Pharmacology Biochemistry and Behavior, Vol. 64, No. 4, pp. 821–826, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00162-8

The Locomotor Effects of Quinpirole in Rats Depend on Age and Gender

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FRANTZ, K. J. AND C. VAN HARTESVELDT. *The locomotor effects of quinpirole in rats depend on age and gender.* PHARMACOL BIOCHEM BEHAV **64**(4) 821–826, 1999.—Periadolescence in the rat [postnatal day (PND) 35–50] is an important but understudied period of neurobehavioral development. In this experiment, an ongoing survey of the effects of quinpirole in developing rats was completed by the addition of periadolescent rats to the range of ages tested. PND40 or 50 rats were injected subcutaneously with the dopamine D_2/D_3 receptor agonist, quinpirole (0.0, 0.02, 0.2, or 2.0 mg/kg), and their locomotor activity was recorded. Periadolescent rats showed adult-like locomotor responses to either the 0.2 or 2.0 mg/kg doses of quinpirole, i.e., the responses were biphasic with respect to time: early suppression of locomotion followed by later activation within a single test session. In younger female rats (PND40) but older male rats (PND50), the lowest dose of quinpirole suppressed activity early in the test session but did not increase it later. In male rats, the magnitude of locomotor activation declined with age. Taken together with previous data from this laboratory, these results suggest that periadolescent rats exhibit locomotor responses that fall along a continuum from a high level of activation just after weaning to a low level of activation in early adulthood. © 1999 Elsevier Science Inc.

Gender Sex differences Novelty Nucleus accumbens Dopamine Glutamate

In the present experiment, the locomotor effects of the dopamine D_2 receptor subfamily agonist, quinpirole, were tested in periadolescent rats to compare the behavior of this age group with previously published data on younger and older rats tested in this laboratory (42–44). Also in this experiment, gender differences in the responses to quinpirole in developing and adult rats were analyzed.

The period from postnatal days (PND)35–50 is defined as "periadolescence" in rats; this is the stage during which rats reach sexual maturity, sex hormone circulation arrives at adult levels, and vaginal opening occurs in females (3,28,36). This developmental stage is not commonly studied, despite striking differences in behavior, physiology, and neurotransmission between younger and older rats (6,36,39,44). Some studies indicate that periadolescent rats are unique with regard to psychopharmacological measures, such as a particular hyposensitivity to the behavioral effects of dopamine agonists (7,25,36). Conversely, some investigators have recorded a hypersensitive response to environmental novelty in periadolescent rats (36), although others have not (5,8–10,25). It would be useful to chart changes in locomotor activation throughout ontogeny, including the periadolescent period, because they may be applicable to research on the profound changes in human behavior and psychopharmacology taking place at that stage. Especially interesting is the study of dopamine transmission, given its involvement in locomotion, stress, reward-related behaviors, and schizophrenia (12,26,31,32,34,35).

The early ontological development of behavioral responses to dopaminergic drugs has been well investigated in rats from before birth to approximately PND30. In this laboratory, locomotor responses to the dopamine D_2 receptor subfamily agonist, quinpirole, have been recorded in PND10, 20, 30, and 60 male and female rats placed in a novel environment (42–44). PND10 and 20 rat pups exhibit locomotor activation in response to a wide dose range of quinpirole. Older rats (PND30 and 60) exhibit locomotion that is biphasic with respect to both dose and time. Low doses of quinpirole result in locomotor suppression relative to activity levels following vehicle injections, whereas higher doses suppress activity initially after drug injection and then increase activity later in a single test session [Figs. 1 and 2E and F; (16,43)]. The duration of quinpirole-induced locomotor suppression is greater in PND60 rats compared with PND30, while the level of activation is lower (44). Whereas sex differences in locomotor responding do not occur in rat pups PND30 and younger, PND60 female rats are more active than males in response to quinpirole injection (42).

In the present experiment, periadolescent male and female rats (PND40 and 50) were injected with quinpirole, and their locomotor activity in a novel environment was recorded. The

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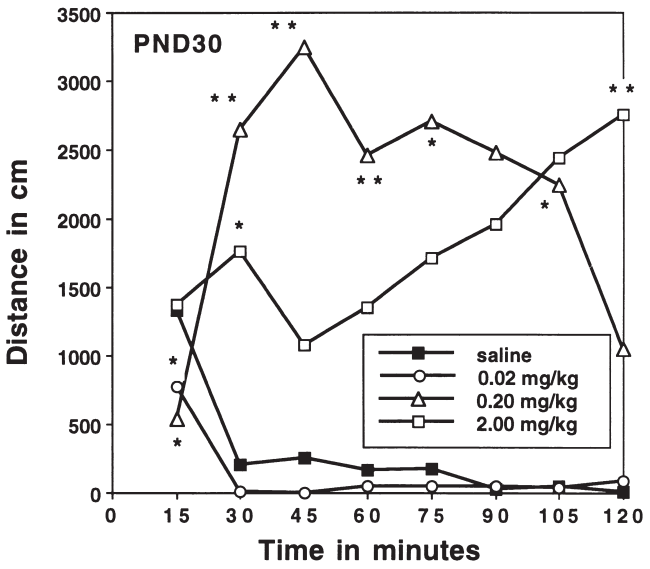

FIG. 1. Total distance (cm) traveled by PND30 rats (n = 10/group) in a 2-h test session after injection with quinpirole. Error bars are omitted for clarity. Significant differences from the saline-injected control group are indicated (*$p < 0.05$, **$p < 0.01$). [Figure reprinted from Van Hartesveldt et al. (44) with permission from Elsevier.]

aim of the study was twofold: 1) to complete the survey of quinpirole-induced locomotion in developing rats in our laboratory's paradigm; and 2) to investigate further the possibility that periadolescent rats are hyposensitive to dopaminergic drugs.

METHODS

Sprague–Dawley rats were bred in this laboratory, with dams and sires obtained from Zivic Miller Laboratories, Inc. (Portersville, PA). When the offspring reached either 40 or 50 days of age, quinpirole hydrochloride (Research Biochemicals International, Natick, MA) was injected subcutaneously at the nape of the neck in one of several doses (0, 0.02, 0.2, or 2.0 mg/kg) in a volume of 1.0 ml/kg. Saline served as the vehicle. Immediately after the injection, each animal was placed individually in a novel environment (an Omnitech Digiscan Animal Activity Monitor). Each monitor was a 41.91 × 41.91 × 30.48-cm Plexiglas cage with a wire-mesh floor. Photocell beams projected across the arena. They were spaced 2.54 cm apart such that 16 beams crossed side to side and 16 beams front to back, all 3 cm above the mesh floor. A Digiscan Analyzer recorded photocell beam interruptions, and the total distance traveled (cm) was analyzed in 15-min intervals throughout the 2-h test session. A one-way, sound-attenuated observation glass in the wall of the testing room enabled experimenter observation of the subjects from an adjacent laboratory room. The experiment was conducted in accordance with the NIH Guide to Care and Use of Laboratory Animals.

Statistical analyses consisted of multiple-factor analyses of variance (ANOVAs) and post hoc comparisons between groups. Two-way ANOVAs using dose and time as factors were conducted for each age and gender group. If a significant interaction was revealed, then one-way ANOVAs were conducted at each time interval using dose as the main factor. Subsequently, Duncan's Test was used for individual dose comparisons. Each animal was tested only once.

RESULTS

As published previously (44), PND30 rat pups responded to subcutaneous quinpirole injections in a dose- and time-dependent manner (Fig. 1). The low dose (0.02 mg/kg) decreased the distance traveled relative to the control group for the first 15-min interval. The midrange dose (0.2 mg/kg) suppressed the distance traveled early in the test session and increased it later. The high dose (2.0 mg/kg) significantly increased the distance traveled at the 30 and 120 min intervals. A two-way ANOVA confirmed these results with significant effects of dose, $F(3, 36) = 6.485$, $p = 0.001$, and a dose × time interaction, $F(21, 252) = 5.177$, $p < 0.001$. Other data have shown that there are no gender differences in locomotor responding to quinpirole or another dopamine D_2 receptor subfamily agonist, 7-hydroxy-dipropylaminotetralin (7-OH-DPAT) in PND30 rat pups (19,44).

In PND40 rats, quinpirole injection resulted in gender-, dose-, and time-dependent locomotor effects (Fig. 2A and B). In females but not males, the low dose of 0.02 mg/kg quinpirole inhibited the initial locomotion exhibited by the control group upon placement in the novel environment. In both males and females, the 0.2 and 2.0 mg/kg doses suppressed locomotion early in the test session and increased it above the level of the control group later in the session. A two-way ANOVA for male subjects revealed a significant interaction between the factors of dose and time interval, with time interval as a repeated measure, $F(21, 147) = 11.19$, $p < 0.001$. A significant main effect of dose was also revealed, $F(3, 21) = 4.37$, $p < 0.05$, as was a significant effect of time, $F(7, 147) = 20.28$, $p < 0.001$. For female subjects, a two-way interaction between dose and time was significant, $F(21, 168) = 10.44$, $p < 0.001$, as was the main effect of dose, $F(7, 168) = 11.01$, $p < 0.001$. Follow-up testing with one-way ANOVAs and Duncan's test exposed significant drug effects on the total distance traveled at specific time intervals (as marked in Fig. 2A and B).

In 50-day-old rats, locomotor responses to quinpirole also depended on gender, drug dose, and time after drug injection (Fig. 2C and D). In males, all three doses of quinpirole significantly decreased initial activity, but none increased activity later in the test session. In females, the 0.2 and 2.0 mg/kg doses of quinpirole suppressed initial activity, and the midrange dose of 0.2 mg/kg also increased activity later in the session. A two-way ANOVA for male subjects revealed a significant interaction between the factors of dose and time interval, with time interval as a repeated measure, $F(21, 112) = 8.01$, $p < 0.001$. A significant main effect of time was also revealed, $F(7, 112) = 22.87$, $p < 0.001$. For female subjects, a two-way interaction between dose and time was significant, $F(21, 98) = 4.94$, $p < 0.001$, as were the main effects of dose, $F(3, 13) = 4.68$, $p < 0.05$, and time, $F(7, 98) = 6.47$, $p < 0.001$. Follow-up testing with one-way ANOVAs and Duncan's test exposed significant drug effects on the total distance traveled at specific time intervals. (Results are marked in Fig. 2C and D.)

As also published previously (44), locomotor responses of PND60 rats to quinpirole depended on drug dose and time and after drug injection (Fig. 2E and F). In males, the only significant effect of quinpirole was a late increase in distance traveled after the 2.0-mg/kg dose. In females, the two higher doses suppressed initial activity and the high dose also in-

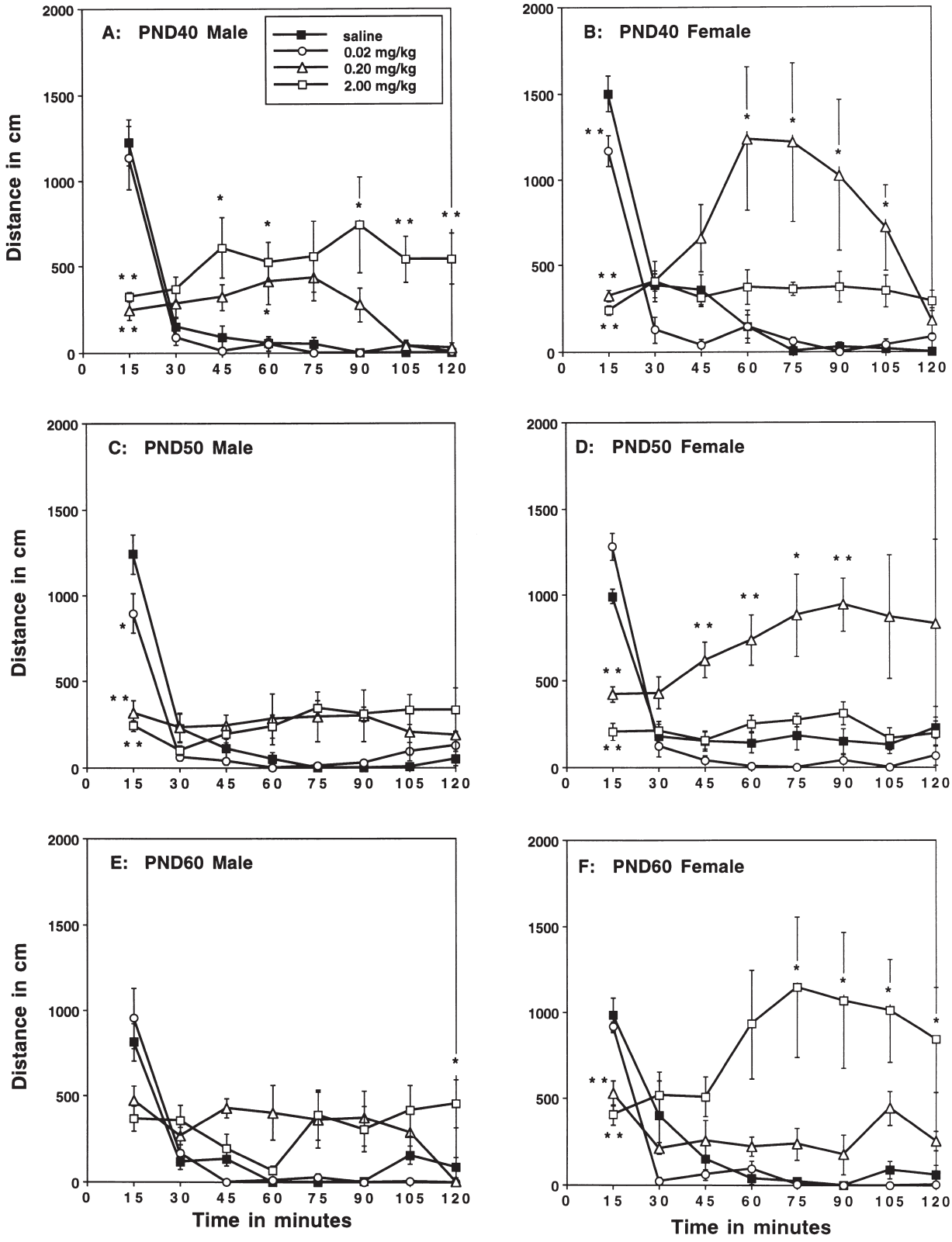

FIG. 2. Total distance (cm) traveled by PND40 male (A, n = 6–7/group) and female (B, n = 7/group), PND50 male (C, n = 3–6/group) and female (D, n = 4–5/group), PND60 male (E, n = 4–6/group) and female (F, n = 4–6/group) rats in a 2-h test session after injection with quinpirole. Significant differences from the saline-injected control group are indicated (*$p < 0.05$, **$p < 0.01$). [Graphs E and F reprinted from Van Hartesveldt et al. (44) with permission from Elsevier.]

creased activity later in the session. In males, a two-way ANOVA revealed a significant interaction between the factors of dose and time, $F(21, 112) = 4.47$, $p < 0.001$, as well as a significant main effect of time, $F(7, 112) = 14.17$, $p < 0.001$. In females, the two-way interaction between dose and time was significant, $F(21, 112) = 6.49$, $p < 0.001$, as were the main effects of dose, $F(3, 16) = 6.73$, $p < 0.005$, and time, $F(7, 112) = 7.72$, $p < 0.001$. The results of follow-up testing are marked in Fig. 2E and F.

DISCUSSION

By providing data on the locomotor behavior of rats in periadolescence, the present results complete a survey of the ontogenic sequence of dose–response patterns to subcutaneous injections of quinpirole (43,44). The data suggest that locomotor responses of periadolescent rats are not unique, but rather fall along the developmental continuum in which the level of quinpirole-induced locomotor activation decreases, especially in males, and the duration of quinpirole-induced locomotor suppression increases, as animals mature (42). Specifically, the ontogenetic sequence of responses includes: 1) locomotor activation only at PND10, induced by a wide dose range of quinpirole; 2) high magnitude of activation induced by high doses of quinpirole at PND20; 3) appearance of the biphasic response at PND30, including the onset of suppression of initial activity (Fig. 1); 4) continuation of the locomotor suppressive phase, diminished magnitude of subsequent activation, and the appearance of significant gender differences at PND40 and 50 (Fig. 2A–D); and 5) relatively low magnitude of activation induced by the high dose of the agonist at PND60 in males and the requirement of a higher dose of quinpirole to increase locomotion in PND60 females than in younger females (Fig. 2E and F). In all cases, locomotor activation induced by the dopamine D_2 receptor subfamily agonist is characterized by a "stiff-legged" exploration of the test chamber, i.e., the rats' hind legs are abnormally extended during locomotion. Stationary motor stereotypies are not seen following quinpirole administration. Locomotor suppression is characterized by a frozen stance.

With respect to locomotion induced by nonspecific catecholamine receptor agonists, periadolescent rats have been shown to be uniquely hyposensitive in comparison with older and younger rats, but the effect is not ubiquitous. For example, PND34–38 rats exhibited less locomotion than PND18–22 and PND45–49 rats in response to amphetamine (24). In addition, periadolescent rats (PND35) showed less locomotion than younger rats (PND14 and 21) in response to cocaine (37) or apomorphine (33). However, it is not clear that PND45–49 rats in the first study above would be considered older than the periadolescent stage, and thus, they may not constitute an appropriate group for comparison. Furthermore, PND37 or 49 rats injected with 2.0 mg/kg amphetamine exhibited more matrix crossings than age-matched controls, whereas younger rats (PND25) required a higher dose of 5.0 mg/kg amphetamine to increase matrix crossings above control levels (38). These periadolescent rats were thus actually more sensitive than weanlings to the dopamine receptor agonist, in terms of dose responsivity. Also in that study, the maximal number of amphetamine-induced matrix crossings was higher at PND25 than PND37, but was similar at PND37 and 49, perhaps supporting the presently proposed gradual developmental decline in magnitude of dopamine agonist-induced locomotor activation. Periadolescent rats have not shown hyposensitivity in neural responses to cocaine or nomifensine either. These two inhibitors of catecholamine reuptake blocked acetylcholine overflow from striatal slices of periadolescent rats and adult rats to the same degree, despite a lesser locomotor response to amphetamine shown by the periadolescent rats (7). The equivocal nature of the results on this topic may be attributed to differences in the precise age of experimental subjects, pharmacological activity of the agonists, parameters of the testing situations, or the lack of both younger and older age groups in the same testing conditions for comparison [as acknowledged by Spear and Brick (36)].

In the present study, the periadolescent group was bracketed by age groups well outside the periadolescent range; all animals were tested within the same experimental paradigm, all were given the same drug, and behavior was recorded continuously for 2 h postinjection. In this case, the periadolescent response was indeed lower in magnitude than that of younger animals, as recorded previously. However, this lower level of responding appeared to be a part of a developmental progression of declining sensitivity to the locomotor activating effects of quinpirole, rather than a unique hyposensitivity to dopamine receptor agonists. These results may indicate a developmental dissociation between locomotor responding to stimulation of both dopamine D_1 and D_2 receptor subfamilies (via indirect or mixed dopamine receptor agonists), on the one hand, and selective stimulation of the dopamine D_2 receptor subfamily, on the other hand. This idea is supported by the hypothesis of Bolanos et al. (7) that D_1 receptor stimulation may be disproportionately influential over neural activity and behavior compared with D_2 receptor stimulation during periadolescence. Removal of dopamine D_1 receptor subfamily stimulation by using a selective D_2 receptor subfamily agonist could, therefore, result in locomotion that does not show unique periadolescent characteristics.

The present effects concerning novelty-induced locomotion in saline-injected control groups are consistent with others showing comparable levels of motor activity in periadolescent and adult rats placed in a novel environment (5,7–10,25). The activity of saline-injected control groups declined only slightly between 30 and 60 days of age under the present conditions. The general pattern of novelty-induced activation was the same in control groups of all ages; it included initial exploration of the test monitor for approximately 20 min, followed by habituation and low levels of activity.

Gender differences are common in studies of motor activity. Female rats are generally more responsive than males to the locomotor activating effects of both novelty and dopamine agonists (4,25). This effect has its ontological onset around or just after puberty, and increases thereafter (9,10,38). Accordingly, in this study, the midrange dose of quinpirole increased the activity of PND40 female rats, whereas the high dose was required to increase the activity of PND40 male rats. Also, PND50 females were more prone to locomotor activation by the mid-range dose of quinpirole than males of the same age, and females were less susceptible to locomotor suppression by the low dose of quinpirole. Moreover, by PND60, female rats were also slightly more sensitive than males to the locomotor suppressive effects of quinpirole. Differences in novelty-related stress or drug metabolism may underlie the gender-dependent effects. The higher level of variability in the female subjects may reflect an influence of the estrous cycle on the responses to quinpirole. More substantial gender differences in the present study may have been obscured by odors in the test chambers influencing each gender differentially [Omnitech/Accuscan, personal communication; (4)].

Pharmacological evidence points to the nucleus accumbens as the anatomical seat of locomotor activity induced by novelty or dopamine receptor agonists (22,26,29). Given quinpirole's pharmacological action as a dopamine D_2/D_3 receptor agonist, developmental changes in locomotor responding to the drug may be expected to correlate with changes in expression of dopamine receptors in the nucleus accumbens. However, dopamine D_2 receptor levels peak transiently between PND25 and 60 in male rats, and remain steady and comparable across genders from PND60 to 120 (2). Thus, responses to quinpirole, which peak at PND20, decline gradually into adulthood, and are more robust in female rats than males, starting at approximately PND40 do not parallel changes in D_2 receptor binding. D_3 receptor levels in the nucleus accumbens rise from PND14 to 21, but only to approximately 40–45% of the level in PND60 rats (39). This pattern does not correlate with changes in the activational effect of quinpirole either, although it could be related to quinpirole-induced locomotor suppression. Furthermore, D_1 receptor levels could influence responding to a D_2/D_3 receptor agonist, but they increase substantially from PND25 to 40 in both males and females, and are maintained at higher levels in males than females into adulthood (2). Consequently, quinpirole-induced activation that peaks at PND20 does not correlate either positively or negatively with changes in dopamine D_1 receptor expression. Here again, though, the D_1 receptor expression could be related to the quinpirole-induced locomotor suppression that appears first at approximately 3 weeks of age and increases into adulthood, more robustly for males than females (42). Dopamine receptor affinity does not change across ontogeny (2,39), and many other aspects of dopamine neurotransmission reach adult levels before periadolescence (27), meaning that the gradual changes in dopamine-related behaviors are likely to involve more complex mechanisms. For example, there are ontological changes in transmission of the amino acid, glutamate, which indicate that glutamate could also be involved in the presently reported developmental changes in locomotor behavior (11,20,21,40).

Periadolescent developments in dopamine system function and their modulation by other neurotransmitters are interesting, mainly because of their hypothesized roles in neuropsychiatric disorders (12,15,45,46) and drug abuse (23,48,49). For example, symptoms of schizophrenia change from barely discernable childhood motor dysfunctions to profound postpubertal psychological dysfunctions (30,45), possibly due to periadolescent maturation of corticofugal glutamate projections into the mesolimbic dopamine system (47). Moreover, human experimentation with drugs of abuse most often begins during adolescence, and it is not clear that this phenomenon is solely a function of societal trends that enable humans to obtain abused drugs for the first time at that stage (17). Developmental changes in neurotransmission in the nucleus accumbens may contribute to the ontological onset of recreational drug use. An additional reason to investigate psychopharmacology in adolescent subjects is to develop age- and gender-appropriate pharmacological treatments for psychological disorders (13,41). This is especially important in the current era of increased diagnosis of teenage anxiety, depression, and psychotic disorders in youth of both genders (14,18), and this decade in which the Food and Drug Administration of the United States government is requiring more appropriate testing of drugs for prescription to pediatric patients (1).

ACKNOWLEDGEMENTS

The authors would like to thank Ms. Bonnie McLaurin for her excellent technical assistance. This research was supported by a Whitehall Foundation grant to C.V.H.

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