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Temporal and Environmental Effects on Quinpirole-Induced Biphasic Locomotion in Rats

CAROL VAN HARTESVELDT

Psychology Department, University of Florida, Gainesville, FL 32611-2250

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VAN HARTESVELDT, C. *Temporal and environmental effects on quinpirole-induced biphasic locomotion in rats*. PHARMACOL BIOCHEM BEHAV **58**(4) 955–960, 1997—The dopamine D_2/D_3 agonist quinpirole induces suppression of locomotor activity at low doses, and suppression followed by activation at high doses when given to rats of 30 days of age and older that are immediately placed in activity monitors. The duration of suppression is longer and the level of activation is lower at 60 than at 30 days of age, suggesting that the mechanism responsible for the suppression may play a role in the lesser activation in the older rats. However, habituation limits the ability to measure the duration of locomotor suppression. Therefore, 0, 0.2, or 0.2 mg/kg quinpirole was injected SC either 30, 60, or 120 min before placing male or female rats of 30 or 60 days of age in activity monitors for 30 min. At both ages, both doses of quinpirole suppressed activity when the animal was placed in the monitor 30 or 60 min after injection; at 60 days the drug also suppressed activity at 120 min after injection. Previously, 0.2 mg/kg quinpirole elicited locomotor activity 60 min after injection in rats placed immediately in activity monitors at both ages. Thus, not only time after injection but novelty of the environment are critical factors in the expression of locomotor suppression or activation in response to quinpirole. © 1997 Elsevier Science Inc.

Dopamine Locomotion Quinpirole Ontogeny Rat

PREVIOUS research has shown that many dopamine agonists have biphasic effects on locomotor activity related to dose. For example, at low doses, dopamine agonists suppress activity; at higher doses, dopamine agonists such as apomorphine (10,30) 3-PPP (4), 7-OH-DPAT (1,8), and quinpirole (11,34) enhance activity. But even at high doses, apomorphine (24), 7-OH DPAT (14), and quinpirole (11,34) have biphasic effects over time, first suppressing and later increasing activity. The mechanism underlying the biphasic nature of these effects, and in particular the suppression of activity, has been the subject of vigorous debate. It was initially thought that the suppression of activity, when the dose of drug reaching the brain was low, could be ascribed to the drug effect at the dopamine autoreceptor (10). According to this hypothesis, drug action at the autoreceptor leads to a decrease in the synthesis and/or release of dopamine at the synapse, reducing behavioral activity (the "autoreceptor hypothesis") (28). Because selective destruction of forebrain DA terminals decreases locomotor activity (13), a decrease in available dopamine would be expected to have the same result. The later increase in dopamine agonist-induced activity would then result from postsynaptic drug effects.

This explanation seemed consistent with the effects of dopamine agonists on developing animals. Until about 20–30 days of age, dopamine agonists elicit only activation, regardless of dose (4,20,26,27,35); in older animals, both suppression and later activation can be elicited with an appropriate dose. Early reports suggested that the dopamine autoreceptor was not functional until the age when dopamine agonists suppress activity (25,27).

Recently, however, it has been shown that first, the dopamine autoreceptor in some brain regions is functional neurochemically not only in the early postnatal period (2,15) but even prenatally in the rat (9). Second, because the time course and duration of the behavioral effects elicited by low doses of dopamine agonists do not coincide with the decrease in extracellular dopamine, there is doubt whether there is a causal connection between the neurochemical and behavior effects (28).

Not only is there a change in the biphasic locomotor response to a dopamine agonist between 20 and 30 days of age in the rat, but there are further changes between 30 and 60 days of age. As illustrated in Fig. 1, the level of quinpirole-induced activation is lower in 30 than 60 day olds (35); a finer grain analysis has shown that the duration of drug-induced

suppression of activity is longer in the 60 than 30 day olds (35). It was previously suggested that these two changes might be causally related; that is, that the onset and continued development of the dopamine agonist-induced suppression might contribute to the decrease in activation (4,29). To pursue this hypothesis, the duration of the suppression must be known. In the paradigm previously employed, the suppression induced by a low dose of quinpirole was tested against the exploratory activity elicited by placing the rat in a novel environment; after habituation of the controls, there was a floor effect beyond which suppression could not be measured. To determine whether the suppressive effects of quinpirole are of sufficient duration to diminish its activating effects, rats were injected with either a low or medium dose of quinpirole and introduced into the activity chamber either 30, 60, or 120 min later. The exploratory activity elicited by the novel environment at these times was used to determine whether the suppressive effects of quinpirole were still detectable.

METHOD

Subjects

Sprague–Dawley dams and sires were obtained from Charles River Farms, Wilmington, MA, and bred in this laboratory. 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 the 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 approximately equal numbers of males and females. Pups were housed with their dams until 25 days when they were removed from their dams and group housed with their same-sex littermates. A total of 216 rats were used: at 30 days of age, 54 females (about 125 g) and 54 males (about 150 g); at 60 days of age, 54 females (about 240 g) and 54 males (about 400 g).

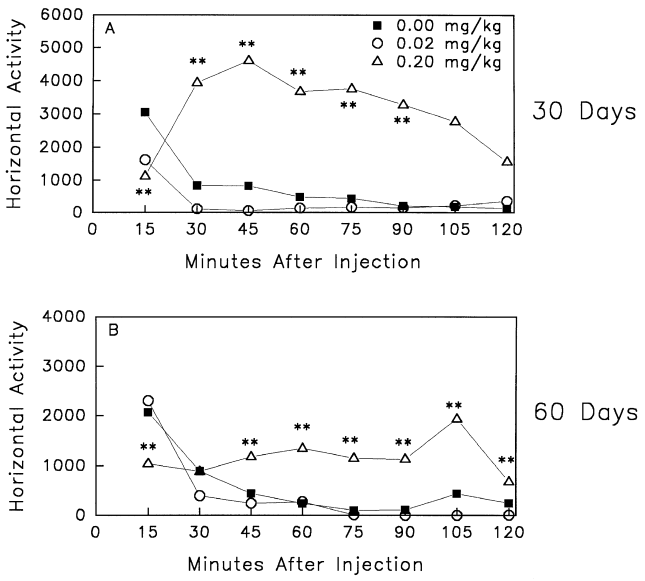

FIG. 1. The effects of quinpirole on horizontal activity in rats of 30 (A) and 60 (B) days of age. Rats were injected with the drug and placed immediately in activity monitors. Error bars are omitted for clarity. Mean SEMs for A for 0.00, 0.02, and 0.2 mg/kg were 169, 107, and 954, respectively. Mean SEMs for Panel B for 0.00. 0.02, and 0.20 mg/kg were 122, 59, and 285, respectively. $n = 10$ per group. Relative to controls (0.00 mg/kg), $^{**}p < 0.01$. Figure prepared from data collected by Van Hartesveldt et al. (35). Reprinted by permission of the publisher from "Ontogeny of biphasic locomotor effects of quinpirole," C. Van Hartesveldt, M. E. Meyer, and T. J. Potter, Pharmacology Biochemistry and Behavior, 48:781–786. © 1994 by Elsevier Science Inc.

Drugs

The dopamine D_2/D_3 agonist quinpirole (LY 171555; Research Biochemicals International) was administered peripherally at doses of 0.02 and 0.2 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

Following SC drug injection, pups were returned to their homecages for either 30, 60, or 120 min. Each rat pup was then placed in the center of an Omnitech Digiscan Animal Activity Monitor and data were collected. Litters were tested on either 30 or 60 days of age. Each animal was tested only once. Animals from each age, dose, and delay group were tested for 30 min with data collection at each 5 min interval. Approximately equal numbers of males and females were tested in each group, and $n = 12$ pups in each group.

Apparatus

The acrylic cage within the monitor measured 41.91 cm wide × 41.91 cm long × 30.48 cm tall. The monitor rested on a wire grid floor and was equipped with 16 beams 2.54 cm apart from side to side and 16 beams from front to back, 3 cm above the floor. The Digiscan analyzer converted the total numbers of breakages of beams per time unit to a measure called horizontal activity. This measure was chosen for analysis because the purpose of the experiment was to determine the duration of behavioral suppression, and this was the most sensitive measure available. Both in this lab and others (11), in the dose range used here, quinpirole elicits neither grooming nor stereotyped behavior except for perseveration of travel along fixed routes.

Statistics

For each of the two ages, 30 and 60 days of age, a four-way ANOVA was carried out, with between-subjects factors of sex (male and female), dose (0, 0.02, and 0.2 mg/kg quinpirole), delay (30,60 and 120 min), and the within-subjects factor of intervals (six 5-min intervals). When appropriate, this ANOVA was followed up by lower level ANOVAs and pairwise comparisons using Duncan's Multiple Range test.

RESULTS

Significant effects found in ANOVAs for the results for rats at 30 and 60 days of age are presented in Table 1. Probability values expressed in the text but not identified by an effect are from the subsequent analyses.

30 Days

The highest dose of quinpirole elicited the greatest activity (dose, $p < 0.001$), and activity was higher at the 30-min delay than later (delay $p = 0.005$). At the 30-min delay (Fig. 2A), rats given 0.02 mg/kg quinpirole had significantly less activity

TABLE 1

SIGNIFICANT EFFECTS FOUND IN ANOVAs FOR 30- AND 60-DAY-OLD RATS

Effect	F	*df*	*p*
30 days of age			
Dose	13.9	2, 90	<0.001
Delay	5.6	2, 90	0.005
Dose × delay	8.0	4, 0	<0.001
Intervals	153.3	5, 450	<0.001
Dose × intervals	18.0	10, 450	<0.001
Delay × intervals	5.9	10, 450	<0.001
Dose × delay × intervals	5.5	20, 450	<0.001
60 days of age			
Sex	21.6	1, 90	<0.001
Dose	28.2	2, 90	<0.001
Sex × dose	3.6	2, 90	0.031
Dose × delay	4.4	2, 90	<0.003
Intervals	168.7	5, 450	<0.001
Sex × intervals	5.3	5, 450	<0.001
Dose × intervals	21.2	10, 450	<0.001
Delay × intervals	4.8	10, 450	<0.001

than controls for the first five intervals (dose × delay and dose × delay × intervals, $p < 0.001$; $p < 0.01$ for the first three intervals, and $p < 0.05$ for the fourth and fifth). Rats given 0.2 mg/kg quinpirole were significantly less active than controls in the first interval ($p < 0.01$), but significantly more active for the last four intervals (ps < 0.01). At the 60 min delay (Fig. 2B), rats given either 0.02 or 0.2 mg/kg quinpirole had significantly less activity during the first interval; rats given 0.2 mg/kg were significantly more active than controls only at the fifth interval ($p < 0.05$). At the 120 min delay (Fig. 2C), rats given either dose of quinpirole had less activity than controls, but not significantly less.

60 Days

Rats given either dose of quinpirole were less active than those given the vehicle (dose, $p < 0.001$). However, the females were more active than the males (sex, $p < 0.001$) at every drug level (sex × dose, $p = 0.031$). The disparity in the activity levels of the sexes was greater at 0.2 mg/kg quinpirole ($p < 0.01$) than when given the vehicle ($p < 0.05$) or 0.02 mg/kg quinpirole (not significantly different). Separate analyses of the within-session data were carried out for the 60-day-old males and females (sex × intervals, $p < 0.001$) and the data are presented in Figs. 3 and 4, respectively.

For each sex, at the 30-min delay both doses of quinpirole significantly decreased activity for the first 5 min ($p < 0.01$), and 0.02 mg/kg continued to do so in the last 15 min (Figs. 3A and 4A). The males, however, had a significant suppression for the first 15 min at both drug doses ($p < 0.01$), while the females initial suppression was for only 10 min, and only at the 0.02 mg/kg dose ($p < 0.01$). The higher dose in the females did not significantly suppress activity after the first 5 min, and their scores rose to the level of the controls.

At the 60-min delay (Figs. 3B and 4B), both doses of quinpirole suppressed activity for the first 5 min in both sexes ($p < 0.01$). The lowest dose continued to suppress activity in the females up to 25 min ($p < 0.01$, Fig 4B); this effect was not as pronounced in the males (Fig. 3B).

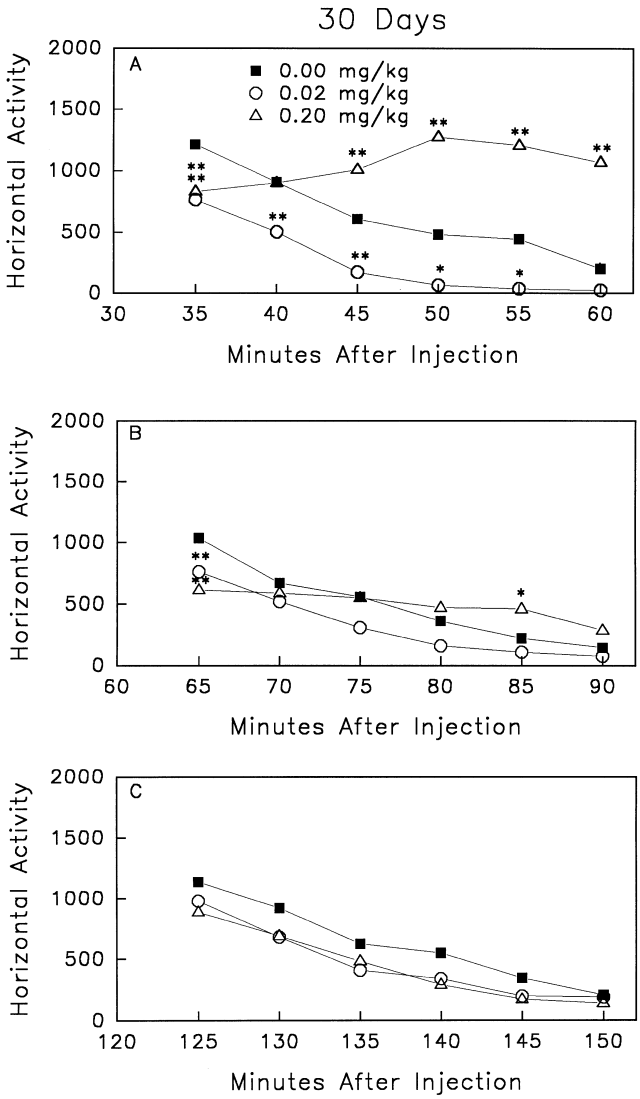

FIG. 2. The effects of quinpirole on horizontal activity in rats of 30 days of age when they were placed in the activity monitors at delays of 30 (A), 60 (B), or 120 (C) min after drug injection. Mean SEMs for Panels A, B, and C were 95, 75, and 72, respectively. Error bars are omitted for clarity. $n = 12$ per group. Relative to controls (0.00 mg/kg), *$p < 0.05$; **$p < 0.01$.

At the 120-min delay there was a minimal drug effect in females (Fig. 4C), but in males the highest dose suppressed activity significantly for 15 min ($p < 0.01$; Fig. 3C).

DISCUSSION

The results of this experiment show that quinpirole can suppress locomotor activity for up to 120 min, depending on dose and age. The lowest dose of quinpirole (0.02 mg/kg), at both 30 and 60 days of age, elicited a decrease in exploratory activity lasting for at least an hour, long after a decrease could be detected in the standard paradigm. In addition, at the 60- and 120-min delays, the suppression of activity was of longer duration (in a sex-dependent manner) in 60 than 30 day olds. These findings are consistent with the hypothesis that quinpirole alters locomotor activity by means of two separate processes,

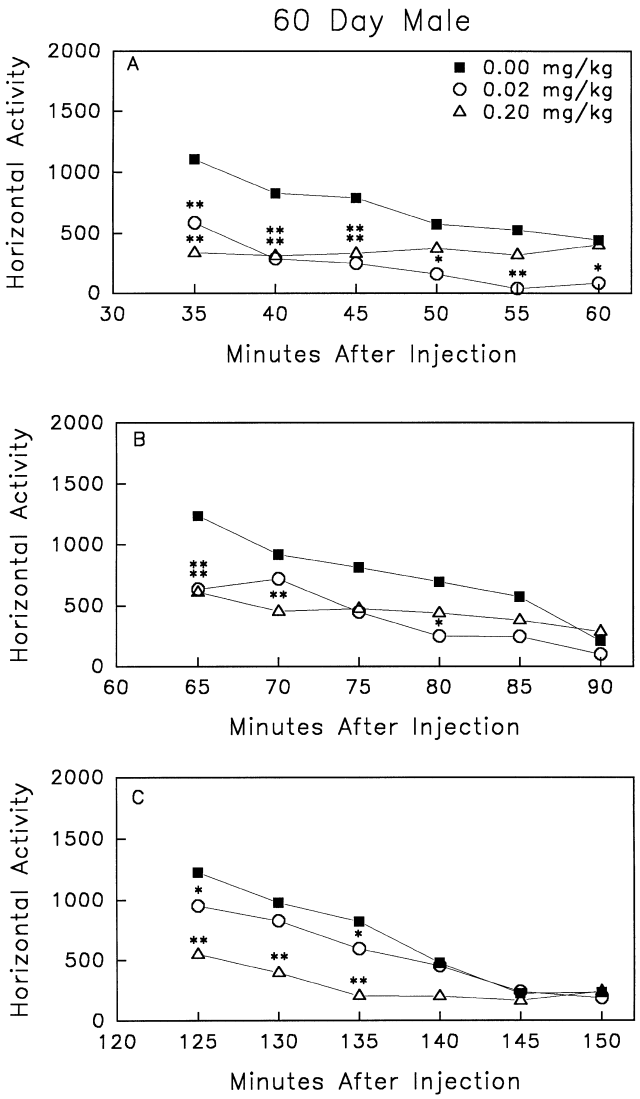

FIG. 3. The effects of quinpirole on horizontal activity in male rats of 60 days of age when they were placed in the activity monitors at delays of 30 (A), 60 (B), or 120 (C) min after drug injection. Error bars are omitted for clarity. Mean SEMs for Panels A, B, and C were 84, 103, and 89, respectively. $n = 6$ per group. Relative to controls (0.00 mg/kg), $*p < 0.05$; $**p < 0.01$.

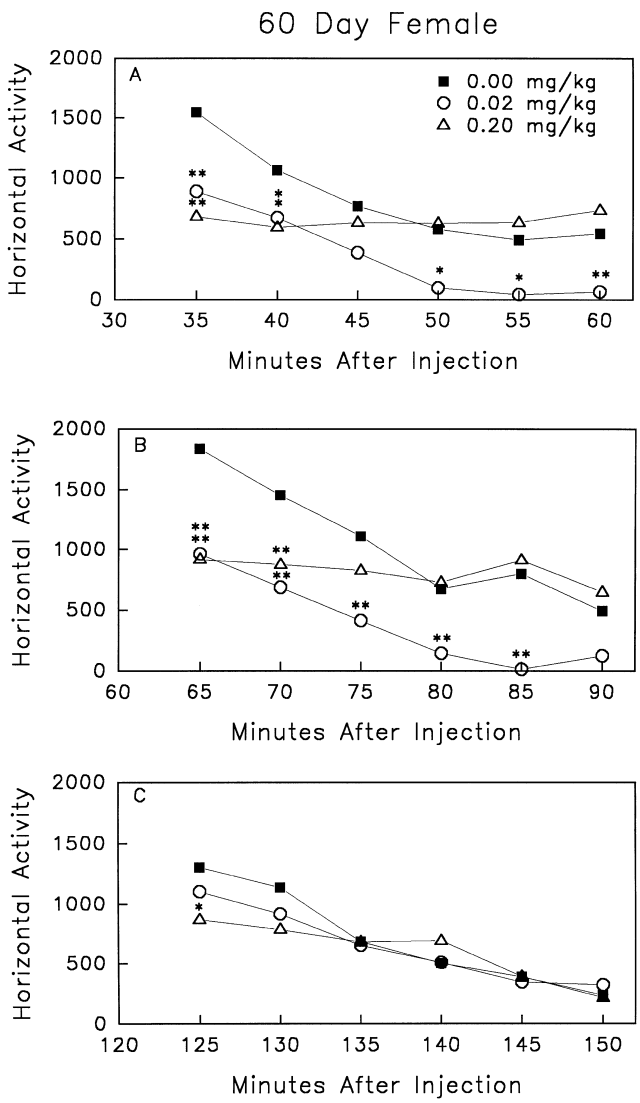

FIG. 4. The effects of quinpirole on horizontal activity in female rats of 60 days of age when they were placed in the activity monitors at delays of 30 (A), 60 (B), or 120 (C) min after drug injection. Mean SEM's for Panels A, B, and C were 108, 118, and 125, respectively. Error bars are omitted for clarity. $n = 6$ per group. Relative to controls (0.00 mg/kg), $*p < 0.05$; $**p < 0.01$.

suppression and activation, and that an increase in the drug-induced suppression across age may result in less activation.

The results for the higher dose of quinpirole, 0.2 mg/kg, further emphasize the critical role of the novel environment in the drug's locomotor effects. Previous research had shown that at 60 min after injection (and immediate placement in the activity monitor), 0.2 mg/kg quinpirole elicited an increase in locomotor activity in both 30- and 6-day-old rats [(35); see Fig. 1]. Yet in the present experiment, when rats given the same dose of quinpirole were first introduced into the test chamber 60 min after injection, their activity decreased relative to controls. This interesting result indicates that the capacity for quinpirole to induce suppressive effects on locomotion apparently coexists with the capacity to elicit increased activity. At doses and times at which activation can be elicited, the suppressive effect of the drug is revealed when the animal is placed in a novel environment. These results are not readily interpretable by the "autoreceptor hypothesis," (28) but emphasize the critical role of the novel environment in altering brain activity and shaping the behavioral response to a dopamine agonist.

Novelty or stress increases DA release and/or turnover in both the medial prefrontal cortex (12) and the nucleus accumbens (5,18). In addition, the behavioral effects of dopamine injected directly into the nucleus accumbens differ not only as a function of dose and time after injection, but also the familiarity of the environment. For example, while intraaccumbal dopamine usually elicits a brief increase in activity in a familiar environment (7,19), in a novel environment it decreased activity at low doses (6,31), and briefly decreased it before ac-

tivation at high doses (31). Similarly, when quinpirole was injected directly into the nucleus accumbens of a rat in a novel environment with partitions to elicit a high level of locomotor activity, the drug decreased locomotion (21,22); in a novel environment without partitions, in rats with a lower level of activity, it increased locomotion (36).

Wu et al. hypothesize that quinpirole increases locomotion by acting on postsynaptic dopamine receptors in the nucleus accumbens, and decreases it by acting on presynaptic dopamine receptors on the terminals of hippocampal—accumbens axons to reduce their release of glutamate (36). Reduced glutamate in the accumbens would decrease the amount of DA released by mesolimbic DA terminals, decreasing locomotor activity. In addition, the effects of a dopamine agonist on receptors in the medial prefrontal cortex or amygdala might also ultimately affect the output of the nucleus accumbens (23) to the ventral pallidum (17) to the brainstem, and alter locomotor activity.

Thus, exposure to a novel environment not only alters activity in the meso-accumbens–dopamine system, according to the hypothesis above, but also in limbic system structures that interact with it. Therefore, the ontogenic appearance and changes in dopamine agonist-induced behavioral suppression may be related to the maturation of limbic–accumbens pathways. Interpreting the results of the present experiment in light of this hypothesis, the suppressive effect of quinpirole would not appear until these pathways were functional, and would increase as they reached full maturity. Thus, at 30 days of age, rats given 0.2 mg/kg quinpirole at the 30 min delay had a significant increase in activity following the early suppression, while the 60 day olds did not; and the duration of suppression was longer at 60 than 30 days of age. Because both the hippocampus and medial prefrontal cortex are relatively late maturing, the ontogenetic timetable for the onset of drug-induced suppression would be consistent with these results. Caution is in order concerning such a specific interpretation, however, because in the present experiment quinpirole was given systematically and could be acting at other brain sites. For example, in adult rats, quinpirole injected directly into the striatum has suppressive and activating effects quite similar to those seen after systemic injection (34).

Whatever the mechanisms underlying the suppressive and activating effects of dopamine agonists, they are somewhat different in male and female rats. Consistent with most of the literature (3), the postpubertal (60 day) females were more active than the males. In the females but not the males, the high dose of quinpirole increased activity after the early suppression at the 30 and 60-min delays. Interactions between the gonadal steroid hormones and both the mesostriatal (33) and mesolimbic dopamine systems (16,32) have been documented. However, until the mechanisms underlying responses to quinpirole are further identified, the nature of gender interaction with them must remain a matter for speculation.

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