DAD1- and DAD2-like Agonist Effects on Motor Activity of C57 Mice: Differences Compared to Rats

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ABSTRACT Studies on rats indicate that DAD1- and DAD2-like agonists produce a biphasic action on motor activity, with low doses reducing activity below control levels, and higher doses initially reducing, then elevating, activity for a prolonged period. Although some of the reported effects of DAD1- and DAD2-like receptor agonists on motor activity of mice are consistent with their effects on rats, the possibility of species differences is also apparent. In the current study the effects of DAD1- and DAD2-like agonists on motor activity of C57BL/6 (C57) mice were determined to establish species consistencies and differences with respect to their effects on rats. The partial DAD1-like agonist SKF 38393 reduced the activity of C57 mice at low doses and elevated activity above control levels at higher doses, if the mice were thoroughly habituated to the test chamber. The full DAD1 agonist SKF 82958 also increased the activity of C57 mice, and along with the SKF 38393 results indicates a response to DAD1 receptor stimulation similar to that reported for rats. In contrast to the species similarity in response to DAD1 stimulation, the DAD2-like agonist quinpirole produced only a dose-responsive monotonic reduction in the activity of C57 mice, whether the animals were nonhabituated or well-habituated to the testing environment, male or female, young or mid-aged, injected intraperitoneally (IP) or subcutaneously (SC), and with either low or high doses. This apparent species difference in response to quinpirole might reflect distinguishable functional properties of the DA subreceptor systems. **Synapse 26:81–92, 1997.**

INTRODUCTION

DAD1- and DAD2-like agonists have generally been reported to produce a biphasic action on motor activity of various rat strains (reviewed in Beninger, 1983; Garcia-Rill, 1986; Hyttel and Arnt, 1986; Kebabian et al., 1995; Seeman, 1981; Stoof and Kebabian, 1984). For example, the partial DAD1 agonist SKF 38393 was reported to reduce the activity of Sprague-Dawley rats at a low dose of 0.01 mg/kg; however, a high dose (10 mg/kg) elevated activity (Meyer and Shults, 1993; Moody and Spear, 1992). A similar biphasic dose-response effect was reported for the full DAD1 agonist, SKF 82958 (Meyer and Shults, 1993). Quinpirole, an agonist with an affinity for DAD2 and DAD3 receptors, was reported to reduce the activity of male Long-Evans hooded rats for 0–30 min after subcutaneous injections of a low dose (0.03 mg/kg) (Eilam and Szechtman, 1989). At higher doses (0.5–8 mg/kg), a period of hypomotility was followed by increasing activity, with hypermotility observed until 2 hr postinjection near the end of testing. Similar biphasic effects on motor activity across time were reported for male Long-Evans hooded rats after injections of 0.1 and 1.0 mg/kg doses of the full D2 agonist N-0434 (Meyer and Potter, 1993), and for Sprague-Dawley rats (Hartesveldt et al., 1994), with a low dose of quinpirole (.02 mg/kg) decreasing locomotion and higher doses (0.2 and 2.0 mg/kg) initially decreasing, but then elevating, activity later in the test session.

The literature regarding the effects of DAD1- and DAD2-like receptor agonists on motor activity of mice is consistent with some of the above-noted effects on rats, but also suggests the possibility of some species differences. Consistent with its previously noted effects on

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rats, high doses (8–64 mg/kg) of the partial DAD1-like agonist SKF 38393, given to mice of several strains, elevated activity of well-habituated mice above saline control levels (Arnt et al., 1992; Shannon et al., 1991). Our preliminary experiment in this area (Exp-1) indicated that SKF 38393 reduced activity of C57BL/6 (C57) mice at low doses, but that activity increased with increasing dose and was above control levels if the mice were thoroughly habituated to the test chamber (Exp-2).

The effects of DAD2-like agonists on the locomotor activity of mice may differ from their effects on rats. Although quinpirole reportedly reduces the locomotor activity of mice, as reported for rats, high doses of this drug and other DAD2-like agonists apparently do not elevate the locomotor activity of this species, which is contrary to their effects on rats. For example, Shannon et al. (1991) reported that quinpirole reduced the activity of habituated mice of several strains at doses ranging from 0.125–32 mg/kg. These results were confirmed for C57 mice injected with quinpirole (.03–.27 mg/kg) by a preliminary experiment conducted in our laboratory. Heightened motor activity associated with high quinpirole doses, as observed in rats, was not observed in either of these studies (Shannon et al., 1991; our preliminary experiment).

This apparent species difference might reflect distinguishable functional properties of DA subreceptor systems. However, because of differences in procedures across the different studies, the apparent discrepancies between reports on mice and rats might reflect methodological rather than biological differences. Accordingly, in the present series of experiments we evaluated the effects of DAD1- and DAD2-like agonists on the motor activity of male and female, and young and mid-aged C57 mice at several doses under different conditions of habituation to the testing environment. By eliminating methodological variables, the present series of experiments provides indirect evidence of biological similarities and differences between mice and rats. The outcome of our studies suggests a species similarity in response to the DAD1 agonists SKF 38393 and SKF 82958. In contrast, the response of C57 mice to the DAD2/D3 agonist quinpirole was a monotonic decrease in motor activity rather than the biphasic action reported for rats, suggesting a species difference in neuronal systems involving DAD2-like receptors.

MATERIALS AND METHODS

Subjects

The subjects for all experiments were male and/or female C57 mice of various ages. The gender and age of the animals tested varied according to experiment, and will be specified for each particular experiment. The mice were maintained on a light:dark cycle (On, 0700 h; Off, 1900 h) at 20–22°C in a colony room adjacent to the behavioral laboratory. They had free access to food and water.

Apparatus

A Digiscan Animal Activity Monitor system, model RXYZCM(8) TAO with a two-animal option (Omnitech Electronics, Columbus, OH), was used to assess motor activity. Two activity units, with two chambers or quadrants per unit, were located in 90 × 54 × 35 cm sound-attenuation boxes (one unit per box). A fan connected to each sound-attenuation box provided ventilation and sound-masking noise. Each activity unit contained 16 photo beams positioned 5 cm apart, 8 on the x-axis, and 8 on the y-axis. Photocells located on the wall directly opposite each photo beam were activated when the beams were interrupted. The Digiscan analyzer recorded the interruption of each beam and provided the distance the animal traveled (in cm) during testing as a measure of horizontal activity. Each unit was partitioned with acrylic into 20 × 20 cm quadrants, and mice were tested in one of two quadrants of each unit (i.e., four mice per test). The Digiscan analyzer was interfaced with an IBM XT computer using ILAM software (Coulbourn Instruments, Lehigh Valley, PA). All testing was completed in a dark environment, and occurred between 1200–1700 h. Motor activity was recorded as total centimeters traveled over the testing intervals described for each experiment. The chambers were cleaned of fecal matter and urine, and wiped with disinfectant (50/50 solution of distilled water and alcohol) after each test to eliminate olfactory cues from previous runs.

Drugs

The effects of the DAD1-like agonists (SKF 38393 and SKF 82958) and the DAD2-like agonist (quinpirole hydrochloride) were determined. All drugs and their vehicles were injected intraperitoneally (IP) in volumes of 0.02 ml/g body weight, except for experiment 8 (Exp-8) noted below, in which the subcutaneous (SC) route was used. Animals were first adapted to the injection procedures with vehicle injections. SKF 38393 (±-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride) is a DAD1-like partial agonist, and was dissolved in a saline vehicle. SKF 82958 (±-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetra-hydro-1H-3-b enzazepine hydrobromide) is a DAD1-like full agonist and was dissolved in a 50-nM acetic acid solution. Quinpirole (trans-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g]-quinol ine hydrochloride) is a DAD2/D3 receptor agonist and was dissolved in normal saline. All drugs were dissolved immediately prior to use, and were used within a 5-h period.

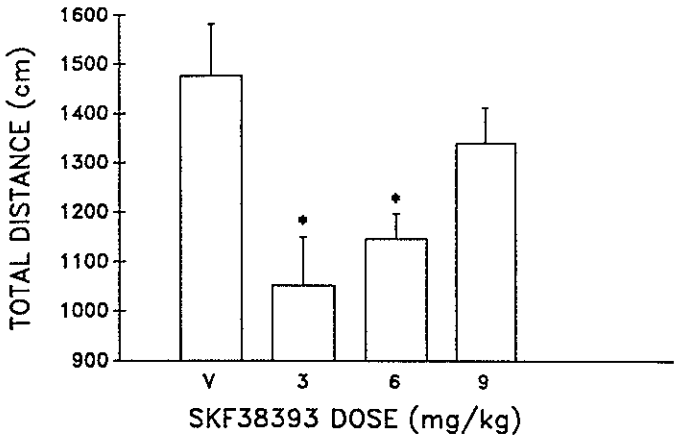

Fig. 1. Effects of IP vehicle (V) or SKF 38393 (3.0, 6.0, or 9.0 mg/kg) on motor activity ($\bar{x} \pm SE$) of female C57 mice over a 20-min test period. *Significantly different from V, $P < 0.01$, Dunnette's test.

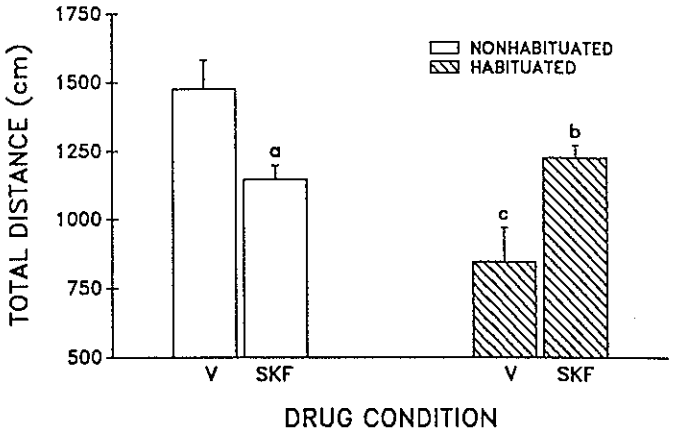

Fig. 2. Effects of IP vehicle (V) or SKF 38393 6 mg/kg (SKF) on motor activity ($\bar{x} \pm SE$) of female C57 habituated and nonhabituated mice over a 60-min test interval. a: SKF < V, $P < 0.05$; b: SKF > V, $P < 0.01$; c: nonhabituated V > habituated V, $P < 0.01$, Duncan's test.

Experiments

Experiment 1: SKF 38393 effects on nonhabituated mice

Our initial experiment was to determine the effects of SKF 38393 on motor activity of C57 mice, using doses previously reported to elevate and decrease activity of rats.

Procedure. Seven female C57 mice were tested at age 120 days. Motor activity was assessed for 20 min at weekly intervals for 6 weeks following IP injections of the vehicle or SKF 38393 (9.0, 6.0, and 3.0 mg/kg). Each animal was tested with each dose, and the order of dosing was counterbalanced to control for the effects of prior drug exposure or testing history.

Results. The results of the experiment are summarized in Figure 1. The results of a single-factor repeated measures analysis of variance (ANOVA) indicated that activity varied as a function of SKF 38393 dosage ($F(3, 18) = 7.635$, $P < 0.001$). Multiple comparisons utilizing Dunette's test indicated that activity was significantly reduced in comparison to control injections following injections of the two low doses. With increasing dose, however, activity had increased to control levels by the highest dose (9 mg/kg).

Experiment 2: SKF 38393 effects on motor activity of habituated mice

Since the stimulatory and depressive effects of drugs are to some extent determined by the ongoing basal activity levels (Wenger, 1989), Exp-2 was conducted to determine if basal activity level influenced whether SKF 38393 increased or decreased motor activity relative to vehicle levels.

Procedure. The 7 female mice used in Exp-1 were thoroughly habituated to the test environment (30 min) immediately prior to tests (60 min) with either vehicle or SKF 38393 (6.0 mg/kg body weight). They were tested twice at weekly intervals. Half of the animals received vehicle the first week, and the other half received SKF 38393.

Results. In Figure 2, the activity of the habituated mice of Exp-2, injected with either vehicle or SKF 38393, is compared with the activity of the nonhabituated mice of Exp-1, following similar drug injections. Of importance in this comparison is the significant interaction between the drug and the habituation conditions ($F(3, 18) = 11.241$, $P < 0.001$). In contrast to the significant reduction in the activity of nonhabituated mice injected with the 6 mg/kg dose of SKF 38393 relative to control levels, this same dose elevated activity of habituated mice, relative to control levels. Interestingly, there was no difference in the activity of the habituated and nonhabituated mice injected with SKF 38393, whereas the habituated mice injected with the vehicle were significantly less active than the nonhabituated controls. Thus, whether the intermediate dose of SKF 38393 elevated or reduced motor activity to a large extent depended upon basal activity levels.

Experiment 3: Effects of SKF 82958 on motor activity of young adult and mid-aged, and male and female mice

To extend the generality of the effects of DAD1 stimulation on motor activity, we conducted an experiment (Exp-3) in which the full D1 agonist SKF 82958 was given to both sexes and to young mature as well as mid-aged mice.

Procedure. Twenty male and 20 female experimentally naive mice, either 6 or 12 months old, were used (N = 10 mice per sex-age group). The animals were tested 15 times over a 7-week period (twice per week). Ascending and decending dose schedules were alternated with saline injections. Drug doses were 0.10, 0.05, 0.01, 0.005, and 0.00 (vehicle) mg/kg body weight. On test

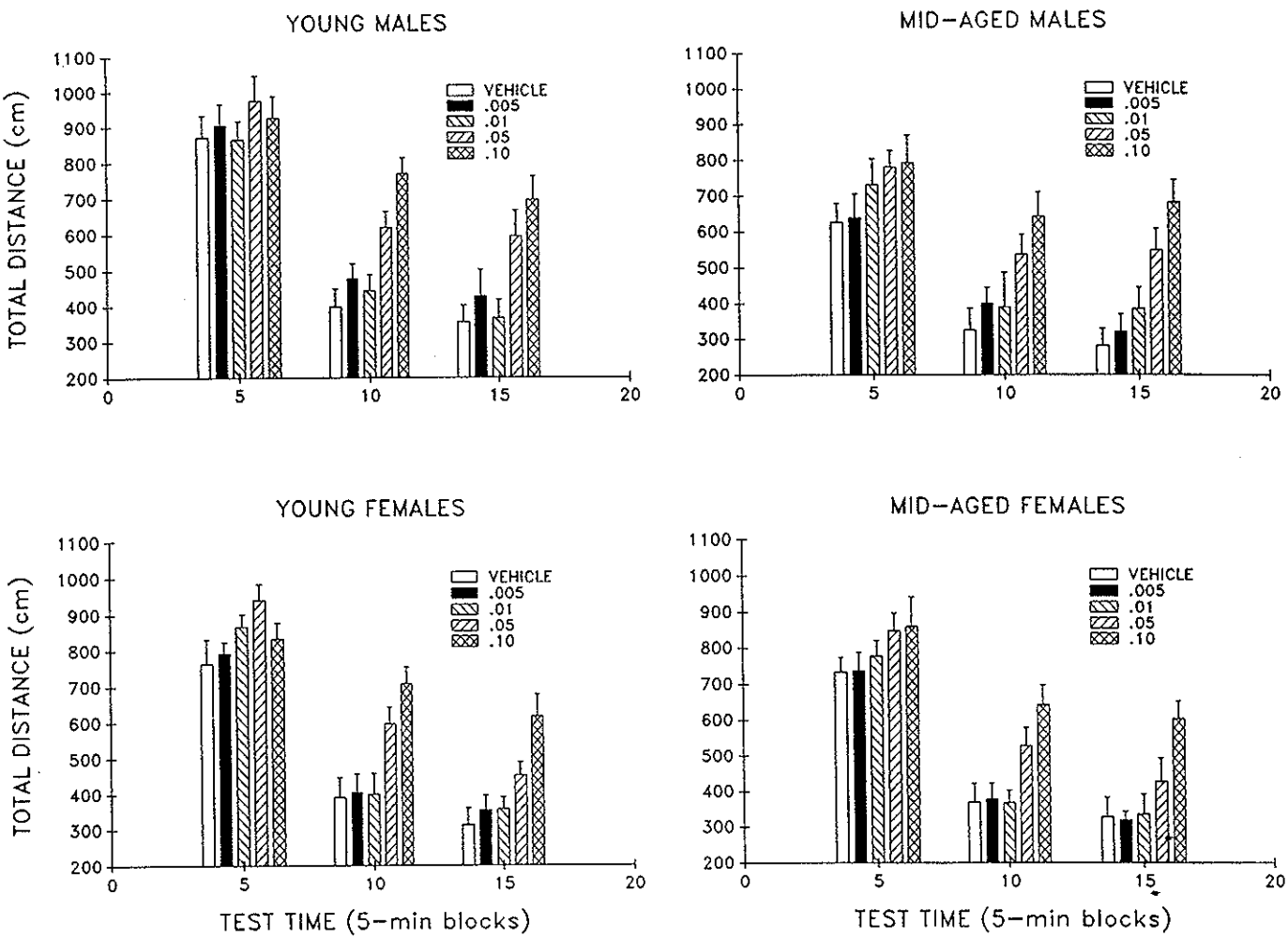

Fig. 3. Effects of IP vehicle or SKF 82958 (0.005, 0.01, 0.05, and 0.10 mg/kg) on motor activity ($\bar{x} \pm SE$) of young and mid-aged, and male and female C57 mice at intervals over a 15-min test period.

days, animals were injected and then returned to home cages for 5 min prior to recording activity for 15 min.

Results. Data for this experiment are summarized in Figure 3. These data were initially subjected to a 2(age) × 2(sex) × 5(dose) × 3(time) ANOVA. The results of the ANOVA indicated that activity increased with increasing SKF 82958 dose (dose: $F(4, 124) = 32.716$, $P < 0.001$); that young adults were more active than mid-aged mice (age: $F(1, 31) = 4.280$, $P < 0.05$); and that activity declined across the 15-min test period (time: $F(2, 62) = 488.345$, $P < 0.001$). Activity was not influenced by sex in this experiment; however, it was influenced by the sex × age × time interaction ($F(2, 62) = 3.14$, $P < 0.05$). This complex interaction was characterized by greater activity in the young adults than in the mid-aged mice during the first 5 min. During the subsequent time periods, activity declined more extensively for young adult female than male mice; however, this sex-dependent change was not observed for the mid-aged mice.

Although motor activity was influenced by age in this experiment, it is important to note that neither sex nor age interacted with SKF 82958 dose in its effect on motor activity. Because neither of these factors interacted with dose, data were collapsed across age and sex

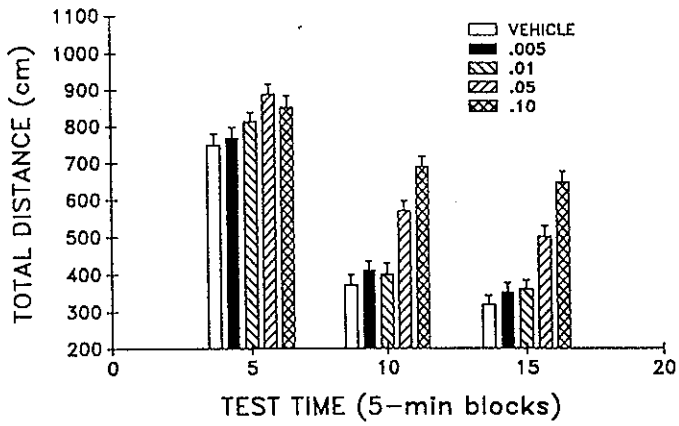

Fig. 4. Effects of IP vehicle (0.0) or SKF 82958 (0.005, 0.01, 0.05, and 0.10 mg/kg) on motor activity ($\bar{x} \pm SE$) of C57 mice over a 15-min test period. Graph represents combined data for Exp-3 collapsed across age and sex.

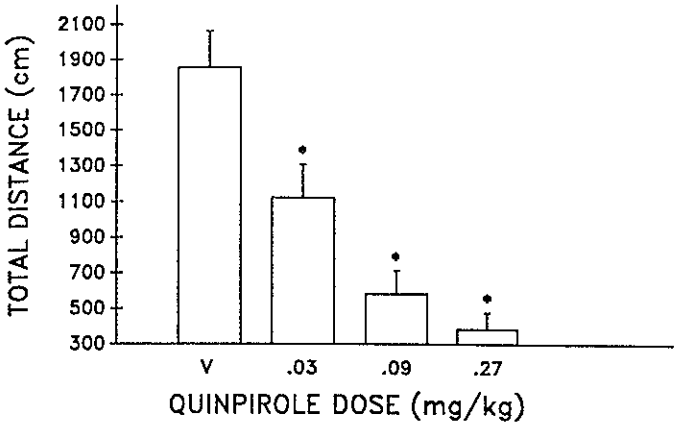

Fig. 5. Effects of IP vehicle (V) or quinpirole hydrochloride (0.03, 0.09, and 0.27 mg/kg) on motor activity ($\bar{x} \pm SE$) of female C57 mice over a 20-min test period. Quinpirole < V, $P < 0.01$, Dunnette's test.

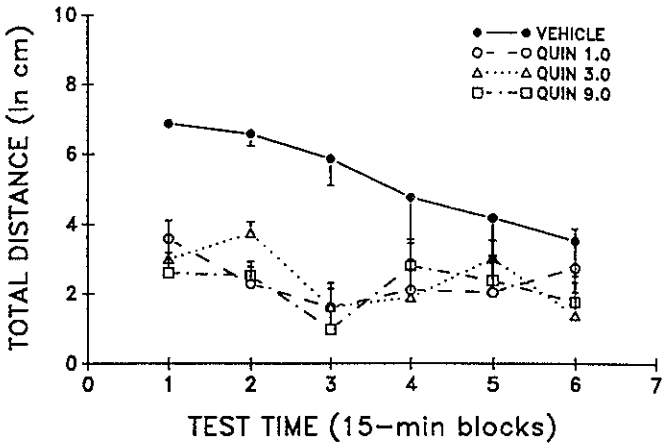

Fig. 6. Effects of IP vehicle or quinpirole (1.0, 3.0, and 9.0 mg/kg) on motor activity ($\bar{x} \pm SE$) of female C57 mice, habituated for 30 min and then tested for 90 min.

groups for further analyses. These data are summarized in Figure 4 across increasing doses for the three time periods. SKF 82958 elevated activity, and its effect interacted with postinjection time ($F(8, 248) = 13.962$, $P < .001$). The two highest doses (0.05 and 0.1 mg/kg) elevated activity during all time periods, with the effect being greater during the later time periods, when the activity associated with vehicle injections was substantially reduced. Although the 0.01 mg/kg dose elevated activity during the early postinjection period, this effect had subsided during the 10- and 15-min intervals. These results suggest that 0.01 mg/kg is the minimal dose necessary to stimulate the activity of C57 mice under these conditions. The results of this experiment indicate that stimulation of DAD1 receptors of C57 mice with the full-efficacy DAD1 receptor agonist SKF 82958 produces a monotonic increase in locomotion with increasing doses, an effect not greatly influenced by either sex or age within the range of young adult to mid-age (i.e., 12 months).

Experiment 4: Effects of quinpirole hydrochloride on motor activity of nonhabituated female mice

The effects of DAD2-like receptor stimulation on motor activity of C57 mice were initially investigated as described above in Exp-1, except that the agonist was quinpirole hydrochloride rather than SKF 38393.

Procedure. Seven experimentally naive 120-day-old female mice were tested with the saline vehicle or quinpirole hydrochloride (0.27, 0.09, and 0.03 mg/kg), injected 10 min prior to the 20-min test session.

Results. The results of this experiment (Exp-4) are summarized in Figure 5. The DAD2-like agonist produced a monotonic reduction in activity at doses ranging from 0.03–0.27 mg/kg ($F(3, 18) = 36.339$, $P < 0.001$), with each dose producing a corresponding significant drop in locomotor activity. Since the entire dose range of quinpirole (0.03–0.27 mg/kg) reduced locomotor activity, C57 mice differed from rats, which reportedly exhibit a biphasic response to the drug with initially decreased motor activity at lower doses and elevations in activity at higher doses.

Experiment 5: Effects of high quinpirole doses on motor activity of habituated mice

Because quinpirole is reported to elevate activity of rats at high doses, and because of our failure to observe an increase in motor activity following the highest dose of quinpirole in Exp-4, we conducted an experiment in which mice were thoroughly habituated to the test environment immediately prior to tests with very high quinpirole doses.

Procedure. Experimentally naive 120-day-old female mice (N = 6 per dose group) were habituated to the test environment over a 30-min period and then removed, injected IP with either the vehicle or the drug (9.0, 3.0, or 1.0 mg/kg), and replaced in the activity monitor for an additional 90 min.

Results. The results of this experiment are summarized in Figure 6. These data were transformed [natural log] to normalize the variance across the time periods and subjected to a 4(drug dose) × 6(time period) ANOVA. As previously noted for the lower doses of quinpirole injected into nonhabituated mice in Exp-4, the D2-like agonist reduced activity (drug dose: $F(3, 20) = 10.277$, $P < 0.001$) of young, habituated female mice. Activity varied significantly across time ($F(5, 100) = 4.145$, $P = 0.0022$). Although the change across time appeared to be a systematic decline for vehicle-injected mice and somewhat variable for the drugged mice, the dose and time factor interaction was not significant. The absence of a dose-response function in this experiment suggests that the maximum depressive effect of quinpirole on locomotor activity occurs at a dose <1.0 mg/kg. It is important to note that at no point did any of the high doses increase motor activity above

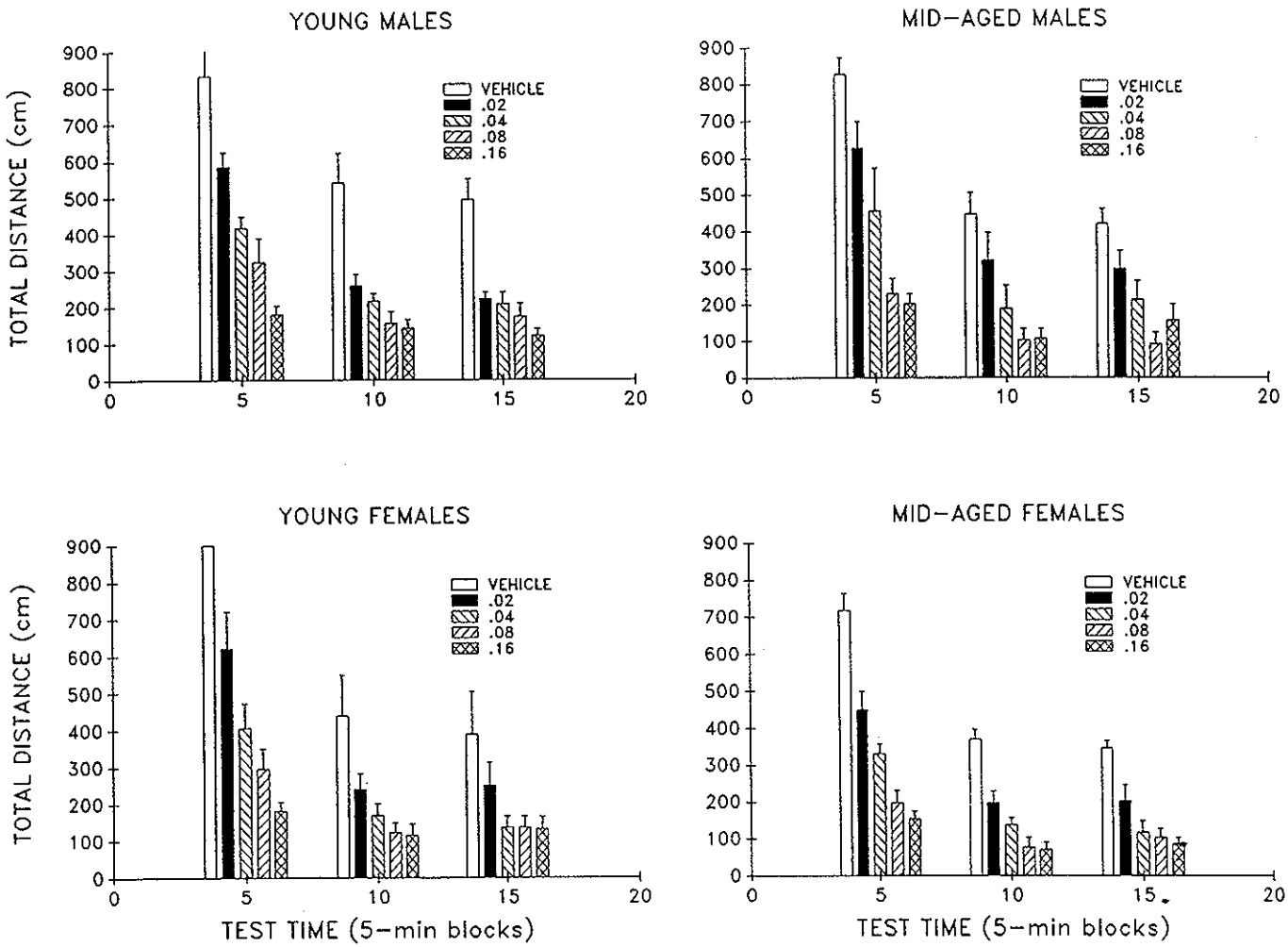

Fig. 7. Effects of IP vehicle (0.0) or quinpirole (0.02, 0.04, 0.08, and 0.16 mg/kg) on motor activity ($\bar{x} \pm SE$) of young and mid-aged, and male and female C57 mice at intervals over a 15-min test period.

saline control levels. Thus, the effects of quinpirole on C57 mice are a monotonic decrease in activity with increasing doses up to 9.0 mg/kg, an effect quite different from the biphasic action which characterizes quinpirole's effects on the locomotion of rats.

Experiment 6: Effects of quinpirole on young adult and mid-aged, and male and female mice

To further characterize the effects of quinpirole on the motor activity of the C57 mice, and to possibly account for the difference between the results of our experiments and those reported for rats, we assessed the influence of gender and age on the response to quinpirole in a manner similar to that described for Exp-3.

Procedure. The subjects were 18 male and 18 female experimentally naive mice, either 6 or 12 months old (N = 9/sex-age group). The procedure was identical to that described for Exp-3. Quinpirole hydrochloride doses were 0.16, 0.08, 0.04, 0.02, and 0.00 (vehicle) mg/kg body weight.

Results. Data for this experiment are summarized in Figure 7, and were initially subjected to a 2(age) × 2(sex) × 5(dose) × 3(time) ANOVA. Results of the ANOVA indicated that activity decreased monotonically with increasing quinpirole dose (dose: $F(4, 124) = 114.195$, $P < 0.001$), and that activity declined across the 15-min test period (time: $F(2, 62) = 345.220$, $P < 0.001$). The latter effect was due to a reduction in locomotion between the 5- and 10-min time periods with no further change. Activity was not influenced by either sex or age in this experiment; however, it was influenced by the sex × age × time interaction ($F(2, 62) = 3.912$, $P = .025$), as noted for the D1 agonist in Exp-3. The interaction in the present experiment was due predominantly to the constant lower activity of mid-aged female mice across time as compared to the other groups, which were initially more active and then declined across time.

As noted for the D1 agonist, age and sex did not interact with the quinpirole dose effect on activity. Thus, data were collapsed across these two factors, and

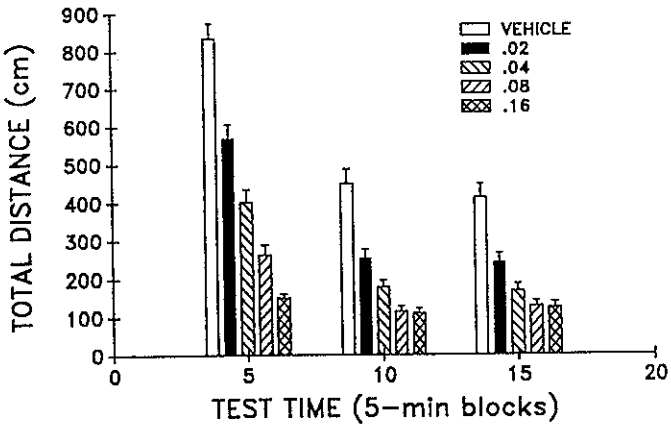

Fig. 8. Effects of IP of vehicle (0.0) or quinpirole hydrochloride (0.02, 0.04, 0.08, and 0.16 mg/kg) on motor activity ($\bar{x} \pm SE$) of C57 mice over a 15-min test period. Graph represents combined data of Exp-6 collapsed across age and sex.

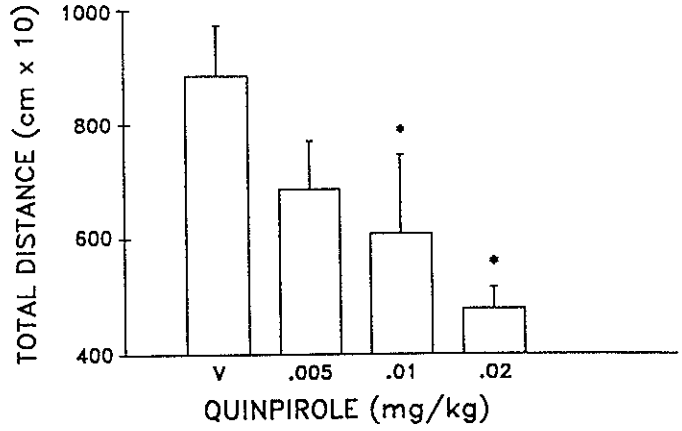

Fig. 9. Effects of IP vehicle (V) or of low doses of quinpirole hydrochloride (0.02, 0.01, and 0.005 mg/kg) on motor activity ($\bar{x} \pm SE$) of male C57 mice over a 2-h test period. *$P < 0.05$ with reference to V.

are summarized in Figure 8 as activity across the increasing doses for the three time periods of measurement. The effects of quinpirole dose and time interacted ($F(8, 248) = 31.983$, $P < 0.001$). As noted in Figure 8, the highest dose (.16 mg/kg) reduced activity maximally across the three time periods. As the dose decreased, a more gradual reduction in activity across the three intervals was observed. The decrease in activity is significant at the lowest dose of quinpirole (.02 mg/kg), thus confirming the effect noted in female mice in Exp-4. Quinpirole's dose-dependent decrease in locomotor activity appears to approach a lower bound at the two highest doses of 0.08 and 0.16 mg/kg. Thus, the results of this experiment confirmed the monotonic reduction in activity following quinpirole injections in Exp-4 and Exp-5, and eliminated age and sex as possible confounding factors in the differences observed between C57 mice and rats in prior reports.

Experiment 7: Effects of low doses of quinpirole on motor activity of mice

Since the lowest doses of quinpirole hydrochloride used in our previous experiments (0.02 mg/kg) substantially reduced activity, an additional experiment was conducted to extend the dose-response function to an undetectable level. This experiment was designed to rule out the slight possibility that the reduction in activity noted in the previous experiments was the result of neurotoxicity.

Procedure. Some reports indicated activity elevations in male rats injected with quinpirole during the latter stages of long test periods. Therefore, 36 9-month-old experimentally naive male mice (9/group) were injected IP with vehicle or with quinpirole hydrochloride (0.02, 0.01, or 0.005 mg/kg, expressed as the salt). Immediately after the injection, they were placed in an activity arena, and the total distance traversed during a 2-h test was determined.

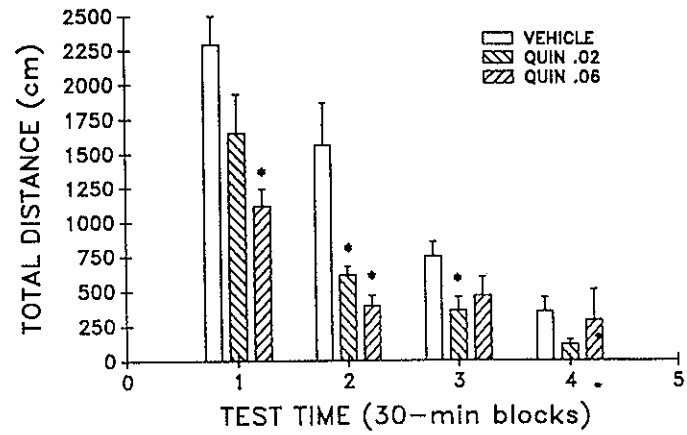

Fig. 10. Effects of SC vehicle (V) or of quinpirole hydrochloride (0.02 or 0.06 mg/kg) on motor activity ($\bar{x} \pm SE$) of male C57 mice at intervals over a 2-h test period. *$P < 0.05$ with reference to V.

Results. The data for this experiment were analyzed with a 4(drug dose) × 4(time) ANOVA. Although activity declined across 30-min intervals of the 2-h test period ($F(3, 93) = 120.447$, $P < 0.001$), the dose × time interaction was not significant. Therefore, data for total activity are summarized in Figure 9. As noted in our previous experiments with quinpirole, activity decreased monotonically with increasing dose ($F(3, 31) = 3.077$, $P < 0.0414$). Comparison of means using Duncan's multiple comparison test indicated that the two higher doses reduced activity. Thus, it appears that the lowest quinpirole dose necessary to reduce motor activity is near 0.01 mg/kg.

Experiment 8: Effects of subcutaneous injections of quinpirole on motor activity of habituated mice

Since the subcutaneous (SC) route was used in some of the previous studies which indicated elevated activ-

ity in rats (Eilam and Szechtman, 1989; Meyer and Potter, 1993; Hartesveldt et al., 1994), the SC route was used on mice in the present experiment. This experiment was intended to rule out the possibility that rate of drug delivery to the central nervous system (CNS) might influence whether quinpirole elevated activity.

Procedure. Twenty-four 9-month-old male mice were injected SC with vehicle or with quinpirole hydrochloride (0.02 or 0.06 mg/kg). The mice were placed in the activity arena immediately after injection, and activity was recorded for a 2-h period.

Results. The results are summarized in Figure 10 as the effects of the different drug doses on motor activity at 30-min intervals for 2 h after injection. The data were initially analyzed with a 3(dose) × 4(time block) ANOVA. The results were consistent with those of our previous experiments. Quinpirole reduced activity according to dose ($F(2, 18) = 11.385$, $P < 0.001$), and the reduction depended upon time after injection (dose × time: $F(6, 54) = 3.262$, $P = 0.0084$). As seen in Figure 10, quinpirole reduced activity below control levels during the first two intervals for the higher dose (0.06 mg/kg) and during the second two intervals for the low dose (0.02 mg/kg). As time continued, the effects of both doses diminished to become no different from controls. It is again important to note that under no condition was activity elevated by quinpirole. This experiment eliminates the route of drug administration as a possible reason for the absence of elevated activity associated with quinpirole injections in C57 mice. Thus, it is apparent that the observed differences between C57 mice and several strains of rats in their response to quinpirole are pervasive and may be reflective of a functional difference in DAD2, D3 receptor subsystems.

DISCUSSION

As noted in previous studies on rats (Eilam et al., 1992; Meyer and Shults, 1993; Mogenson and Wu, 1991; Moody and Spear, 1992), the DAD1-like agonists tested in the present study either elevated or reduced the locomotion of C57 mice, the particular effect depending upon dose and testing conditions. However, in contrast to the several reports indicating that DAD2-like agonists produce a biphasic action on motor activity of rats (Eilam and Szechtman, 1989; Hartesveldt et al., 1994; Meyer and Potter, 1993), quinpirole produced a monotonic reduction in locomotion of C57 mice. This reduction in activity occurred whether the mice were male or female, young or mid-aged adults, naive or well-habituated to the test environment, or injected with very low or very high doses administered either IP or SC. Based on these results, we conclude that the receptor systems mediating the effects of DAD1-like agonists on the motor activity of C57 mice, and probably other strains, are similar to those of rats; however, the receptor systems mediating the effects of the DAD2-like agonist quinpirole are dissimilar for the two species.

The DAD1-like partial agonist SKF 38393 injected IP in low doses reduced the locomotion of nonhabituated C57 mice relative to control levels (Exp-1). With increasing dose, however, locomotion increased, and the activity of mice following a 9.0 mg/kg dose did not differ from control values. In addition, Exp-2 indicated that familiarity with the test environment to a large extent determined whether SKF 38393 elevated or reduced activity relative to control levels. Specifically, at a constant dose (6.0 mg/kg), SKF 38393 reduced locomotion relative to control levels when mice were unfamiliar with the testing environment, but increased locomotion when the mice were well-habituated to the test environment. Most importantly, the apparent change in the drug's effect on motor activity relative to control levels was due to a reduction in the activity levels of the vehicle-injected control habituated mice rather than to a difference in the drug's effect on habituated vs. nonhabituated animals. This result is consistent with a previous report (Wenger, 1989) in which differences in control activity levels rather than differences in drug-treated mice accounted for the large strain differences observed in mice treated with d-amphetamine, scopolamine, and morphine. Thus, basal activity level provides a powerful constraint upon the observed effect of drugs, including the DAD1-like agonists.

The demonstrated influence of basal activity level on the effects of SKF 38393 provides a logic for the reported increases (Tirelli and Terry, 1993), decreases (Eilam et al., 1992), or lack of effect (Mogenson and Wu, 1991) of the drug on motor activity. It is our contention that differences in control activity level may account for the reported inconsistencies between the effects of DAD1-like agonists on mice and rats; that each of the reported effects are logical results of DAD1-like receptor stimulation under specific dose, route, and habituation conditions; and that the underlying receptor-mediating systems are similar for the two species.

The elevated activity observed in C57 mice injected with SKF 38393 in the present study is consistent with that in previous reports for both rats and mice in experiments with low basal activity levels. Tirelli and Terry (1993) reported a biphasic effect of SKF 38393 on the activity of C57 mice across time, an effect which appears to be related to changes in the basal activity level. Early in the test when basal activity was high for vehicle-injected mice, the activity of drug-injected mice was reduced. Later in the test, while the activity of vehicle-injected mice declined, the activity of SKF 38393-injected mice remained relatively constant, resulting in elevated activity relative to control levels. Furthermore, Moody and Spear (1992) reported that SKF 38393 elevated the activity of Sprague-Dawley rat pups when control activity levels were low. To illustrate the generality of the motor activity increase associated

with SKF 38393, several studies indicated that intraaccumbens infusions of SKF 38393 increased locomotor activity of various rat strains (Dreher and Jackson, 1989; Meyer, 1993; Meyer et al., 1993), and additional studies indicated that SKF 38393 elevated activity when injected (IP or SC) into either mice (Arnt et al., 1992; Shannon et al., 1991; Zarrindast and Eliassi, 1991) or rats (Bruhwyler et al., 1991; Mazurski and Beninger, 1991; Molloy and Waddington, 1985, 1987; Molloy et al., 1985; Setler et al., 1978).

The reduction in activity of C57 mice injected with low doses of SKF 38393 is also consistent with reports in the literature; however, the reduction occurs when basal activity levels are relatively high. Meyer and Shults (1993) reported that SKF 38393 reduced the activity of Long-Evans hooded rats which were not habituated to the test environment and thus had relatively high basal activity levels. Eilam et al. (1992) reported a similar result when Sprague-Dawley rats were not habituated to the test environment and basal activity levels were high. These findings on rats are also in accordance with those reported for C57Bl/6J mice (Tirelli and Terry, 1993).

These reports, when viewed in light of the influence of basal activity levels on the effects of drugs, form a logical account of the conditions under which DAD1-like agonists elevate or reduce locomotion. Furthermore, the response of mice and rats to DAD1 stimulation with SKF 38393 is consistent within this framework. Thus, SKF 38393 can elevate, reduce, or have no effect upon locomotor activity of either mice or rats, depending upon basal activity level as well as dose and time course, suggesting that the underlying receptor-mediating systems for the response to SKF 38393 are similar in mice and rats.

The generality of the C57 mouse response to DAD1 stimulation was assessed in the present study by determining the effect of the full DAD1 agonist SKF 82958 on mice of both sexes and two different ages. In our experiments, SKF 82958 produced a dose-responsive increase in locomotor activity of both young adult and mid-aged mice of either sex. This finding confirms the role of DAD1 receptors in mediating the activity elevations noted upon stimulation with SKF 38393, and is consistent with the literature using either mice or rats. Arnt et al. (1992) reported that all DAD1-like agonists tested increased locomotor activity of mice, with the greatest effect observed for the full DAD1 agonist SKF 81297.

In rats, SKF 82958 and other DAD1 full agonists increased locomotor activity at low doses (Meyer and Shults, 1993), but were biphasic with respect to time at higher doses. As noted above for the biphasic action of other agonists, the reduction in activity occurred early in the session when control activity levels were high. Later, as basal activity decreased for controls, the activity of the treated mice remained constant, and a relative increase was observed.

The biphasic activity resulting from high doses of SKF 82958 injected into rats (Meyer and Shults, 1993) was not observed in C57 mice in our study. The bidirectional effect of the drug on the activity of rats, however, was observed at a dose 10 times greater than the highest dose used in our experiments (i.e., 1 mg/kg vs. 0.1 mg/kg). Thus, the maximum dose used in our experiments may have been insufficient for a biphasic action. Furthermore, it should be noted that the biphasic action of the full agonist on rats differed from that observed for the partial DAD1 agonist SKF 38393. Rather than low doses decreasing activity as observed for the partial agonist, low doses of SKF 82958 elevated activity. Importantly, however, the predominant effect of the full agonist in rats was an increase in activity throughout the majority of the test period (Meyers and Shults, 1993), which was also observed in mice in our experiment. We agree with Meyers and Shults (1993) that the ability of SKF 82958 to increase locomotor activity at low doses is due to its high efficacy for the DAD1 receptor. However, the mechanism for the type of biphasic action observed at high doses in their study was not discussed and is not readily apparent.

To summarize, both rats and mice exhibit either increased or decreased motor activity to injections of the partial DAD1 agonist, SKF 38393, the response depending upon the interaction of basal activity level, dose, and postinjection time. The consistency in the behavioral response to this agonist suggests species similarity in the underlying DAD1-like subreceptor systems. The species similarity is for the most part also noted for the effects of the full agonist, SKF 82958; however, further experiments will be needed to clarify whether mice exhibit a biphasic response to the drug at high doses, as reported for rats (Meyer and Shults, 1993).

In contrast to the species consistency noted for the effects of DAD1 receptor stimulation on locomotor activity, there are apparent species differences for the effects of DAD2 stimulation. Stimulation of DAD2-like receptors with the agonist quinpirole in the present series of experiments produced a dose-responsive monotonic reduction in activity of C57 mice whether the animals were nonhabituated or well-habituated to the testing environment, male or female, young or mid-aged, or injected IP or SC, with either low or high doses. These findings, while consistent with previous reports for mice, are not readily reconcilable with the effects of quinpirole or other DAD2-like agonists on the activity of rats.

The effect of quinpirole on motor activity of rats is well-documented, and is typically reported to be biphasic with respect to time and dose. In both cases, activity is reduced at low brain concentrations and increased at higher concentrations. Eilam and Szechtman (1989)

reported that quinpirole reduced activity at early postinjection times (0–30 min), followed by increasing hypermotility relative to control levels. At higher doses (0.5 and 8 mg/kg) the hypermotility continued until the end of the test period (120-min postinjection). Additional studies replicated this biphasic effect across time (Hartesveldt et al., 1994; Meyer and Potter, 1993). In addition, Hartesveldt et al. (1994) reported that low doses of quinpirole (0.02 mg/kg) only decreased activity of rats. Higher doses, however, produced a biphasic effect across time with hypermotility sufficient to result in an overall dose-dependent increase above controls levels (Eilam and Szechtman, 1989; Hartesveldt et al., 1994).

Because the literature suggests that the biphasic effects of high quinpirole doses on rats occur in well-habituated animals, we attempted to duplicate these effects in C57 mice well-habituated to the testing environment (Exp-5). In this experiment we ensured that the time parameters were comparable to those for one of the rat studies demonstrating a biphasic effect of quinpirole (Eilam and Szechtman, 1989), that the mice were well-habituated to the testing environment, which lowered basal activity levels, and that they were injected with high doses of quinpirole (up to 9 mg/kg). In spite of this attempt to facilitate the detection of increased activity, only a reduction was observed. Furthermore, since the reductions in activity produced by the two higher doses of quinpirole (6 and 9 mg/kg) did not differ significantly from one another, an upper limit for the drug's effect on motor activity was likely reached.

Since DAD2 receptor binding and, by inference, the response to DAD2 agonists appears to be influenced by age and by sex (Boggan et al., 1996; Di Paolo et al., 1988; Dorce and Palermo-Neto, 1994; Gilad and Gilad, 1987; O'Boyle and Waddington, 1984), the effects of quinpirole on young adult and mid-aged mice of both sexes were examined (Exp-6). Quinpirole at doses ranging from 0.02–0.16 mg/kg produced a monotonic reduction in activity regardless of sex or age.

Because the lowest doses of quinpirole used in the first four experiments reduced activity, the effect of lower drug doses was examined (Exp-7). This experiment established that the minimal dose of quinpirole necessary to reduce activity was near 0.005 mg/kg, with lower doses having no effect.

Lastly, because rat studies noting elevated activity with quinpirole had utilized the subcutaneous route of administration (Eilam and Szechtman, 1989; Hartesveldt et al., 1994) while our experiments and others on mice (Shannon et al., 1991) utilized IP injections, we injected mice SC with various doses of quinpirole (Exp-8). In spite of the change in route of administration, however, activity was reduced for up to 90 min after all doses, a finding consistent with another study on mice (Arnt et al., 1992). Thus, the route of drug administration was eliminated as a possible reason for the apparent difference in the effect of quinpirole on rats and mice. Although the extended testing times of Exp-7 and Exp-8 (120 min) to uncover potential activity elevations late in the testing were performed only on male mice, we suspect that the results generalize to female mice, since Exp-6 failed to establish sex differences in reaction to the drug. However, the reaction of female mice under these conditions remains unobserved.

The reduction in activity of young and aged male and female mice produced by quinpirole in our study extends a finding that the drug reduced motor activity of habituated young male mice of several strains at several doses (Shannon et al., 1991). The consistent monotonic reduction in motor activity of mice upon DAD2-like stimulation by quinpirole contrasts with the drug's biphasic action on rats. Thus, after eliminating a number of possible methodological factors which could have accounted for the species difference (e.g., dose, postinjection time, route of administration, habituation level), we conclude that the receptor systems mediating the response to DAD2-like stimulation by quinpirole differ in mice and rats.

The absence of sex and age differences in response to either quinpirole or SKF 82958 in our experiments eliminated age and sex as possible methological explanations for the observed species difference in reaction to quinpirole. The absence of age and gender differences, however, was somewhat unexpected, since DA receptor binding studies indicate that the number of DAD1 and DAD2 receptors decline by age 1 year in C57 mice (Randall et al., 1981, 1985), and that cycling female rats have fewer DA receptors than male rats (Boggan et al., 1986; Di Paolo et al., 1988; Miller, 1983). Although the mid-aged male and female mice exhibited a tendency toward a reduced response to the agonists in our studies, as would be expected, these differences were not supported statistically. Possibly, different age comparisons and controls over the estrus state would be necessary to establish differences in response to the DA agonists. Further, it is possible that tests of longer duration would have reflected age- and sex-related differences. It should be noted, however, that the ages used in our study were representative of the subjects used in evaluating DA agonists throughout the literature.

Potential explanations for the observed differences between the response of rats and mice to quinpirole include species differences in the regional and/or synaptic localization of the DAD2 receptors, in the affinity states of the receptors, or perhaps in the relative concentrations of DAD3 receptor protein. Since DA agonists can bind preferentially to pre- or postsynaptic sites (Martin and Bendesky, 1984), differential distribution of the drug across the synapse, as suggested by Carlsson (1975) and Di Chiara et al. (1978), may apply (for further references see Seeman, 1981). A study of the

pre- vs. postsynaptic distributions of the DAD1 and DAD2 proteins in both mice and rats is called for. Species differences in the interconversion of DA receptors from high- to low-affinity states (Leff et al., 1985; Seeman et al., 1985) in response to changes in Na+ and GTP concentrations (Grigoriadis and Seeman, 1985; Hamblin and Creese, 1982; Makman et al., 1982; Watanabe et al., 1985) may also be held to account. High-affinity DAD2 receptor density is reported to be the best predictor of movement initiation in rats (Wilcox et al., 1988), and a similar mechanism has been postulated to account for differences in the response to apomorphine by different inbred mouse strains (Cabib and Puglisi-Allegra, 1985; Michaluk et al., 1982; Randall and Randall, 1986). Thus, an experiment comparing the affinity states of the DAD2 receptors of mice and rats, as described by Skirboll et al. (1979), would be useful. Lastly, because quinpirole can bind to DAD3 receptors, and because these receptors are prominent in specific limbic regions known to affect locomotor activity (Teitelbaum et al., 1979), they may be important in the regulation of locomotor behavior (Booze and Wallace, 1995; Gehlert et al., 1992; Levant et al., 1993; Sokoloff et al., 1990; Wallace and Booze, 1995). In fact, 7-OH-DPAT, a high-affinity ligand for DAD3 sites, has been shown to reduce locomotor activity in rats (Daly and Waddington, 1993; McElroy et al., 1993; Svensson et al., 1994), while the DAD3 antagonist U99194A has been shown to increase locomotor activity (Waters et al., 1993). Since the mouse has been shown to exhibit a novel form of the DAD3 receptor protein (Fishburn et al., 1993), the specific binding of quinpirole by this receptor in comparison to that of rats should be examined.

In summary, the present study indicates that the behavioral response of C57 mice to DAD1 agonists is consistent with that described for rats. This suggests similar DAD1 subreceptor systems for the two species. In contrast to the similar effects of DAD1-like agonists on the two species, C57 mice in the present study exhibit only a monotonic reduction in activity when injected with the DAD2-like agonist quinpirole, rather than the biphasic effects reported for rats. After systematically eliminating possible methodological differences which might contribute to the species difference in their behavioral response to quinpirole, we conclude that the DAD2 subreceptor systems mediating the response to this drug differ for the two species. Although not tested in the present study, species differences in receptor distribution (pre- vs. postsynaptic or anatomical), in affinity state, and in sub-receptor type are testable in future experiments and may, individually or in combination, account for the species difference in the behavioral response to the drug. Thus, although the mechanism remains unknown, the present study clearly establishes a species consistency in the response to DAD1-like agonists, and a species difference in the response to DAD2-like agonists.

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