibited the GBL-induced increase in tyrosine hydroxylase activity at 28 but not 4 days in the striatum of the developing rat (6).

While it is agreed that dopamine autoreceptor functions mature relatively late during development, it is not entirely clear whether the onset of autoreceptor function has a causal connection to dopamine agonist-induced locomotor suppression. In part, it is not clear because it is not known in which brain regions the agonist acts to produce the suppression. In the adult rat, intracerebral injection of quinpirole into either the striatum or nucleus accumbens resulted in suppression of locomotor activity, depending on the dose (22). However, in mice, both apomorphine and dopamine injected into the nucleus accumbens, amygdala, septum, or ventral tegmental nucleus resulted in motor inhibition (4). In the rat, any of these regions may also be involved in quinpirole-induced locomotor suppression. The age at which behavioral suppression occurs as a result of systemic quinpirole injection may be a function of averaging drug effects across brain regions, and may not represent the maturational timetable of any particular region.

As in previous research, quinpirole increased activity at every age tested, but to different amounts at different ages. For example, Moody and Spear (12) found that 0.5 mg/kg quinpirole increased forward locomotion more at 20–21 than 3–4 or 10–11 days of age. In the present experiment, quinpirole-induced locomotor activity peaked at 20 days of age and declined thereafter. This pattern of dopamine agonist-induced locomotor activity is very similar to that found for apomorphine (17). The age at which the peak level of quinpirole-induced locomotor activity began to decline (30 days of age) coincided with the age of onset of its behaviorally suppressant effects, which increased with age. Significant suppression of locomotion had a duration of 10 min at 30 days of age, but lengthened to 15 min at 60 days, depending on the dose. Perhaps as a consequence of increasing suppression of locomotion, the latency to quinpirole-induced activation also increased with age: depending on the dose, quinpirole significantly activated locomotion at a latency of 5 or 10 min up to 20 days of age, 15 min at 30 days of age, but as late as 75 min at 60 days of age. Further, at 60 days of age, only the highest dose of quinpirole increased locomotion. Thus, it appears that the locomotor suppressant effects of quinpirole increase with age, while its locomotor activating effects decrease.

It is interesting to consider whether there may be a relationship between the onset and increasing duration of suppression of locomotor activity beginning at 30 days of age with the longer latency to activity, the decreasing level of activity after 20 days of age, and the decreasing potency of quinpirole after 20 days of age. It has been suggested that the activating effects of (+) 3-PPP decrease with age due to the maturation of the dopamine autoreceptor (1). Of course, during this time period further maturation of both dopamine and nondopamine transmitter systems takes place, as well as changes in peripheral factors such as absorption and metabolism. Further research is necessary to determine the possible relationship between dopamine agonist-induced locomotor suppression and activation.

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