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BRIEF COMMUNICATION

Dosing Regimen Differentiates Sensitization of Locomotion and Mouthing to D2 Agonist Quinpirole

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EILAM, D. AND H. SZECHTMAN. *Dosing regimen differentiates sensitization of locomotion and mouthing to D2 agonist quinpirole*. PHARMACOL BIOCHEM BEHAV 36(4) 989–991, 1990.—The study examines whether the order of administering 2 doses of quinpirole (0.5 and 8 mg/kg) affects the development of behavioral sensitization, as measured by the amount of forward progression and mouthing. Results show that injection of the high dose greatly enhances the subsequent locomotor response to the low dose of quinpirole, but not vice versa. Mouthing activity is not influenced by order of administration but is significantly greater at the higher dose of quinpirole. The present findings are consistent with a hypothesis that locomotor sensitization involves down-regulation of a D1 tone normally inhibitory to D2 locomotor activation.

Behavioral sensitization Rats Dopamine Locomotion Mouthing D1/D2 interaction

THE augmentation in response to repeated injections of dopaminergic drugs has received increasing attention in recent years because of the potential relevance of this phenomenon to the development of psychosis [e.g., (13,14)] and to pharmacotherapy (1). Several factors appear to influence the process of behavioral sensitization. These include: number [e.g., (7)] and timing of injections [e.g., (6,12)], passage of time [e.g., (3)], behavior measured [e.g., (17)], stress history [e.g., (2)], and environmental conditioning [e.g., (8,15)]. In the present study we examine whether development of sensitization is influenced by increasing or decreasing the injection dosage of the D2 dopamine receptor agonist quinpirole. Our findings show that dosing regimen greatly influences sensitization of locomotion but has no effect on the mouthing activity induced by quinpirole.

METHOD

Subjects and Design

Eighteen experimentally naive Long-Evans male hooded rats (Charles River, Canada) and weighing 420 ± 16 g (mean ± SEM) at the time of testing, 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 (light on at 0700 hr and off at 1900 hr).

Rats were divided into two groups with equivalent mean amount of forward progression, as assessed in a 30-min preexposure to the open field. Testing began 2 to 4 weeks later. One group (Group LoHi) was injected SC in the nape of the neck with 0.5 mg/kg of quinpirole hydrochloride (LY171555; Lilly Research Laboratories) and tested in the open field for 2 hours. Approximately a month later (34 ± 4 days), the same animals were injected with 8 mg/kg of quinpirole and tested again for 2 hours. The other group (Group HiLo) was treated the same except that the 8 mg/kg dose was injected at test 1 and the 0.5 mg/kg dose at test 2.

Procedure and Analysis

Immediately after injection, a rat was placed gently into the center of the open field [glass table: 160 × 160 and 60 cm high; (9)], and filmed continuously for 2 hr. The amount of forward progression was measured during playback of the video records. It was scored continuously across the 2 hr of observation and therefore these data are a full summary of this activity. Progression was scored as the length of the distance that the animal travelled, in units of one rat body length (20 cm) as detailed elsewhere

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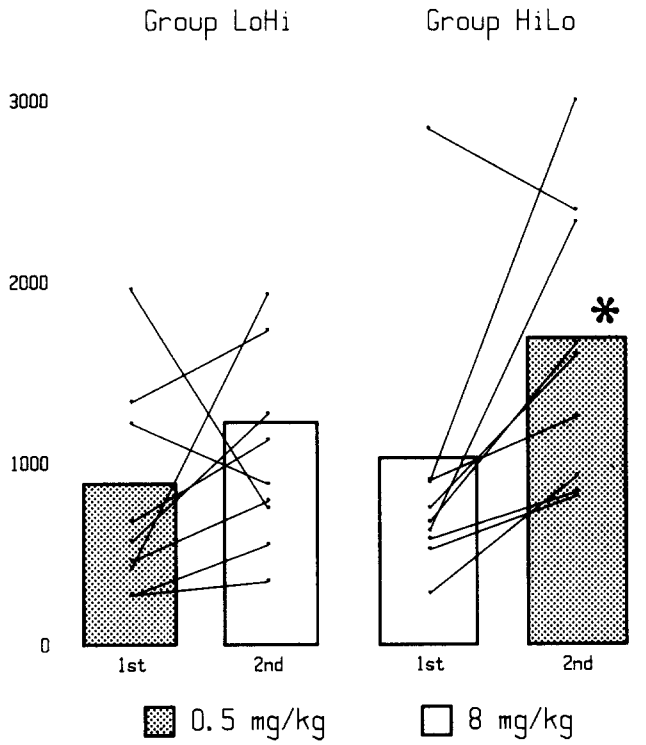

FIG. 1. The effect of pretreatment with a low dose of quinpirole on the subsequent locomotor response to a high dose (Group LoHi), and vice versa (Group HiLo). Bars indicate group means; lines connect the individual rats' response to each dose. Shaded and open bars correspond to the 0.5 and 8 mg/kg dose of quinpirole, respectively. Values refer to the amount of forward progression (in units of one rat body length) in a 2-hr test. *$p=0.019$, $p=0.021$, and $p=0.073$, compared to the 0.5 mg/kg LoHi, 8 mg/kg HiLo and 8 mg/kg LoHi means, respectively; other comparisons not significant.

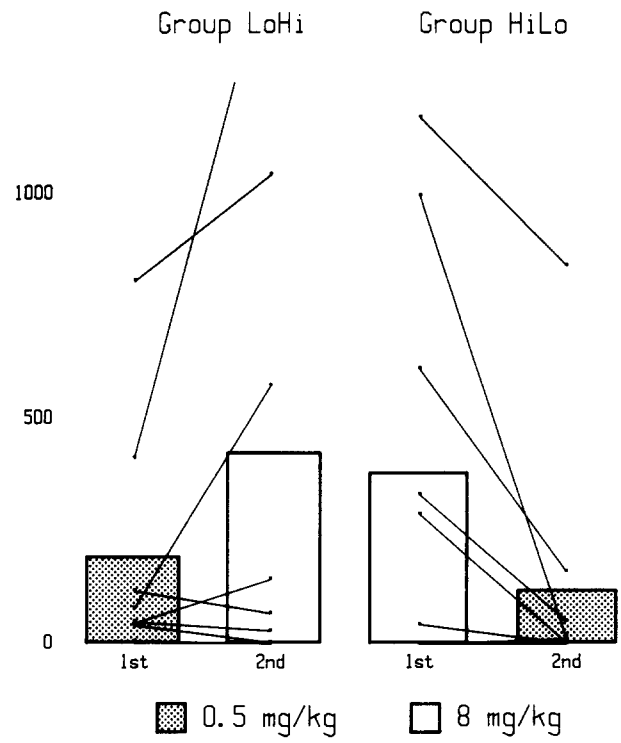

FIG. 2. The effect of pretreatment with a low dose of quinpirole on the subsequent mouthing response to a high dose (Group LoHi), and vice versa (Group HiLo). Bars indicate group means; lines connect the individual rats' response to each dose. Shaded and open bars correspond to the 0.5 and 8 mg/kg dose of quinpirole, respectively. Values refer to the duration of mouthing (in seconds) in a 2-hr test. Only the effect of Dose is significant, $F(1,16)=7.70$, $p=0.014$.

(9,10). The same tapes were reanalysed to score the duration of mouthing (licking or biting of open field) across the entire 2-hr test. A computer keyboard interfaced with the videocassette recorder allowed the assessment of duration with a resolution of 1/30 of a second.

Statistical comparisons were made using *t*-tests for independent or dependent measures as appropriate, following a significant interaction effect in a Group × Dose analysis of variance (ANOVA) with repeated measures on the second factor. Locomotor activity of the two groups after the first injection of quinpirole was described previously (10); the new data provided here include the locomotor findings from the second injection and mouthing durations from both injections. As reported, the first injection of 0.5 or 8 mg/kg of quinpirole produced a significant elevation in the amount of forward progression, compared to saline controls (10).

RESULTS

Figure 1 presents the amount of forward progression in rats injected with 0.5 and then 8 mg/kg of quinpirole (Group LoHi), and in those administered these doses in the reverse order (Group HiLo). The main effects of Group, $F(1,16)=1.82$, $p=0.197$, or Dose, $F(1,16)=1.97$, $p=0.179$, were not significant but the Group by Dose interaction was significant, $F(1,16)=7.69$, $p=0.014$. Paired *t*-test revealed that when the 8 mg/kg dose followed an injection of 0.5 mg/kg of quinpirole, the amounts of forward progression were not statistically different, $t(8)=1.00$, $p=0.349$. In contrast, when the low dose followed pretreatment with a high dose of quinpirole, the low dose induced significantly more forward progression than the high one, $t(8)=2.88$, $p=0.021$. Moreover, this amount was higher than every other mean; none of the other possible comparisons were significant (Fig. 1). Thus, the high dose significantly augmented the response to the low dose, but not vice versa.

In contrast to locomotion, Fig. 2 shows that order of dosing did not affect mouthing [Group Effect: $F(1,16)=0.02$, ns; Group × Dose Interaction: $F(1,16)=0.11$, ns]. Only the dose of quinpirole was important. The high dose induced significantly more mouthing than did the low dose [Dose Effect: $F(1,16)=7.70$, $p=0.014$].

DISCUSSION

The present study reveals an unexpected property of behavioural sensitization to the D2 agonist, quinpirole. It shows that despite their equivalent acute locomotor effects, two doses of quinpirole are not equally effective in inducing sensitization. Rather, the higher dose induces greater locomotor sensitization than does the lower dose of the drug. The fact that a supramaximal dose is more effective implies that a change beyond stimulation of D2 receptors underlies development of this sensitization.

One possibility is that this change involves D1 receptors. In the present study the higher dose of quinpirole induced significantly more mouthing. Mouthing appears to reflect the coactivation of D1 and D2 receptors (4, 5, 11). Thus, the acute effects of the

higher dose of quinpirole probably involve greater activation of D1 receptors. Such coactivation of D1 receptors may in part underlie the development of locomotion sensitization.

A similar proposal has been made for amphetamine sensitization. Because microinjections of a D1 blocker into the ventral tegmental area prevented the appearance of an augmented response to repeated administrations of amphetamine, Stewart and Vezine (16) proposed that the development of locomotor sensitization to amphetamine depends on a change in D1 receptors in the ventral tegmental area (VTA). The present hypothesis for an identical mechanism underlying the sensitization induced by quinpirole is consistent with our previous conjecture that amphetamine and quinpirole have comparable modes of action, as evidenced by their similar behavioural profiles (10).

Pronounced activation of D1 receptors inhibits completely the acute quinpirole-induced locomotion (Eilam and Szechtman, in preparation). This suggests that D1 stimulation normally opposes D2 locomotor activation. Accordingly, locomotor sensitization is most likely the result of a down-regulation of D1 receptors in the VTA.

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