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Differential Effects of Dopamine D_2 Agonist Quinpirole Upon the Dorsal Immobility Response in Rats

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MEYER, M. E., M. E. MEYER, T. J. POTTER AND C. VAN HARTESVELDT. *Differential effects of dopamine D_2 agonist quinpirole upon the dorsal immobility response in rats.* PHARMACOL BIOCHEM BEHAV **42**(2) 257–259, 1992. – The effects of various dose levels of systemically injected quinpirole upon the dorsal immobility response (DIR) over a time course was investigated in male rats. A low dose of quinpirole (0.01 mg/kg) significantly attenuated the duration of the DIR following the 10-min interval, whereas the highest dose (1.0 mg/kg) had a biphasic effect so that at the 10-min interval the duration of the DIR was significantly potentiated and at the 60-min interval the duration of the DIR was significantly attenuated. The intermediate dose (0.1 mg/kg) had intermediate behavioral effects. The data support the growing evidence that quinpirole has differential effects upon behavior over time as a function of the dose levels. The present data were discussed in reference to presynaptic and postsynaptic dopamine D_2 receptor theory.

Quinpirole Dopamine D_2 receptor Biphasic effect Dorsal immobility response

DURING the last 10 years, the existence of subtypes of dopamine receptors has become well accepted. Currently, the dopamine receptors are classified as either D_1 or D_2 receptor subtypes (12). The D_1 receptor is typically associated with stimulation of adenylate cyclase, while the D_2 receptor is either independent of adenylate cyclase or mediates its inhibition. The availability of agonists and antagonists acting primarily at the D_1 or D_2 receptor sites has stimulated research to characterize the functional effects of each receptor subtype. While it has been proposed that both D_1 and D_2 receptors must be stimulated to achieve the full range of dopamine-mediated behaviors (2), quinpirole (LY 171555), a D_2 agonist, differentially influences locomotor behavior as a function of the dose levels (0.03, 0.125, 0.5, and 8 mg/kg) and of the durations of its time course (4). A low dose level (0.02 mg/kg) of systemically injected quinpirole induces a decrease in locomotor activity over a short duration and at the higher dose level (2.0 mg/kg) results in a biphasic effect with an initial inhibition of locomotor activity followed by an increase in activity (13). On the other hand, it has been reported that quinpirole (0.5–5.0 mg/kg) induces dose-dependent catalepsy in various strains of mice (9,10).

The dorsal immobility response (DIR) is one of a number of complex inhibitory responses that can be experimentally induced in various species of animals (14–16). The DIR is a species-typical response experimentally elicited by grasping an animal by the dorsal skin at the nape of the neck and lifting the animal off its feet. The rat immediately exhibits a stereotypical immobility that persists for a period of time (group means in drug-free animals approximates 60 ± 10 s) until the animal emits escape-like behaviors. Within the context of naturally occurring inhibitory behaviors, the DIR may mimic the transport response in the young of some mammalian species when the adult picks up and carries the young by the dorsal skin (1,3,7), and may also mimic the immobility of a prey when carried by a predator (5,6,11).

In the present experiment, we explored the effects of various dose levels of quinpirole over a time course of 60 min upon duration of the DIR. Because of its differential and biphasic effects upon locomotor activity as a function of the dose and time course, we were interested in the generality of those effects upon inhibitory behaviors. From the locomotor activity data, we predicted that the low dose level of quinpirole would attenuate the duration of the DIR, whereas the high dose level would result in a biphasic effect with an initial potentiation followed by an attenuation of the DIR over the 60-min time course.

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METHOD

Animals

Forty 50- to 60-day-old male Long-Evans rats weighing 200–225 g were obtained from Charles River (Wilmington, MA). They were individually housed, had food and water ad libitum, and were maintained on a 12 L:12 D (0700–1900) cycle. This study was carried out in compliance with the rules set forth in the NIH Guide for the Care and Use of Laboratory Animals.

Drug Procedures

Quinpirole hydrochloride (LY 171555, Lilly Research Laboratories, Indianapolis, IN) was dissolved in distilled water that served as vehicle (VEH). Ten animals were randomly assigned to receive one of the following doses of 0.00 (VEH), 0.01, 0.1, or 1.0 mg/kg quinpirole. The drugs were systemically injected into the flank with a volume of 1 ml/kg for each dose.

Behavioral Testing

At the time of testing (between 1200–1600 h), the animal was removed from the home cage, injected, and returned to the home cage. At time intervals of 10, 20, 30, 40, 50, and 60 min following injection, the animal was behaviorally tested. Upon being removed from the home cage, the animal was placed in a V-shaped trough to restrict its general movement for 30 s. To elicit the DIR, the rat was grasped by the dorsal skin at the nape of the neck (between the base of the skull and the back of the ears) and lifted off its feet with no part of the animal's body touching any other surface. As all animals displayed the stereotypical DIR when it was first induced, duration of the DIR was measured from the immediate onset of the response until the animal made directed movements associated with escape-like behaviors or until 300 s had elapsed. Following each trial, the animal was returned to the home cage. Each animal received six trials during the test session with an intertrial interval of 10 min.

Statistics

A two-factor mixed-design analysis of variance (ANOVA) was used to examine the effects of four dose levels of quinpirole upon the duration of the DIR measured over six 10-min time blocks. Dunnett's test for the comparison of treatment means with the VEH control was used to make posthoc comparisons. In addition, within-subjects ANOVAs within the time blocks for each treatment condition were determined. A p value equal to or less than 0.01 was judged significant.

RESULTS

Systemic injections of quinpirole resulted in significant differences in the duration of DIR as a function of the four dose levels, $F(3, 36) = 46.01$, $p < 0.001$, across the six time blocks, $F(5, 180) = 203.31$, $p < 0.001$, and in the dose levels $\times$ time blocks interaction, $F(15, 180) = 58.02$, $p < 0.001$. These main and interaction effects are illustrated in Fig. 1. The within-subjects analyses resulted in significant trends within each of the drug-treated groups ($p < 0.01$); on the other hand, the trend for the vehicle control group was not significant ($p > 0.01$). The subsequent analyses revealed that in comparison to the vehicle controls during the first time block at 10 min duration of the DIR was significantly potentiated with 0.1 and 1.0 mg/kg quinpirole; at 20 min, duration of the DIR was potentiated with 1.0 mg/kg and attenuated by 0.01 mg/kg quinpirole; at 30 min, 0.01 mg/kg quinpirole attenuated duration of DIR; at 40 and 50 min, both 0.01 and 0.1 mg/kg quinpirole attenuated the DIR; and at 60 min, 0.01, 0.1, and 1.0 mg/kg quinpirole significantly attenuated duration of the DIR ($p < 0.01$).

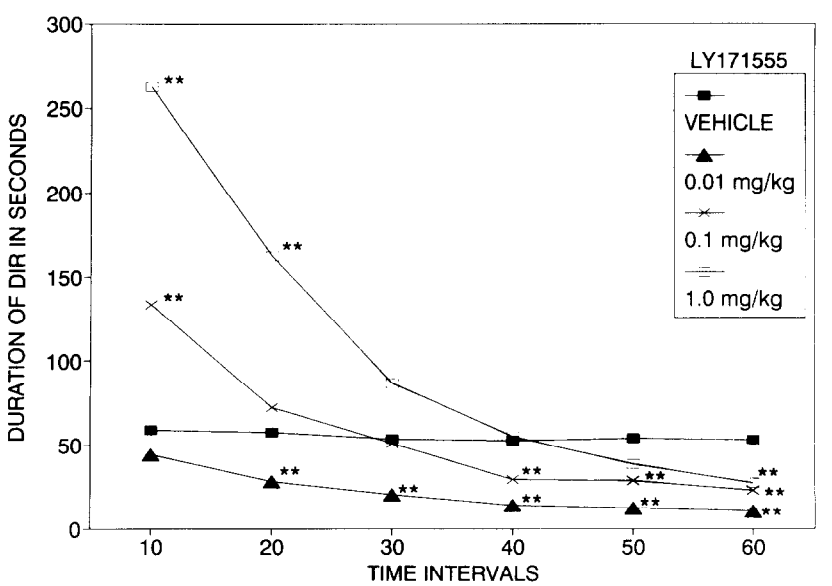

FIG. 1. Effects of systemically administered quinpirole (LY 17155) on mean duration of the DIR over six 10-min time blocks or 60 min. Significant statistical differences from the vehicle control group (VEH) are indicated by $^{**}p < 0.01$. Error bars have been omitted for clarity.

DISCUSSION

The data in the present study clearly show that the dopamine D_2 receptor agonist quinpirole differentially affects duration of the DIR in a dose and time course manner. The low dose of quinpirole (0.01 mg/kg) administered systemically reduced duration of the DIR, whereas the higher dose levels (0.1 and 1.0 mg/kg) produced a biphasic effect. Initially, the higher dose levels increased the DIR and subsequently produced a reduction of the DIR durations below the levels of the controls. These data for the most part were compatible with the behavioral effects of quinpirole on locomotor activity, but with a behavioral inhibitory paradigm. The most striking difference between the effects of quinpirole on locomotor activity and the DIR was that the low dose of quinpirole initially suppressed locomotor activity but did not have any significant behavioral effects after approximately 30 min. On the other hand, a low dose (0.01 mg/kg) attenuated the DIR at 20 min and thereafter during the 60-min session. Furthermore, within the locomotor activity paradigm the vehicle groups typically show significant habituation over time courses. Within the behavioral inhibitory paradigm using the DIR, the vehicle controls showed no significant habituation.

The biphasic effects of the larger doses of quinpirole has been interpreted as a function of both the pre- and postsynaptic dopamine D_2 receptors (13). Stimulation of the presynaptic or autoreceptors inhibits tyrosine hydroxylase activity and dopamine turnover rate, electrical activity, and release (8,17). Such stimulation of the autoreceptors has been proposed to account for the initial depressant effects of dopamine agonists on locomotor activities (8,17). However, covariability does not prove that the early suppression effects on locomotor activity and the potentiation of immobility are mediated by the autoreceptors. Furthermore, such speculation does not account for the attenuation of duration of the DIR with low dose levels nor the biphasic effects with higher dosages of the dopamine D_2 agonist quinpirole. If the autoreceptors do in fact mediate behaviors, their receptivity or sensitivity must differ from the postsynaptic receptors, as well as their rate of habituation.

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