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An Ethopharmacological Analysis of Selective Activation of 5-HT_{1A} Receptors: The Mouse 5-HT_{1A} Syndrome

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5-HT_{1A} receptor agonist 8-OH-DPAT (+)S-20499 Behavior analysis 5-HT_{1A} syndrome Mouse Species difference Serotonin

A NUMBER of previous studies have shown that the centrally acting 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) induces a complex behavioral syndrome. In naive rats [e.g., (3,7,11,17,26)], this comprises a characteristic set of behaviors including flattened body posture, forepaw treading, hyperlocomotion, head weaving, and hindlimb abduction after administration of the drug. More recently, Blanchard et al. (4) extended the knowledge of the behavioral effects of 8-OH-DPAT in rats through detailed ethological analysis. For example, they showed that the locomotor syndrome primarily involves forward movement, heavily guided by the physical environment, and that

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forepaw treading only occurs when an animal reaches a barrier and forward movement is briefly interrupted. The behavioral consequences of selective activation of the 5-HT_{1A} receptor subtype have also been described in other species, such as mice (11,27), Mongolian gerbils (9), guinea pigs (5,10), pigs (21), and monkeys (23). Interestingly, the specific behavioral components of the "5-HT_{1A} syndrome" induced by 8-OH-DPAT may differ among species. Thus, hyperlocomotor effects of the drug have been mostly described in rats and guinea pigs (4,7,10,11,26), whereas authors using mice invariably reported decreased locomotor responses (11,22). In addition, discrepancies among studies using mice as subjects have also emerged. Indeed, although the initial study of Goodwin and Green (14) found that 8-OH-DPAT did not induce any distinct behavioral syndrome when given by subcutaneous (SC) injection, even though doses up to 10 mg/kg were administered, Yamada et al. (27) described a distinct 5-HT_{1A} syndrome, including head weaving, hindlimb abduction, forepaw treading, and tremor, after the drug was given intravenously (IV) in doses greater than 1 mg/kg. The conclusion that the syndrome is only observed if the drug is administered IV, thereby achieving a higher circulating concentration, must be tempered by a recent observation from this laboratory suggesting that SC injection of 8-OH-DPAT may also elicit some component of the 5-HT_{1A} syndrome (15). This study revealed that the drug, administered over a wide dose range (0.5–10 mg/kg), produced rapid perceptible behavior change, including alteration in horizontal and vertical motor activity described as stereotyped uncoordinated ambulation. Moreover, the hypolocomotor-inducing effect of 8-OH-DPAT observed in two recent studies after the drug had been administered SC and intraperitoneally (IP) (11,22) may also be a component of the mouse 5-HT_{1A} syndrome.

To extend the understanding of the behavioral syndrome induced by selective activation of the 5-HT_{1A} receptor subtype in mice, the present experiments were designed to assess the effects of 8-OH-DPAT and (+) S-20499, a recently synthesized full agonist (1,6,12,20), through a detailed ethological analysis similar to that previously used by Blanchard et al. (4) in rats. This approach allows determination of the effects of drug treatment on a wide behavioral repertoire, as well as determination of the time course of these behaviors.

EXPERIMENT 1: EFFECT OF 8-OH-DPAT AND (+) S-20499 ON BEHAVIOR IN A NOVEL CAGE

Methods

Animals. Subjects were 96 naive male Swiss–Webster mice obtained from Simonsen Laboratories (Gilroy, CA, USA); mice were 60–75 days old at the beginning of the experiment. They were housed singly in polycarbonate cages in a room maintained under a 12 L:12 D cycle with light onset at 0600 h. Each subject was used only once.

Drugs. (±)-8-OH-DPAT Hbr (Research Biochemicals Inc., Natick, MA, USA) and (+) S-20499 [(+) 4-(*n*-5-(methoxychroman-3-yl)*n*-propylamino)butyl-8-aza spiro(4,5)decane-7,9-dione] were dissolved in an isotonic saline vehicle to various concentrations such that injections were always at a constant volume of 10.0 ml/kg. Mice were randomly assigned to one of two experiments: a) 8-OH-DPAT, control group (n = 12) and drug treatment groups (0.5, 1, and 10 mg/kg; n = 12, 11, and 12, respectively); or b) (+) S-20499, control group (n = 13) and drug treatment groups (1, 10, and 20 mg/kg; n = 12 each). Mice received a single IP injection of either saline, 8-OH-DPAT, or (+) S-20499.

Procedure. Subjects were injected and immediately placed in an unfamiliar, empty, clean polycarbonate cage (18.5 × 29 × 13 cm) covered by a wire mesh. For each mouse, one lab chow pellet was placed in the center of cage. Behavior was recorded for 2 h by a videocamera mounted on a tripod at the side of the cage.

Statistical analysis. Because some data were not normally distributed, analysis was carried out using nonparametric analysis of variance (ANOVA; Kruskal–Wallis for between-subjects ANOVA, and Friedman ANOVA for within-subjects tests) followed by the Mann–Whitney *U*-test. For data supporting the assumptions of parametric analysis, parametric ANOVA was used.

Behavioral analysis.

Time sample data. Behavioral ratings of the videotape recordings of neutral cage behavior were made for a 1-s period every 30 s throughout the 2-h test period, and data were summed in 10-min blocks. Raters were trained to 95% agreement on each category of behavior, and spot-checks throughout the rating period ensured continued agreement. All rating was done from videotapes, and raters were blind to the drug status of the animals. The behavioral categories scored comprised lie, groom, stand, crouch, locomote, rear, ballistic-type movement, and eat. Furthermore, with the exception of groom, ballistic-type movement, and eat, these behaviors were subdivided to provide a more detailed and sensitive analysis of the effects of both compounds.

Locomote. This behavior involves movement greater than one head length in the 1-s sampling period and is subdivided into eight categories:

a. Curved back ambulation. Gross bodily movement involving all four paws. The arch of the back is above the level of the ears when the animal's head is horizontal to the body. The tail is in contact with the ground.
b. Flat back ambulation. As above, but with the arch of the back below the relevant line.
c. Body on grid, dragging. The animal pulls itself without use of the hindlimbs. The tail is in contact with the ground.
d. Stretch attend. The body shifts forward in a flat back posture, but the legs remain in place.
e. Movement on the ceiling. The animals locomotes when hanging from the wire mesh.
f. As for curved back ambulation, with the tail elevated off the floor.
g. As for flat back ambulation, with the tail elevated off the floor.
h. As for body on grid, with the tail elevated off the floor.

Stand. The animal is immobile with both forelimbs and hindlimbs extended. This behavior is subdivided into two categories:

a. Curved back (as for locomote).
b. Flat back (as for locomote).

Lie. This behavior is characterized by the animal resting in a prone posture on the grid, with no elevation of the body by either forepaws or hindpaws. Lie is subdivided into three categories:

a. Flat back, head down. The head and body rest on the floor in a straight line.
b. Flat back, head up. The animal lies with the head elevated off the ground.
c. Curved back. The head and spine are curved.

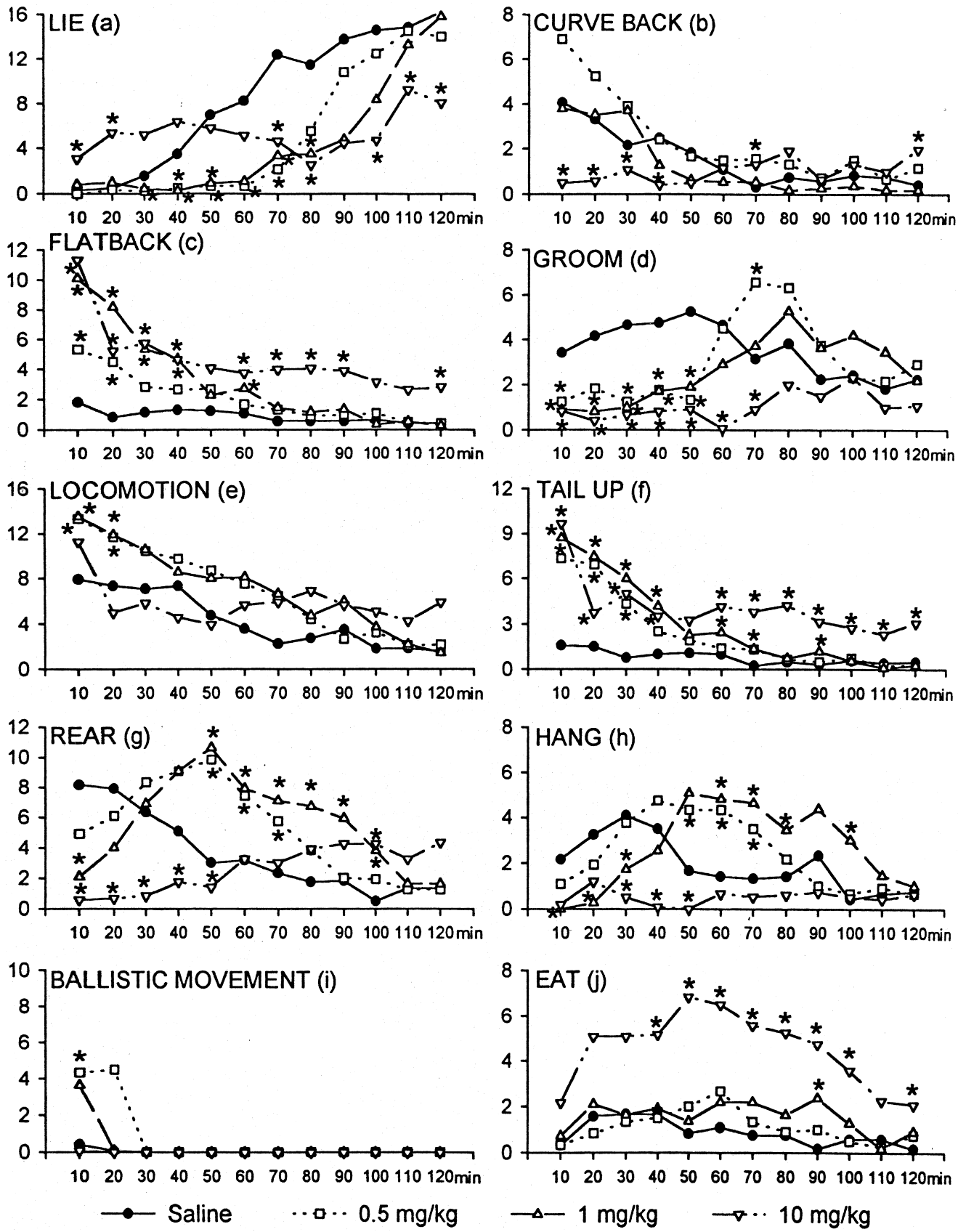

FIG. 1. Time-course analysis of behaviors of mice altered by administration of various doses of 8-OH-DPAT. Data represent mean frequency of observations for each 10-min time period. $p < 0.05$ or less vs. saline.

Crouch. This behavior is distinguished from lie by the elevation of the forelimbs off the floor. Crouch is subdivided into five categories:

a. Weight on floor. The animal's back forms an arch above the level of the ears, when neither hindlimbs nor forelimbs are extended.
b. Forelimbs elevated. The forelimbs are raised from the floor in the "typical" crouch position. The animal's back forms an arch above the level of the ears.
c. Splayed forelimbs. Forelimbs are not parallel, and the body is off the ground.
d. Crouch and sniff. Crouching with head movements in excess of 1 cm/s.
e. As forelimbs elevated, with the animal's back flat.

Rear. Rear behavior is subdivided into four categories:

a. Rear involving movement of the body through the vertical plane with forelimbs touching the wall.
b. As rear type a, but no contact with the wall.
c. Wall climbing. Forepaw movement on the wall.
d. Rear when hanging from the ceiling.

Ballistic-type movement. Rapid movement of the forelimbs toward the side of the head.

Results

A preliminary analysis of all behavioral responses was performed to determine those measures altered by the treatments. This enabled us to restrict the full data analyses to the relevant categories. Following this initial assessment, the behavioral categories from the original list (see Methods) that were affected by both compounds were then summed to form relevant composite measures of associated behaviors, as follows:

Lie: lie (a–c) + crouch (a)
Curve back: locomote (a, f) + stand (a)
Flat back: locomote (b, d, g, h) + stand (b)
Groom
Locomotion: locomote (a–h) + rear (d)
Straub tail: locomote (f, g, h)
Rear
Hang: locomote (e) + rear (d)
Ballistic-type movement
Eat

Lie. In both control groups, lying increased gradually after an initial period of about 40 min of activity following saline injection.

8-OH-DPAT (Fig. 1a). Kruskal–Wallis ANOVA revealed a reliable main effect of treatment [$H(3, 47) = 18.23$, $p < 0.001$], reflecting an overall decrease in lie at 0.5 and 1 mg/kg. In addition, a reliable dose × time interaction was indicated [Friedman ANOVA: $N(11, 47) = 89.22$, $p < 0.0001$]. Mann–Whitney analysis for each 10-min period indicated an increase in lying at 0–20 min with 10 mg/kg of 8-OH-DPAT. This effect was then nullified at 21–60 min as lying in control animals began to increase. At 21–70 min, there was a reliable difference between the high level of lying in controls and the lower levels at 0.5 and 1 mg/kg. This effect was significant at all doses for the 61–70-min period and at 10 mg/kg for 91–120 min postinjection.

S-20499 (Fig. 2a). ANOVA indicated a significant overall effect of treatment [$H(3, 49) = 9.46$, $p < 0.05$] that is due to a reliable decrease in lying at 10 and 20 mg/kg. ANOVA also revealed a reliable dose × time interaction [$N(11, 49) = 126.63$, $p < 0.0001$]. Individual analyses of each time period showed that the drug decreased lying at 41–60 and 91–120 min at 20 mg/kg, and at 31–40, 51–60, and 91–120 min postinjection at 10 mg/kg.

Curve back. In saline-treated animals, the occurrence of curved back stand/locomote was initially high, then progressively decreased until reaching a level close to zero at time block 71–80 min postadministration.

8-OH-DPAT (Fig. 1b). ANOVA indicated a significant dose × time interaction [$N(11, 47) = 101.69$, $p < 0.0001$]. Independent analyses of each 10-min time block indicated that the drug decreased curve back posture at 0–40 min at the highest dose (10 mg/kg). This effect was nullified at 41–60 min postadministration, because control levels had decreased. At 61–70 min, there was a reliable difference between the low level of curve back in controls and the higher levels at 0.5 mg/kg. Also, in the 111–120-min period, curve back was reliably increased at 10 mg/kg.

S-20499 (Fig. 2b). ANOVA revealed a reliable main effect of drug treatment [$H(3, 49) = 21.46$, $p < 0.0001$], reflecting an overall increase in curved back stand/locomote at all doses (1–20 mg/kg). In addition, a reliable dose × time interaction was indicated [$N(11, 49) = 95.56$, $p < 0.0001$]. Mann–Whitney analysis for each 10-min time period showed that the drug increased curve back posture from time period 31–40 min until the end of the 2-h observation time at the two highest doses (10 and 20 mg/kg). Also, at the lowest dose (1 mg/kg), the compound reliably increased curve back posture at 41–50 and 71–80 min postinjection.

Flat back. In both saline-treated groups, animals displayed a very low level of flat back posture/movement throughout the 2-h session.

8-OH-DPAT (Fig. 1c). ANOVA indicated a reliable treatment effect [$H(3, 47) = 24.45$, $p < 0.0001$] due to an overall increase in flat back posture/movement at all doses (0.5, 1, and 10 mg/kg). The interaction dose × time was also reliable [$N(11, 47) = 173.95$, $p < 0.0001$]. Individual analyses for each time block indicated that the drug increased the occurrence of flat back at 0–40 min, at 51–90 min, and during the last time block (111–120 min) at the highest dose (10 mg/kg). Similarly, 8-OH-DPAT increased the posture during time periods 0–40 min and 51–60 min at 1 mg/kg. Finally, an initial (0–20 min) increase in flat back posture was also observed at the lowest dose (0.5 mg/kg).

S-20499 (Fig. 2c). ANOVA revealed a reliable dose × time interaction [$N(11, 49) = 24.01$, $p < 0.0001$], and subsequent Mann–Whitney analyses indicated that the drug significantly increased flat back posture/movement during the initial 10-min time period at 10 and 20 mg/kg.

Groom. The initial level (approximately three episodes) of grooming was little changed throughout the 2-h session.

8-OH-DPAT (Fig. 1d). ANOVA revealed a reliable drug treatment effect [$H(3, 47) = 19.99$, $p < 0.001$] due to an overall decrease in grooming at 1 and 10 mg/kg. In addition, a reliable dose × time interaction was indicated [$N(11, 47) = 25.65$, $p < 0.01$]. Individual analyses of each 10-min time period showed that the drug suppressed grooming behavior during the initial 50 min at all doses (0.5, 1, and 10 mg/kg) and also at 51–70 min postinjection at 10 mg/kg. Finally, at 61–70 min, 0.5 mg/kg of 8-OH-DPAT induced a reliable increase in the occurrence of grooming.

S-20499 (Fig. 2d). ANOVA revealed a significant overall drug effect [$H(3, 49) = 26.55$, $p < 0.0001$] due to a decrease in grooming at 10 and 20 mg/kg. However, Friedman ANOVA

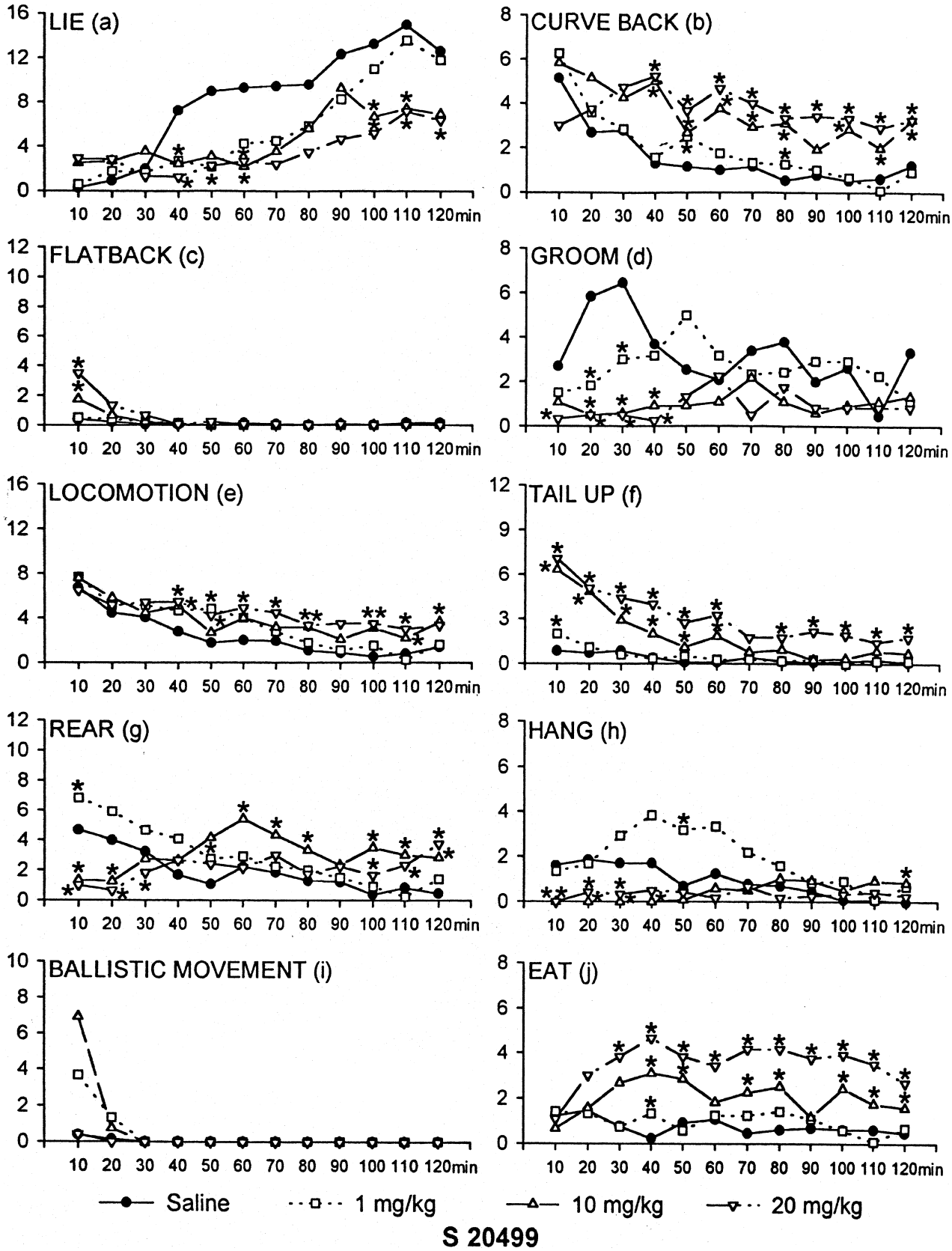

FIG. 2. Time-course analysis of behaviors of mice altered by administration of various doses of (+) S-20499. Data represent mean frequency of observations for each 10-min time period. $p < 0.05$ or less vs. saline.

failed to show any reliable dose × time interaction [$N(11, 49) = 8.48$].

Locomotion. After an initial period of activity, locomotor responses declined gradually until reaching a level close to zero at 91–100 min postinjection.

8-OH-DPAT (Fig. 1e). ANOVA revealed a reliable treatment effect [$H(3, 47) = 9.72$, $p < 0.05$] due to an overall increase in locomotion at 0.5 and 1 mg/kg. In addition, Friedman ANOVA indicated a reliable dose × time interaction [$N(11, 47) = 183.08$, $p < 0.0001$]. Subsequent individual analysis of each 10-min time period revealed that the drug significantly increased locomotor responses at 0–20 min at 0.5 and 1 mg/kg.

S-20499 (Fig. 2e). ANOVA indicated a significant drug treatment effect [$H(3, 49) = 10.31$, $p < 0.05$] confirmed by an overall increase in locomotor responses at all doses (1, 10, and 20 mg/kg). Also, a reliable dose × time interaction was revealed [$N(11, 49) = 137.46$, $p < 0.0001$]. Independent analyses of each 10-min time block showed that the compound significantly increased locomotor responses at 31–80 min and at 91–110 min postinjection at 20 mg/kg. A similar effect was also observed at 10 mg/kg at 71–80 min and 101–110 min, and at 1 mg/kg at 41–50 min.

Straub tail. Very few straub tail responses were observed in drug-free animals. Most of them occurred in the first half of the 2-h experiment.

8-OH-DPAT (Fig. 1f). ANOVA showed a reliable main effect for treatment [$H(3, 47) = 21.54$, $p < 0.0001$] due to an overall increase in straub tail response at all doses. In addition, Friedman ANOVA indicated a reliable dose × time interaction [$N(11, 47) = 243.89$, $p < 0.0001$]. Individual analyses of each 10-min time block revealed a reliably higher occurrence of tail-up vs. control at all doses at 0–30 min. At 31–40 min, this effect was still reliable at 1 and 10 mg/kg, but then disappeared in all drug-treated animals in the following time period (41–50 min). At 51–120 min postinjection, reliably more straub tails were observed at 10 mg/kg, whereas the 1-mg/kg-treated animals only occasionally displayed more tail-up (at 51–70 min and at 81–90 min).

S-20499 (Fig. 2f). ANOVA indicated a reliable treatment effect [$H(3, 49) = 25.63$, $p < 0.0001$], reflecting an overall increase in the occurrence of straub tails at all doses. Reliable dose × time interaction was also indicated [$N(11, 49) = 138.06$, $p < 0.0001$]. Separate analyses for each 10-min time block revealed that the tail-up effect of the drug showed very rapid onset following drug administration. This effect lasted until time period 51–60 min at 10 and 20 mg/kg, whereas it dissipated within 10 min at 1 mg/kg. Analysis of time blocks at 71–120 min revealed reliable effects at 20 mg/kg for all time periods, whereas the 10-mg/kg dose induced more straub tails only at 101–110 min. Finally, a higher level of tail-up was also observed at 1 mg/kg at 41–50 min postinjection.

Rear. The overall pattern of rearing in drug-free controls was very similar to that of locomotion. The initial period of activity was followed by a progressive decline in rearing behavior until rearing reached a level close to zero at 91–100 min postinjection.

8-OH-DPAT (Fig. 1g). ANOVA revealed that the drug significantly altered the occurrence of rearing responses [$H(3, 47) = 17.78$, $p < 0.0005$]. Subsequent analysis with the Mann–Whitney *U*-test indicated that the drug tended to increase the frequency of rears at 1 and 10 mg/kg. In addition, a reliable dose × time interaction was indicated [$N(11, 47) = 121.98$, $p < 0.0001$]. Independent analyses for each 10-min time block indicated an initial decrease in rears at the two highest doses. This effect lasted up to 50 min at 10 mg/kg, whereas it dissipated within 10 min at 1 mg/kg. When rearings in control animals started to decrease, a reliable difference between control and drugged animals reappeared, but with the latter showing enhanced rearing at the intermediate dose (1 mg/kg) from time period 41–50 min to 91–100 min. Similarly, a reliably higher level of rears was observed at the highest dose at 91–100 min and at 0.5 mg/kg at 41–70 min postinjection.

S-20499 (Fig. 2g). ANOVA revealed a reliable main effect for drug treatment [$H(3, 49) = 7.87$, $p < 0.05$] due to an overall increase in the frequency of rearing at 1 and 10 mg/kg. In addition, Friedman ANOVA indicated a significant dose × time interaction [$N(11, 49) = 33.2$, $p < 0.0005$]. Separate analyses for each 10-min time block showed that the drug increased rears in the initial time period at 1 mg/kg, whereas it tended to suppress this response at 10 and 20 mg/kg. These latter effects lasted up to 20 and 30 min, respectively. Furthermore, when rearing responses in drug-free mice had clearly declined (at 51–120 min), animals treated with the 10-mg/kg dose of S-20499 displayed a reliably higher level of rears compared with controls. A similar effect was seen at 20 mg/kg at 91–120 min. Finally, it is noteworthy that in the initial 10-min period, when baseline performances were high, animals receiving 1 mg/kg of S-20499 showed a reliably higher level of rearing responses compared with drug-free controls.

Hang. Saline-treated controls tended to hang on the wire mesh more often during the first 50 min. The hanging performances then remained consistently low until the end of the 2-h observation period.

8-OH-DPAT (Fig. 1h). ANOVA revealed a reliable dose × time interaction [$N(11, 47) = 50.52$, $p < 0.0001$]. Subsequent individual analyses of each 10-min period showed an initial low level of hanging responses at 1 and 10 mg/kg. This effect lasted up to 30 min and 50 min, respectively, then returned at 1 mg/kg at 51–80 min, when hanging performances in drug-free controls declined. Finally, mice treated with 0.5 mg/kg of 8-OH-DPAT displayed reliably more hangs at 41–70 min postadministration.

S-20499 (Fig. 2h). ANOVA indicated a reliable drug effect [$H(3, 49) = 14.58$, $p < 0.002$] due to an overall suppression of hanging responses at 20 mg/kg. In addition, Friedman ANOVA revealed a significant dose × time interaction [$N(11, 49) = 21.46$, $p < 0.03$]. Separate analyses of each 10-min time block indicated that hanging behavior on the wire mesh was rapidly suppressed by the administration of 10 and 20 mg/kg S-20499. This effect dissipated at 21–30 min and 31–40 min, respectively, then returned in the last time block (111–120 min) at the highest dose, when baseline levels reached a level near zero. Finally, a reliable increase in hanging was also seen at 0.5 mg/kg at 41–50 min postinjection.

Ballistic-type movement. Very few saline-treated mice displayed rapid movement of the forelimbs toward the head in the initial time period, and this behavior completely disappeared thereafter.

8-OH-DPAT (Fig. 1i). ANOVA showed a significant treatment effect [$H(3, 49) = 13.76$, $p < 0.003$] due to an overall increase of these ballistic-type movements at the lowest dose (0.5 mg/kg). Furthermore, a reliable dose × time interaction was revealed by the Friedman ANOVA [$N(11, 47) = 147.75$, $p < 0.0001$]. Independent time block analyses indicated a significantly higher level of ballistic-type movements in the initial 10-min period at 0.5 mg/kg.

S-20499 (Fig. 2i). Although Friedman ANOVA revealed a reliable dose × time interaction [$N(11, 49) = 158.53$, $p < 0.0001$], subsequent individual analyses of each 10-min time

period failed to show any significant effect of S-20499 on ballistic-type movements throughout the 2-h testing period.

Eat. The occurrence of eating in drug-free controls was rather low over the 2-h test.

8-OH-DPAT (Fig. 1j). ANOVA indicated a reliable main effect [$H(3, 49) = 16.1$, $p < 0.001$] due to an overall increase in eating at 1 and 10 mg/kg. In addition, a significant dose × time interaction was revealed [$N(11, 47) = 69.83$, $p < 0.0001$]. Although animals treated with the high dose of 8-OH-DPAT (10 mg/kg) showed a rapid increase of eating responses compared with controls, separate analyses of each 10-min time block revealed that this effect only reached statistical significance at 31–40 min postinjection. Furthermore, the increase of eating at this dose level lasted until the end of the 2-h period. Finally, a small but reliable increase was also noted at 1 mg/kg at 81–90 min.

S-20499 (Fig. 2j). ANOVA revealed a reliable drug treatment effect [$H(3, 49) = 26.6$, $p < 0.0001$] due to an overall increase in eating at 10 and 20 mg/kg. However, Friedman ANOVA failed to show a dose × time interaction [$N(11, 49) = 14.62$].

EXPERIMENT 2: RUNWAY ANALYSIS

Previous analysis of the effects of 8-OH-DPAT administration in the rat (4) revealed a syndrome of continuous forward locomotion when these effects were examined in a situation that would allow such activity to occur. To determine whether comparable effects are found in the mouse, experiment 2 involved administration of 8-OH-DPAT and (+) S-20499 to Swiss–Webster mice in an oval runway permitting continuous forward locomotion. Because a specific behavior was to be evaluated rather than a number of behaviors interacting over time, these responses were investigated during a time (20–30 min postinjection) selected to coincide with the period of maximum effect of the drugs administered.

Methods

Subjects and drugs. These were identical to those of experiment 1, with eight subjects per control or treatment (drug dose) group.

Apparatus. The test was conducted in an oval runway 0.40 m wide, 0.30 m high, and 6.0 m in total length, consisting of two 2-m straight segments joined by two 0.4-m curved segments and separated by a median wall (2.0 m long × 0.30 m high × 0.006 m thick). The apparatus was elevated to a height of 0.8 m from the floor. All parts of the apparatus were made of black Plexiglas. Activity was recorded with videocameras mounted above the apparatus. Experiments were performed under red light between 0900 and 1300 h.

Procedure. Subjects were injected with a dose of saline, 8-OH-DPAT, or (+) S-20499 appropriate to their group assignment 20 min prior to placement in the runway. Immediately after the animals were placed into the oval runway, their behavior was recorded for a 10-min period by an overhead videocamera; behaviors were analyzed from these videorecordings.

Behavioral analysis. Behavioral analysis of locomotor movement in the oval runway included the following categories:

a. Movement away from the walls.
b. Movement against the walls.
c. Direction change.
d. Sniff-stop. Characterized by the animal stopping and moving its snout in a sniffing pattern.
e. Rear. Characterized by the animal stopping with the forelimbs elevated with or without contact with the wall.
f. Rotate. Characterized by small, spatially restricted movements of the animal's head and body with its hindlimbs planted on the floor.
g. Circle. Characterized by the animal moving in a circular pattern within a 0.1 × 0.1-m area.

Statistical analysis. Data were analyzed by ANOVA followed by Newman–Keuls analyses, as appropriate.

Results

Figures 3 and 4 present the number of line crossings for subjects given 8-OH-DPAT or (+) S-20499, respectively. Both drugs produced reductions in line crossings [$F(3, 28) = 22.99$ and $F(3, 28) = 36.72$, respectively, $p < 0.0001$ for each]. Subsequent Newman–Keuls tests indicated that line crossings were reliably reduced at doses of 1 and 10 mg/kg for DPAT ($p < 0.001$ for both) and at doses of 1 and 10 mg/kg ($p < 0.01$) and 20 mg/kg ($p < 0.001$) for (+) S-20499. An extremely similar pattern was obtained for the frequency of complete traverses around the runway. Both compounds reliably reduced traverses [$F(3, 28) = 10.62$, $p < 0.001$ and $F(3, 28) = 19.73$, $p < 0.001$, for 8-OH-DPAT and (+) S-20499, respectively]. Subsequent Newman–Keuls tests showed a significant reduction for 1 and 10 mg/kg of DPAT and for 10 and 20 mg/kg of (+) S-20499 ($p < 0.001$ for all comparisons).

The duration of forward movement showed a similiar pattern of effects, with DPAT [$F(3, 28) = 36.13$, $p < 0.0001$] and (+) S-20499 [$F(3, 28) = 25.28$, $p < 0.0001$] both producing reduced duration of movement. Subsequent Newman–Keuls tests showed a reliable reduction at 10 mg/kg for both drugs ($p < 0.01$) and a reduction at 20 mg/kg for (+) S-20499 ($p < 0.01$). However, all forward movement durations (i.e., both against and away from the walls) appeared to be equally affected by these drugs, with no reliable drug × direction of movement interactions obtained. Animals showing forward movement frequently changed directions. The effect of 8-OH-DPAT on the duration of movement involving direction change was reliable [$F(3, 28) = 8.42$, $p < 0.01$]. Subsequent Newman–Keuls analysis indicated a reliable increase at 1 mg/kg and a suppression at 10 mg/kg ($p < 0.01$ for each). (+) S-20499 also produced a reliable effect [$F(3, 28) = 3.51$, $p < 0.01$], but suppressed such movement at 20 mg/kg without producing the lower dose increase found with 8-OH-DPAT.

The main effect of 8-OH-DPAT on duration of rearing was not reliable [$F(3, 28) = 2.13$, $p > 0.05$], but this was significant for (+) S-20499 [$F(3, 28) = 6.50$, $p < 0.01$], and subsequent Newman–Keuls tests indicated that durations for the 10- and 20-mg/kg groups were reliably reduced ($p < 0.01$ for both).

The activity that showed the greatest increase in duration following administration of these compounds was stand and sniff [$F(3, 28) = 33.23$, $p < 0.001$ and $F(3, 28) = 44.18$, $p < 0.001$ for 9-OH-DPAT and (+) S-20499, respectively]. Newman–Keuls tests showed that stand/sniff was reliably increased at 10 mg/kg for 8-OH-DPAT ($p < 0.001$) and at 10 and 20 mg/kg for S-20499 ($p < 0.05$ and $p < 0.001$, respectively).

Although the increases in rotation around the hindlimbs after drug administration were of lesser magnitude than the stand/sniff increases, they involved a baseline that was near zero, so the proportional increase was higher. The main effects of both 8-OH-DPAT and (+) S-20499 on this behavior

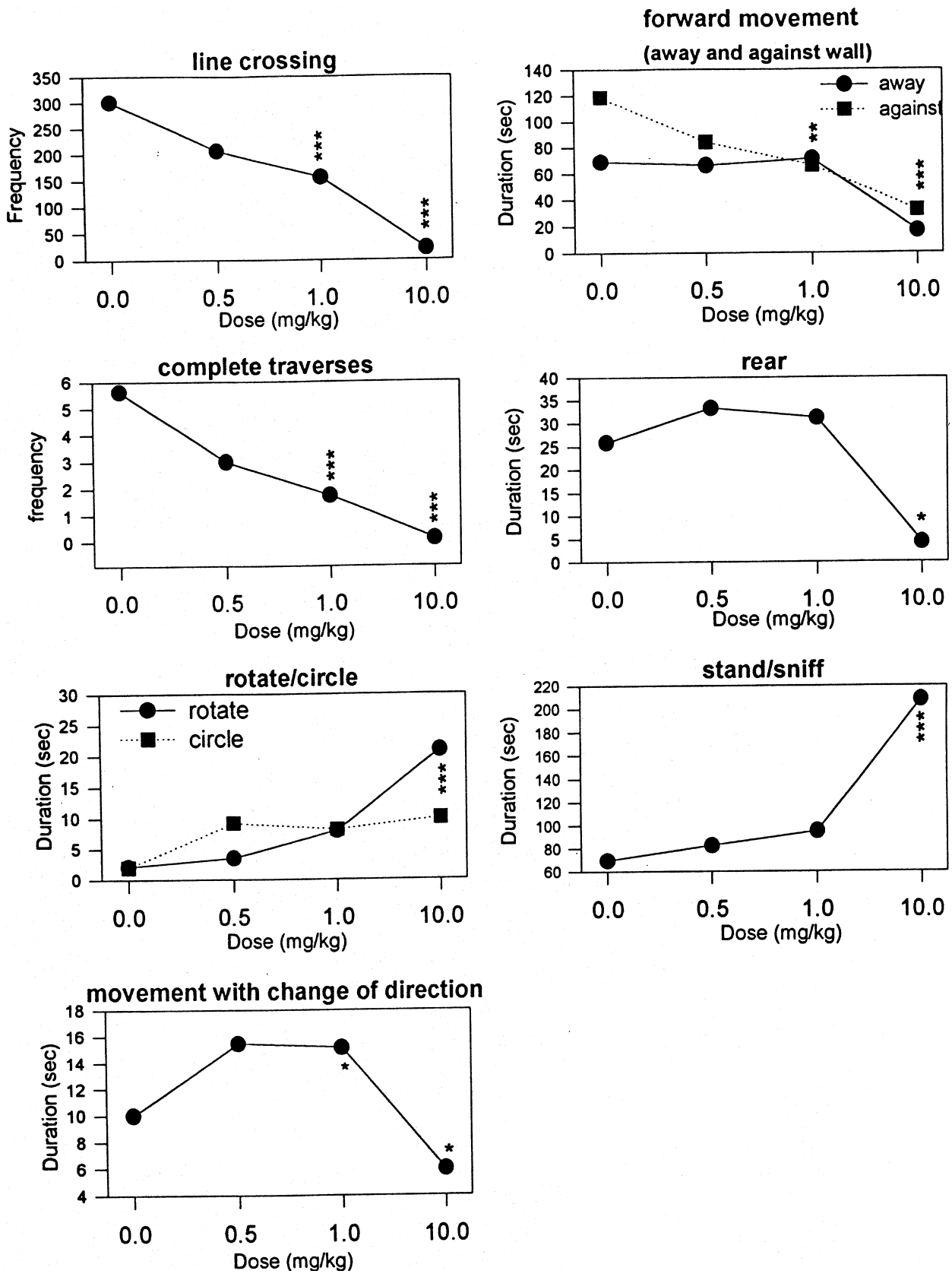

FIG. 3. Effects of various doses of 8-OH-DPAT on behaviors of mice in the runway.

were reliable [$F(3, 28) = 8.42$, $p < 0.001$ and $F(3, 28) = 16.66$, $p < 0.001$, respectively]. Subsequent Newman–Keuls analyses indicated that the 10-mg/kg dose of DPAT ($p < 0.001$) and the 10- ($p < 0.05$) and 20- ($p < 0.001$) mg/kg doses of S-20499 were all reliable. No reliable differences were obtained for the frequency of circling [$F(3, 28) = 0.59$, $p > 0.05$ and $F(3, 28) = 1.03$, $p > 0.05$, for 8-OH-DPAT and (+) S-20499, respectively].

SUMMARY

The behavioral profile displayed by drug-free control mice in experiment 1 was quite similar to one we recently obtained in rats with a similar experimental procedure (4) and can be summarised as follows. In both studies, saline-treated animals showed an initial period of activity illustrated by a high level of locomotion, curve back postures, and rearing, as well as an intense period of grooming. Consequently, lying was infrequent. With the sole exception of grooming, active behaviors gradually declined in subsequent time periods until reaching a level near zero approximately 80 min after injection, at which time lying was frequently observed. Moreover, in the present study as well as in the rat experiment, control values of flat back posture/movement were essentially zero at all points. Finally, a rather low and somewhat variable level of eating was found in both studies during the 2-h observation period.

The findings with 8-OH-DPAT and (+) S-20499 in experiment 1 indicate that selective activation of central 5-5-HT$_{1A}$ receptors in mice rapidly induced a distinct pattern of behavior changes that in some cases lasted up to 2 h postinjection. Rearing data from these studies are in agreement with previous findings in mice indicating that 8-OH-DPAT and (+) S-20499 produced a very rapid reduction of rearing activities (e.g., rear and hang categories) when administered at a higher dosage (11,15,16,22), but that for 8-OH-DPAT a relative increase in rearing was seen over time as control baselines declined (11).

However, although several studies have recently demonstrated that the administration of 8-OH-DPAT and (+) S-20499 in mice tended to decrease horizontal locomotor activity up to 30 min postinjection (11,15,16,22), the data from experiment 1 indicate that 8-OH-DPAT increased this activity at 0.5 and 1 mg/kg, whereas (+) S-20499 did not alter horizontal locomotor responses in the initial stage of the experiment. Because we used a similar dose range and the same administration route as at least some of these studies (16,22), this discrepancy requires alternative explanations. One possibility for the inconsistency is that these authors used criteria to define a "locomotor" response that were more restricted than those of the present studies. In these other studies, locomotion was defined as line crossings (11,15,16) or compartment changes (22) exclusively involving perceptible location changes and forward locomotion, whereas in the present experiment the locomotor category also included finer or smaller movements (at least one head length). Moreover, in a recent mouse study (15), 8-OH-DPAT at doses similar to the present range dramatically decreased the frequency of line crossings while markedly increasing small and spatially restricted movements, with frequent circular movement (unpublished observations).

The view emerging from these comparisons—that 8-OH-DPAT and (+) S-20499 may reduce forward locomotion but increase circular movement—was supported by data from experiment 2. Although experiment 2 involved a more limited time span than did experiment 1, the time selected (20–30 min after injection) represents a period of high-level drug effect, similar to the period in which previous measurements have often been taken (11,15,16,22), and the reduced forward locomotion seen is very similar to what was obtained in these studies. During this period, it is notable that, for (+) S-20499, the dose–response curves for four active behaviors (forward movement, line crossing, complete traverses, and rear) were extremely similar, with reliable reductions for each measure at the two highest doses (10 and 20 mg/kg) only. Movement with a change of direction showed a rather similar trend but was reliable only at the 20-mg/kg dose. This pattern was precisely opposite the reliable increases seen in two behaviors, stand/sniff and rotate, at the two highest doses, suggesting that the drug produced a shift from movement to stand/sniff at this time period and, in particular, that it may have elicited the rotational behavior seen at 10 and 20 mg/kg, which was virtually absent at lower doses.

A similar but somewhat more complex pattern was seen for the dose–response curves for 8-OH-DPAT. Again, forward movement, line crossing, and complete traverses were in perfect agreement, with reliable reductions at the 1.0- and 10.0-mg/kg dose levels. The stand/sniff and rotate increases were also reliable, but only at the highest (10.0 mg/kg) dose. The 1.0-mg/kg dose was associated with reliably higher levels of movement with change of direction, along with continuing high levels of rearing. Thus, the 8-OH-DPAT pattern also suggests a shift from activity to stand/sniff and rotate at the 10.0-mg/kg dose, whereas the forward movement reductions at 1.0 mg/kg may have involved a shift to a less obvious form of change in forepaw movement than the rotation seen at higher doses.

The increased movement with change of direction at the 1.0-mg/kg dose suggests that drug effects on limb, especially forelimb, movement may be a major mechanism for many of the "activity" changes seen in these mice; at lower doses, alterations of forelimb movements might convert forward movement to movement with a change of direction, with more profound effects at higher doses leading to rotation about the stationary hindlimbs. This suggestion that 5-5-HT$_{1A}$ agonists may have particular effects on forelimb movement is also compatible with the data for (+) S-20499, where movement with change of direction showed a less consistently declining dose–response curve than other active behaviors, and with the findings (albeit only early in the test session) of ballistic-type forelimb movements for mice following 8-OH-DPAT (0.5 mg/kg) and (+) S-20499 (10.0 mg/kg) administration.

These ballistic-type movements consisted of very rapid simultaneous movements of the forelimbs to swipe by the sides of the head. Although the 5-5-HT$_{1A}$-activation syndrome has been extensively studied in various species, including mice, no one has yet reported this unusual pattern of motor responses. In our recent study of rats (4), 8-OH-DPAT did not produce ballistic-type movements over a wide dose range (0.2–2 mg/kg) and a similar observation period. Conversely, the mice in the present studies failed to exhibit forepaw treading, a behavior that was reliably increased in rats, occurring particularly when animals locomoted into cage walls or corners. In addition, Yamada et al. (27) did not report any evidence of this behavior in their mouse study. However, these authors did not assess the behaviors of their mice in the 20 min following the drug injection, where the response was produced in the present study. Furthermore, it must be emphasised that although ballistic-type movements were very frequent for some animals, they did not occur in all drug-treated subjects at these doses, indicating a considerable interindividual variability. The reason for this remains to be determined.

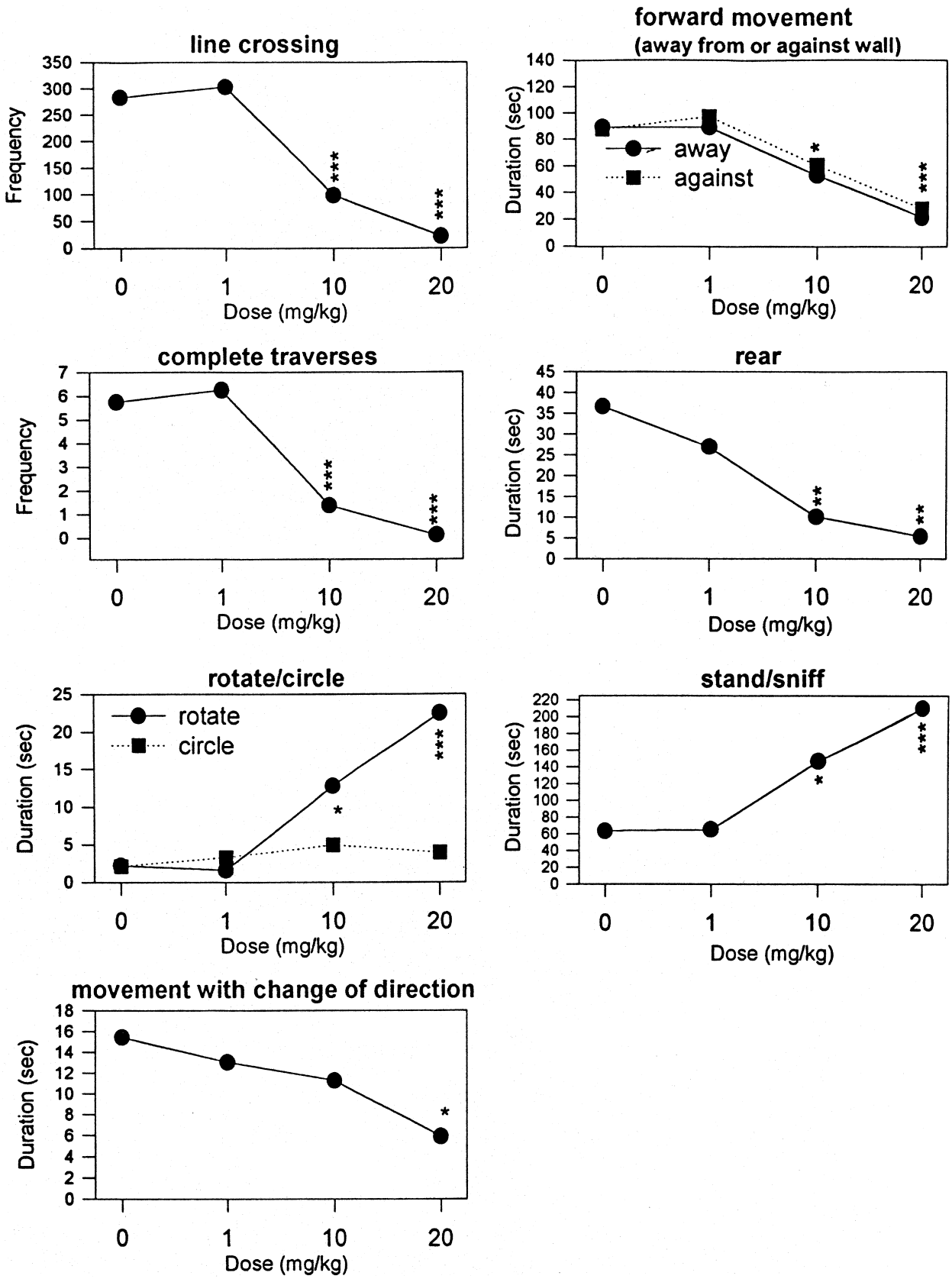

FIG. 4. Effects of various doses of (+) S-20499 on behaviors of mice in the runway.

This view of motor dysfunction for dosed animals is also compatible with reductions in hanging and grooming (two behaviors that require adequate forelimb and forepaw motor control) for (+) S-20499 at both higher doses and for 8-OH-DPAT at the highest dose. It does not, however, appear to agree with findings that 8-OH-DPAT (10 mg/kg) and (+) S-20499 (>20 mg/kg) also significantly enhanced feeding, a result that is in agreement with earlier reports of hyperphagia in rats (2,4,7,8,13) and mice (24). Although our recent study in rats revealed that the enhancement of feeding elicited by 8-OH-DPAT occurred at a low dose (0.2 mg/kg) (4), the present data, in contrast, revealed a similar drug action only at very high doses of 8-OH-DPAT and (+) S-20499 (>10 mg/kg).

The present results also contrast with a recent finding in mice that 8-OH-DPAT significantly enhanced feeding durations at 0.05 and 0.5 mg/kg, whereas the higher dose of 1 mg/kg was ineffective (4,24). In both studies, the authors explained the lack of effect of the drug on feeding at higher doses and/or at certain time periods in terms of competition from the locomotor/syndrome behavioral effects of the compound (4,24). In the present study, enhancement of eating was obtained in association with behaviors typically indicative of the 5-5-HT$_{1A}$ syndrome. Additional examination of tapes for the present study suggested that use of the forelimbs and forepaws is not an essential motor component in eating large chow pellets for mice. Neither controls nor dosed animals picked up the pellets, although controls frequently steadied pellets with their forepaws, as did dosed animals during later portions of the test periods in experiment 1. However, for a period of about 20 min after drug administration, animals receiving high doses of both drugs tended to eat without using the paws or while steadying the pellet with one paw placed on top, an action that appeared to require much less motor coordination than did the (typical control animal's) simultaneous use of both paws, often placed on either side of the pellet.

Identified as a component of the 5-HT syndrome in the initial study of Jacobs (19), the straub tail response has since been described in the rat and the Mongolian gerbil after administration of 8-OH-DPAT (18,25). To our knowledge, the straub tail has not been described in mice after similar drug treatment. However, it is not known whether investigators who used mice as subjects have failed to see the response or have simply failed to measure/report it. The present data with 8-OH-DPAT and (+) S-20499 indicate that both drugs rapidly induced strong straub tail responses at all doses and that this effect lasted with the higher treatment until the end of the 2-h observation period. Compared with 8-OH-DPAT, the effect of (+) S-20499 on tail response is less intense, as the former induced straub tails from the initial period until the end of the experiment at a dose of 10 mg/kg, whereas the effect of (+) S-20499 dissipated at 50 min postinjection at a similar dosage.

These results thus provide many points of agreement with previous (4) ethological analyses of the effects of 8-OH-DPAT in rats. Both rats and (at intermediate dose levels) mice showed increased locomotion, as defined broadly in terms of ratings of movement. However, the type of locomotion potentiated was very different for the two species. Rats showed strong enhancement of forward locomotion, which persisted briefly even when the animal contacted a wall, resulting in forepaw treading for the unsupported forelimbs as the animal rose against the barrier, whereas mice showed less forward locomotion but more movement with a change of direction and more rotation of the body around the hindlimbs. Although both species showed an increase in unusual forelimb/forepaw behaviors, these were again different, consisting of forepaw treading in rats, particularly in the context of forward locomotion into a barrier, whereas mice showed ballistic-type movements in a nonlocomoting context (i.e., while otherwise immobile). Reduced grooming and rearing for both species are consistent with an interpretation of forelimb/forepaw motor involvement, and mice also showed reduced hanging from the cage top, a behavior that is much less common in rats. Finally, although eating was enhanced in both species, specific parameters were again somewhat different, with only the lowest dose of 8-OH-DPAT increasing eating in rats, whereas only the highest dose produced a similar effect in mice. In addition, the time course of these changes varied between species, with an immediate increase in eating following high-dose drug administration in mice, whereas the peak period in rats was about 30 min postinjection, following decreased eating at 11–20 min. The eating data for (+) S-20499 were very similar, suggesting consistency in the effects of 5-HT$_{1A}$ agonists on eating in mice and adding to the view that the parameters of these effects, like the specific effects of these drugs on the type of forepaw movement change, may be systematically different for the two species.

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