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Effects of Dose and Interdose Interval on Locomotor Sensitization to the Dopamine Agonist Quinpirole

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SZECHTMAN, H., H. DAI, S. MUSTAFA, H. EINAT AND R. M. SULLIVAN. *Effects of dose and interdose interval on locomotor sensitization to the dopamine agonist quinpirole.* PHARMACOL BIOCHEM BEHAV **48**(4) 921–928, 1994. – To assess whether the interval between injections affects the course of locomotor sensitzation to quinpirole, groups of rats were injected every 2, 4, or 8 days with quinpirole (0, 0.025, 0.25, 0.5, and 2.5 mg/kg; n = 222) and their locomotor activity monitored after each injection for a total of 10 tests. Results indicate that the number of drug injections, rather than the interval between them, predominantly controls the development of locomotor sensitization to quinpirole. It is suggested that this may reflect a rapid induction but slow decay time for a response-enhancing factor stimulated by each injection of quinpirole, and that the effects of this putative factor are cumulative but saturable.

Locomotion Hyperactivity Rats Reverse tolerance Time course of sensitization

SOME responses to a dopaminergic stimulant such as amphetamine, cocaine, apomorphine, bromocriptine, or quinpirole, increase upon repeated exposure to the drug [e.g. (16,17, 22,32,38)]. This phenomenon of enhanced responding [termed behavioral sensitization (31)] has attracted much interest because of its possible relevance to an understanding of the mechanisms and development of behavioral pathology including schizophrenia (1,14,15,19,31,32), mania (28), drug abuse (26), and posttraumatic stress and panic disorders (2,29), as well as because of its possible implications for pharmacotherapy (3) and neural plasticity (18,30,42). A number of factors have been shown to affect the development and expression of sensitized responding, including number and timing of drug injections (6,7,21,23,27), passage of time (5), dosage regimen (10), the behavior measured [e.g. (37,40)], stress history [e.g. (4)], individual differences [e.g. (33)], and environmental conditioning [e.g. (36)]. Other studies have suggested that development of sensitization may involve multiple independent behavioral changes, ordered in time, and saturable (38) and that the control of these changes may include components that are environment independent, behavior specific, and context dependent, each having a relatively different contribution and mechanism [e.g. (13,35,39,41)].

The present study examines the importance of interdose interval in induction of locomotor sensitization by the D_2/D_3 dopamine agonist quinpirole. A number of investigators suggested that the temporal characteristics of exposure to psychostimulants may regulate the course of responsiveness to repeated treatment, with intermittent exposures inducing enhanced responding and continuous drug infusion (or very short intervals between injections) favoring the development of tolerance (6,8,25,27). In fact, considering that the sensitizing effects may last for months (12,30), the suggestion had been made that frequent injections are unnecessary for induction of sensitization and may even be counterproductive (31); the mere passage of time may be sufficient (3). However, the characteristics of the relationship between number of injections and the spacing of injections are not known for novel

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dopamine agonists such as quinpirole [shown previously to induce robust sensitization of locomotor distance (24,38,41)]. Therefore, the present study assesses how quinpirole injections spaced 2, 4, or 8 days apart affect the course of development of locomotor sensitization.

METHOD

Animals

Subjects were 222 male rats (Charles River, Canada), weighing 290–450 g at start of treatment. Two hundered and two were hooded Long–Evans rats and the remaining 20 were from the Sprague–Dawley strain. The latter animals were employed to assess the generality of the sensitization curve; because locomotor sensitization in this strain was equivalent to the sensitization induced in the Long–Evans rats, the data of all rats are presented together. Rats were housed in polyethylene cages (35 × 30 × 16 cm) in a temperature-controlled room (22°C) with lights on at 0700 h and off at 1900 h. Food and water were provided ad lib. Subjects were handled daily for at least a week before the start of the study. Tests were performed during the light phase of the day–night cycle.

Drugs

Quinpirole hydrochloride (0.025, 0.25, 0.5, and 2.5 mg/kg; Research Biochemicals, Natick, MA) was dissolved in normal saline and injected (in a volume of 1 ml/kg) under the nape of the neck. Control rats received injections of an equivalent volume of saline.

Apparatus

Locomotor activity was measured in Plexiglas activity chambers (40 × 40 × 35 cm, Omnitech Electronics, Columbus, OH) that were interfaced to a Digiscan 16 monitor and an IBM PC computer, providing an automatic record of the distance travelled by the animal. A ventilated Plexiglas lid covered the top of the activity chamber to prevent jumping out of the cage.

Design and Procedures

Groups of rats were administered quinpirole (0, 0.025, 0.25, 0.5, or 2.5 mg/kg) every 2, 4, or 8 days for a total of 10 injections. There were 10 rats per group except for four groups where the n was higher: 42 for the group administered saline every 4 days, 30 for the group given 0.5 mg/kg of quinpirole every 4 days, 20 for saline every 2 days, and 20 for 0.5 mg/kg of quinpirole every 2 days. Because the number of rats that could be tested in 1 day was limited, not all groups were run in parallel. To minimize the confounding of spacing of injections and age of testing, rats were entered into the experiment at varying ages, within the constraint that the duration of the experiment is as short as possible. Consequently, variations in age for groups injected every 8 days was the smallest, possibly accounting for their lower acute response indicated in the Results section.

For each injection of quinpirole or saline, rats were transported to the experimental room, weighed, placed into the activity chambers for 5–10 min, injected, and their locomotor activity monitored for the next 90 min.

Statistics

The acute locomotor response at injection 1 was analyzed by a dose by interval analysis of variance (ANOVA), with five levels on the first and three levels on the second factor; Duncan multiple range test was used for post hoc comparisons. For the percent of acute response scores, a log transformation was computed and these values analyzed using ANOVAs. Because of the biphasic profile of the acute dose–response curve, one ANOVA was performed for the higher doses of quinpirole (0.25–2.5 mg/kg) and a separate one comparing the groups injected with saline and the low dose of quinpirole. For analysis of the higher doses, there were three factors: interval (interinjection interval every 8, 4, or 2 days), dose (0.25, 0.5, or 2.5 mg/kg), and injection (injection #2 to injection #10), with injection being a repeated-measures factor. A similar analysis was performed on the low dose groups, except that the dose factor had only two levels (0 and 0.025 mg/kg).

For analysis of the kinetics of sensitization (Fig. 2), the mean (log percent) response at each injection was computed and the parameters providing the best fit for the following asymmetric sigmoid equation were estimated using a nonlinear curve-fitting algorithm (Fig.P Version 6.0, Fig.P Software Corporation, Durham, NC):

$$R = \frac{(R_{max} \times I^n)}{(I^n + I_{50}^n)}$$

where R is the response after I number of quinpirole injections and the estimated parameters are the maximum response after infinite number of injections (R_{max}), the number of injections to reach the half-maximum response (I_{50}), and some coefficient (n) representing sigmoidicity. In computing R, the response at first injection was subtracted. This equation is a standard function describing linear dose vs. effect relationship. The values of antilogarithms are plotted (on a log scale)

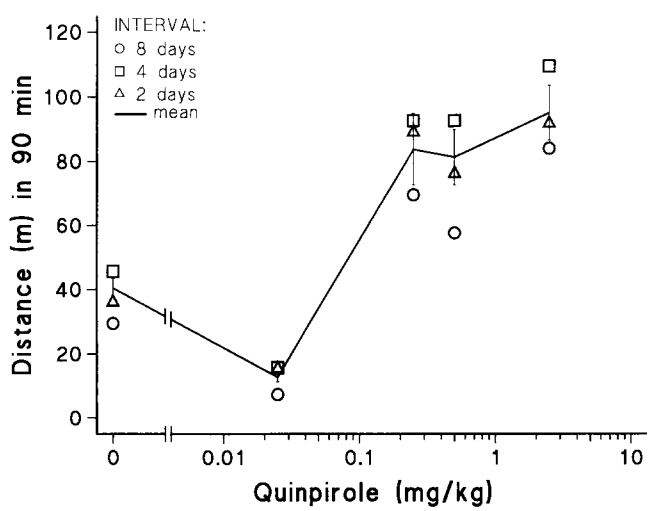

FIG. 1. Locomotor response to an acute injection of quinpirole (0, 0.025, 0.25, 0.5, and 2.5 mg/kg). Symbols represent groups destined to receive subsequent injections at the indicated interinjection intervals; solid line is the overall mean (±SEM) response at the given dose.

in Fig. 2. For all tests, the statistical criterion was set at $p < 0.05$.

RESULTS

Acute Dose-Response Curve

Figure 1 shows the acute locomotor response to different doses of quinpirole. Consistent with previous findings (9,11) the dose-response curve was biphasic: the lowest dose (0.025 mg/kg) induced inhibition and higher doses (0.25–2.5 mg/kg) excitation, with near maximum excitation stimulated by the 0.25 mg/kg dose of quinpirole. Statistical analysis supported this observation: the effect of dose was significant, $F(4, 207) = 18.01, p < 0.001$, and post hoc comparisons (Duncan multiple range test) were significant for each dose of quinpirole vs. saline, and for the higher doses vs. the 0.025 mg/kg dose, but not for the comparisons between the higher doses of quinpirole.

Inspection of Fig. 1 suggests that the allocation of subjects to the different experimental groups resulted in a systematic bias, with the groups destined to receive injections every 8 days displaying least locomotion across every dose of quinpirole. The finding of a significant Interval effect supported this sugggestion, $F(2, 207) = 3.06, p = 0.049$; interaction effect, NS). Therefore, to permit comparison among the groups, responses to subsequent injections were expressed as a percent of the acute response.

Effect of Higher Doses

Figure 2 shows the development of sensitized responding induced by the higher doses of quinpirole (0.25–2.5 mg/kg). [The effect did not differ among these doses; dose effect, $F(2, 111) = 0.23$, NS]. Clearly, the amount of locomotion increased with each injection, consistent with a highly significant main effect of Injection, $F(8, 888) = 139.22, p < 0.001$. The fitted asymmetric sigmoid curve suggests that the half-maximum response was reached after 4.5 (±0.4) quinpirole injections, that the maximum response was 778% (±13%) of the acute response, and that the slope of the curve was 2.2 (±0.29).

Although inspection of Fig. 2 suggests more sensitization with treatment every 8 days, statistical analysis did not show a main effect of interval, $F(2, 111) = 2.17, p = 0.119$. However, a significant interval by injection interaction was observed, $F(16, 888) = 1.84, p = 0.023$, suggesting that the interval between injections contributed to the amount of sensitized responding following some (but not all) injections of quinpirole. Tests for simple effects showed that the interval between injections contributed to differences in performance after the 4th, 6th, and 10th injection of quinpirole (Fig. 2).

Considering that the time course of the effect of acute quinpirole on locomotion is biphasic (inhibition followed by excitation) (9), collapsing the data over the 90-min test period may have obscured an effect of the interdose interval. However, this seems unlikely, as evidenced by an inspection of Fig.

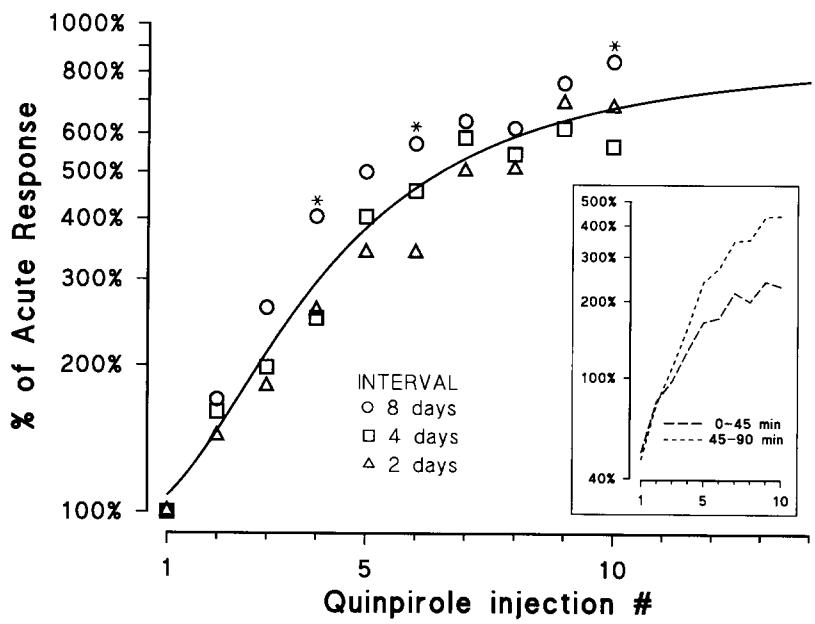

FIG. 2. Effect of interinjection interval on the development of locomotor sensitization to quinpirole (0.25–2.5 mg/kg). Symbols indicate the interinjection intervals; solid line is the best fit (linear dose vs. effect) curve for the overall mean responses at each injection; stars indicate injection number at which there was a significant effect of interval between injections (tests for simple effect, following a significant Interval × injection interaction). Inset: profile of locomotor sensitization for two time periods after drug injection: 0 to 45 min (dashed line) and 45 to 90 min after quinpirole (dotted line). Lines represent the mean locomotor response at the indicated injection normalized to the 90-min acute response.

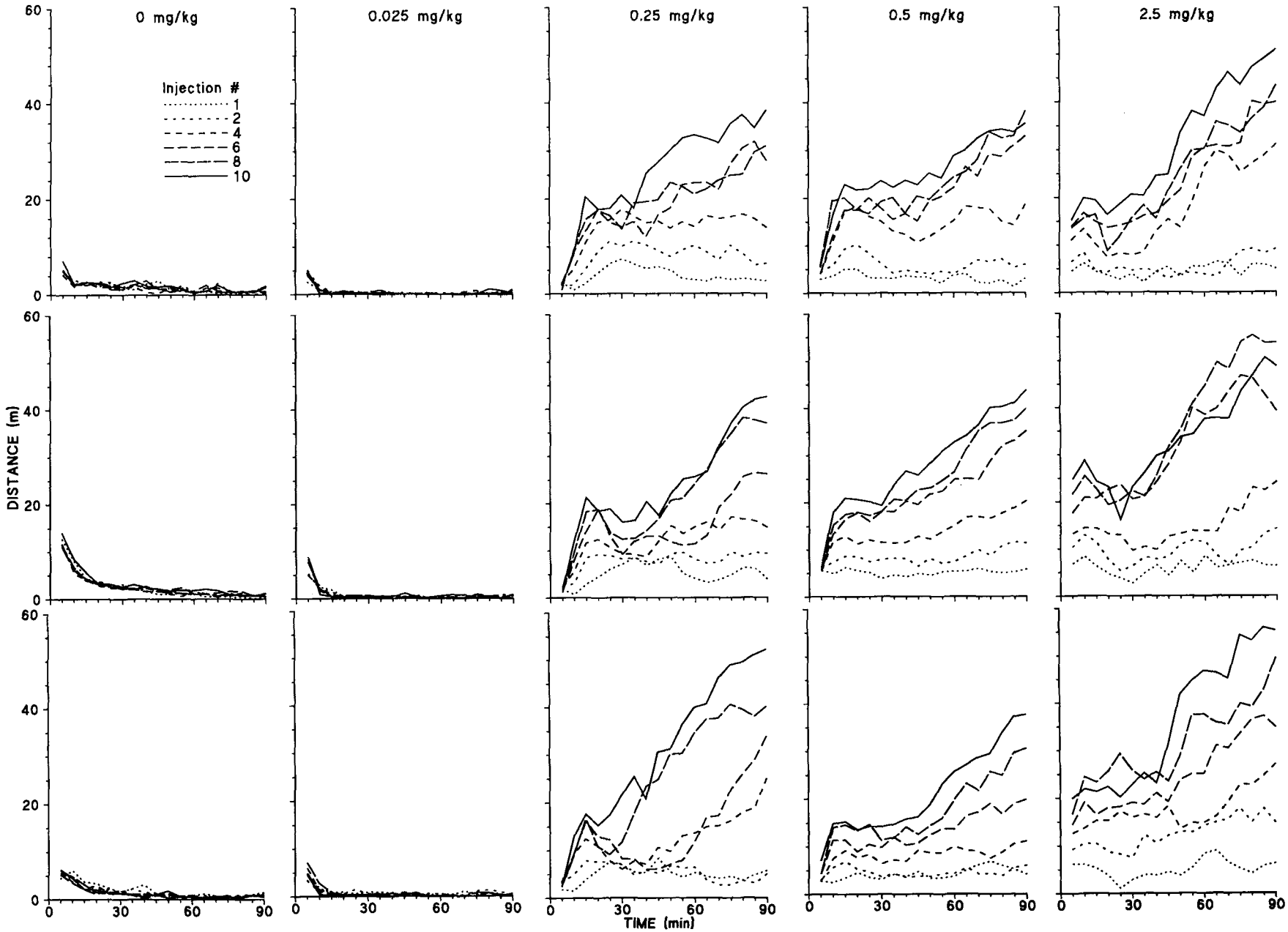

FIG. 3. Time course of locomotor response to various doses of quinpirole in rats injected every 2 (top row), 4 (middle row), or 8 days (bottom row). Each line is the mean distance travelled in the 5-min period at the indicated time after an injection of saline (first column) or quinpirole (next four columns). For visual clarity, not all of the 10 injections are shown.

3, which presents the time course of locomotion after each injection during the course of chronic treatment. More formally, when the data were reanalyzed to include a repeated measures time factor (0–45 min and 45–90 min), there were no significant second-, third-, or fourth-order interactions between time and interval factors [for time × interval, $F(2, 111) = 0.67$, $p = 0.5$; for time × interval × dose, $F(4, 111) = 1.01$, $p = 0.4$; for time × interval × dose × injection, $F(36, 999) = 1.30$, $p = 0.1$], despite the fact that locomotor sensitization in the first 45 min after injection was not as great as in the later time period [Fig. 2, inset; for time, $F(1, 111) = 83.27$, $p < 0.001$; for time × injection, $F(9, 999) = 38.29$, $p < 0.001$]. Thus, statistical analysis did not support the suggestion that interdose interval has a differential influence on locomotor sensitization in the first vs. the second 45 min after injection of quinpirole.

Repeated Treatment With Low Dose

Inspection of Fig. 3 suggests that in the second half of the 90-min test period, rats treated with saline or a low dose of quinpirole (0.025 mg/kg) showed little activity. Consequently, to minimize the likelihood that group differences would be diluted by including the last 45 min of testing, only the 0–45 min period was analyzed statistically. As shown in Fig. 4 (top panel), repeated treatment with quinpirole did not appear to induce either the development of tolerance or sensitization, compared to injections of saline [dose effect, $F(1, 96) = 3.02$, $p = 0.086$], except for one small perturbation at injections 7 and 8 (for dose × injection, $F(8, 768) = 2.13$, $p = 0.031$; main effect of injection, NS]. Interestingly, performance in the activity monitors was affected by the duration of time between testing, as evidenced by a significant main effect of interval, $F(2, 96) = 3.41$, $p = 0.037$, and by significant interaction effects of interval × injection, $F(16, 768) = 1.80$, $p = 0.027$, and interval × dose, $F(2, 96) = 3.57$, $p = 0.032$. The nature of this modulation is shown in Fig. 4 (lower panels), which suggests that testing every 2 days resulted in a habituation of the locomotor response and testing every 4 days in an unchanging response (in both the saline and quinpirole groups), but testing every 8 days yielded higher responding in the quinpirole than saline group. However, the fact that the interaction effect of interval by dose by injection was not significant, $F(16, 768) = 1.16$, $p = 0.3$, suggests that testing every 8 days did not favor the development of tolerance to quinpirole. Rather, as is apparent from an inspection of the figure, the level of responding increased in this group on the second injection and remained at this elevated level from then onwards.

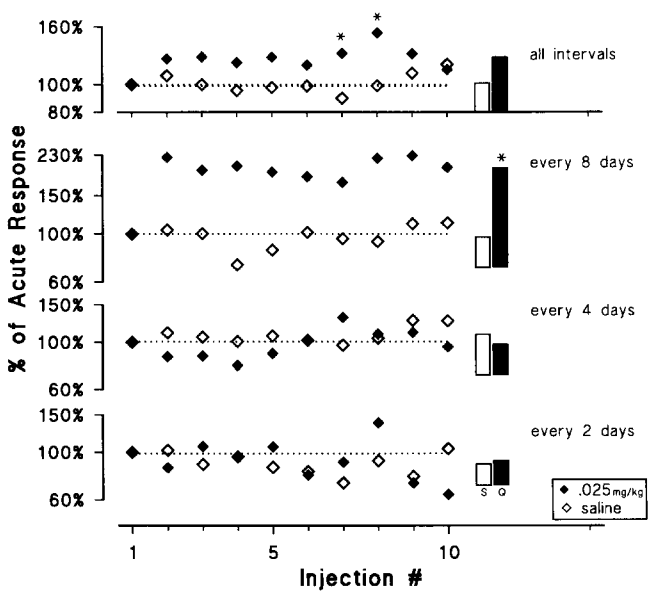

FIG. 4. Locomotor response in rats injected at various intervals with low-dose quinpirole (0.025 mg/kg) or saline. Upper panel compares the locomotor response in quinpirole and saline rats, collapsed across interinjection intervals; the response to low-dose quinpirole differed from saline at injections 7 and 8 only (indicated by a star; test for simple effects); open and closed bars represent the mean response collapsed across injections 2 to 10 for saline (S) and quinpirole (Q) groups, respectively. Lower three panels show changes in locomotor response for each interinjection interval for saline and quinpirole-treated rats; bars indicate the mean response collapsed across injections 2 to 10; star over bar indicates a significant difference compared to saline (test for simple effects, following a significant Interval × Dose interaction).

Thus, there is no evidence that the response to low-dose quinpirole changed systematically from injection to injection (suggestive of development of tolerance or sensitization) or that the time between injections exerted a differential effect on the development of tolerance or sensitization.

Locomotor Changes in First 5 Min

A previous study (38) suggested that repeated injection of a moderate dose of quinpirole (0.5 mg/kg) induces a progressive shortening of quinpirole's inhibitory phase but does not eliminate it completely. Inspection of Fig. 3 suggests that with repeated injection of a higher dose of quinpirole (2.5 mg/kg), this early inhibition does disappear and is supplanted by locomotor excitation. This observation is supported by statistical analysis and is presented more clearly in Fig. 5. It appears, therefore, that locomotor inhibition induced by acute quinpirole has two profiles of response to repeated injections: high doses (2.5 mg/kg) are needed to overcome the earliest inhibitory phase but lower doses of quinpirole (0.25–0.5 mg/kg) are sufficient to replace the later inhibition by locomotor excitation. This raises the possibility that there may be three phases (and different mechanisms) to the acute action of quinpirole: two inhibitory periods (the first one at 0 to 5 min after injection, and the second one ending about 45 min after injection), and a late phase of locomotor excitation (starting about 45–60 min after drug injection).

DISCUSSION

As in a large open field (38,39), so, too, in smaller activity monitors, repeated injection of quinpirole (0.25–2.5 mg/kg) induces robust sensitization of locomotor distance. However, varying the interdose interval from 2 to 8 days between injections has little effect on the growth of sensitized responding. Development of quinpirole sensitization seems largely a function of the number of drug injections: the half-maximum response requires about 4.5 quinpirole injections, and the maximum level of responding is almost eightfold higher than the acute response [these values are within the range found for quinpirole sensitization in a large open field; see (38)]. Thus, the number of injections, rather than the interval between them, predominantly controls development of quinpirole sensitization [see also (7,23)]. The fact that sensitization of locomotor response in mice develops even with a continuous infusion of quinpirole (43), supports this conclusion.

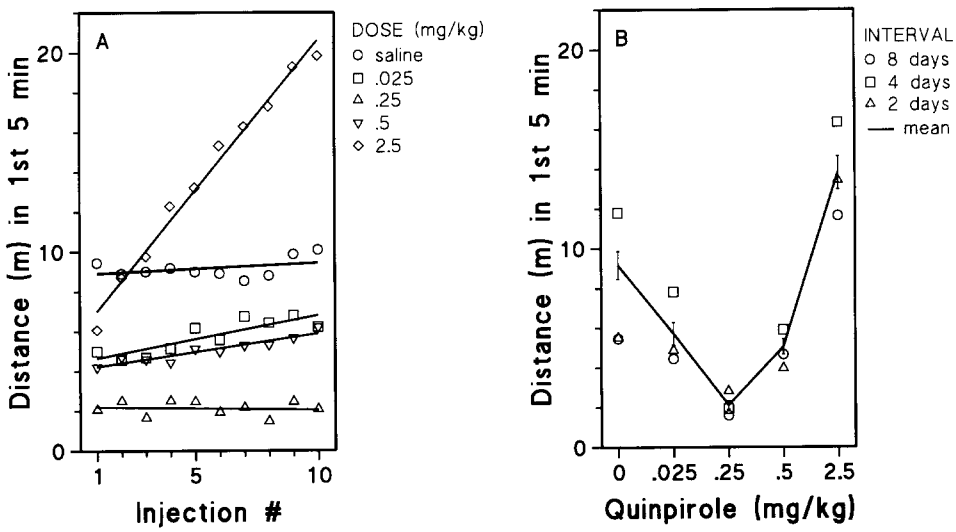

FIG. 5. Effect of repeated administration of quinpirole on the locomotor response in first 5 min after injection. Symbols in panel A show the mean response at each injection for different doses of quinpirole and the line indicates the best fit regression line for each dose (collapsed across interdose intervals); the slope is significantly greater than zero for the 2.5, 0.5, and 0.025 mg/kg doses but not for saline or 0.25 mg/kg of quinpirole. Symbols in panel B indicate the mean locomotor response for rats treated every 8, 4, or 2 days with the indicated dose of quinpirole, and the solid line is the mean (±SEM) distance travelled collapsed across all injections and interdose intervals; the main effects of dose, ($F(4, 207)$ = 40.16, p = < 0.001, and interval, $F(2, 207)$ = 12.42, p = 0 < 0.001, were significant, as was their interaction, $F(8, 207)$ = 2.59, p = 0.01. Significant effects of the interdose interval appear related to the higher response in rats treated every 4 days, especially in the group treated with saline.

However, the present data do suggest that the interval between injections does have some contribution to drug-induced performance. This contribution relates to the pattern of variability from one injection to the next. As may be seen from an inspection of Fig. 2, the amount of sensitized responding increases smoothly and consistently for rats injected every 8 days; however, for rats injected at closer intervals, the increase from one injection to the next one follows a more erratic or oscillatory course. This apparent difference in consistency of the growth curves may account for the observation that at some points during the course of chronic treatment, sensitized responding is highest in rats injected every 8 days (Fig. 2). Considering that testing every 2 days favors habituation of the locomotor response while testing less often does not (Fig. 4), the difference in consistency of the growth curves may reflect an interaction with a shifting baseline.

The fact that development of sensitization is essentially similar regardless of whether quinpirole is injected every 2, 4, or 8 days, suggests that the process of sensitization has the following three characteristics. First, each injection of quinpirole (0.25–2.5 mg/kg) produces a response-enhancing factor that is induced and completes its growth within 2 days of drug injection [1 day is probably sufficient; see (24)]. Second, this response-enhancing factor decays very slowly, persisting unchanged for at least 8 days. Third, the effects of the growth-enhancing factor are cumulative, up to a limit.

A rapid induction of the response-enhancing factor is consistent with a recent demonstration that amphetamine sensitization is blocked when protein synthesis is inhibited within 2 but not 4 h of drug injection (34). A slow decay time for the response-enhancing factor is consistent with many studies showing persistence of sensitized responding even months after the end of drug treatment [e.g. (12,30)]. Finally, cumulative but saturable effects of repeated injections are consistent with recent observations that growth in quinpirole-sensitized locomotion is limited, precluding the emergence of disorganized activity (38).

A profile of rapid induction but slow decay may be useful in some forms of pharmacotherapy. Specifically, in instances when the goal of drug therapy is to establish and maintain a sensitized response level, rapid dosing could be used to quickly reach the maximum level of responding and less frequent injections to maintain it.

In contrast to the sensitization induced by repeated administration of stimulatory doses of quinpirole, the effects of a locomotion-inhibitory dose of quinpirole did not change with repeated injections. However, the failure to observe a potentiation of inhibition may merely reflect the already near maximum locomotor depression induced by acute quinpirole. Indeed, yawning induced by low-dose quinpirole does sensitize (20).

In summary, the number of injections, rather than the interval between them, predominantly controls the development of locomotor sensitization to quinpirole. It is suggested that this may reflect a rapid induction but slow decay time for the response-enhancing factor stimulated by each injection of quinpirole, and that the effects of this factor are cumulative but saturable.

ACKNOWLEDGEMENTS

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