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Modulation of Plus-Maze Behaviour in Mice by the Preferential D_3-Receptor Agonist 7-OH-DPAT

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RODGERS, R. J., N. J. T. JOHNSON, A. J. CHAMPION AND S. MILLS. *Modulation of plus-maze behaviour in mice by the preferential D_3-receptor agonist 7-OH-DPAT.* PHARMACOL BIOCHEM BEHAV **54**(1) 79-84, 1996. – Differences in the behavioural profiles of dopamine D_2 receptor antagonists (e.g., haloperidol vs. sulpiride) in animal models of anxiety have prompted speculation concerning the importance of their relative affinities for D_2-like receptor populations. In an initial attempt to investigate the involvement of D_3 receptors in anxiety, the present study examined the effects of the preferential D_3-receptor agonist, (±)7-OH-DPAT (0.01-10.0 mg/kg), on behaviours displayed by male mice in the elevated plus-maze paradigm. An ethological approach incorporating measurement of a range of defensive acts and postures in addition to conventional parameters was used to provide a comprehensive behavioural profile for the compound. Data analysis indicated a significant increase in percentage of open-arm entries at 10 mg/kg and an altered temporal distribution of behaviour at 1-10 mg/kg. Furthermore, risk-assessment measures (stretched attend postures, closed-arm returns) were dose dependently reduced by drug treatment. Although these behavioural changes would be consistent with anxiety reduction, such an interpretation is negated by dose-dependent decreases in all active behaviours (arm entries, rearing, and head-dipping) and by marked increases in entry latencies and nonexploratory behaviour at the highest dose tested. Overall, these effects are remarkably similar to those previously reported for quinpirole, suggesting either that D_2 and D_3 receptors exert similar behavioural control or that the agents employed are sufficiently potent at D_2 receptors to prevent a resolution of D_2 and D_3 responses.

Anxiety Elevated plus-maze Ethology Risk assessment Dopamine D_3 receptors 7-OH-DPAT

SEVERAL lines of evidence suggest that dopaminergic (DA) mechanisms play an important modulatory role in emotional behaviour. For example, in vitro and in vivo methods have shown that acute exposure to a range of stressors markedly increases extracellular DA in mesocorticolimbic areas, such as the nucleus accumbens septi and medial prefrontal cortex [for reviews, see (14,39)], effects that have recently been related to initial coping attempts (5). There is also evidence that stress-induced increases in DA metabolism can be attenuated (albeit inconsistently) by antianxiety drugs such as diazepam and ICS 205930 (15,20,29,34). Furthermore, early animal studies reported anticonflict effects for DA-receptor antagonists (9,30), whereas clinically, it has been recognized for some time that small doses of chlorpromazine and haloperidol can be as effective as benzodiazepines in the management of anxiety disorders (35).

In recent years, major advances have been made in our understanding of DA receptors and their pharmacology. Stemming from the early identification of D_1 and D_2 receptors (23), it is now thought that at least five DA-receptor subtypes exist, currently classified as "D_1-like" (i.e., D_1 and D_5) and "D_2-like" (i.e., D_2, D_3, and D_4) families (17,21,41,42). Although evidence for the involvement of D_1 receptors in anxiety is weak and inconsistent (3,31,32,38,43), the involvement of D_2-like receptors seems more promising. Thus, D_2 antagonists such as haloperidol, sulpiride, and sertindole have been found to have antianxiety effects in conflict and exploration models (10,30,40). Consistent with these findings, a range of D_2-

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receptor agonists (apomorphine, 3-PPP, RU 24969, Ro 41-9067, and quinpirole) have been reported to increase anxiety and/or defensiveness in both conflict and ethological models of anxiety, with many of these effects blocked and/or reversed by D_2 but not D_1 antagonists (2,3,13,16,19,31-33,43).

In a recent study, we observed that D_1-receptor manipulations (SCH 23390 and SKF 38393) failed to produce selective effects on conventional or ethological measures of anxiety in the murine elevated plus-maze test (38). In contrast, the D_2-receptor antagonist sulpiride produced a dose-dependent anxiolytic-like profile that was uncontaminated by motoric side-effects. This pattern differs markedly from that seen with another D_2 antagonist, haloperidol, which at active doses (0.01-0.1 mg/kg) produced only gross behavioural inhibition (8). Although the D_2-receptor agonist quinpirole has been reported to enhance open-arm activity in the plus-maze, such effects are observed only at high doses (5 mg/kg) and are behaviourally nonselective (2,22). Consistent with these observations, we have previously reported that quipirole very potently suppresses active behaviours at doses as low as 0.06 mg/kg with no evidence of a selective effect on indices of anxiety (38). In view of the binding profiles of sulpiride, haloperidol, and quinpirole at D_2-like receptors [e.g., (41)], particularly their relative affinities for D_2 and D_3 receptors, the present study represents an initial attempt to characterize the involvement of D_3 receptors in behaviours displayed in the murine elevated plus-maze.

The D_3 receptor was initially identified and cloned in 1990 (44), with subsequent research on the regional expression of D_3 mRNA (high in limbic and cortical areas), suggesting an involvement in emotional and cognitive functions (4). In this context, 7-hydroxy-2-(di-*n*-propylamino)tetralin (7-OH-DPAT) has been reported to have high and selective (100-fold preference for vs. D_2) affinity for D_3 receptors (25). However, subsequent research has revealed wide variations (four- to 220-fold) in the D_3/D_2 affinity differential of this ligand (12, 18,28,46), not all of which can be explained by stereospecific factors or by differences in assays employed. Although these and related findings have rightly led several authors to urge caution in attributing behavioural effects of 7-OH-DPAT to an action at D_3 receptors [e.g., (24,27)], the compound remains a valuable tool in studies on the behavioural pharmacology of dopamine receptors. In this article, we report the effects of 7-OH-DPAT on behaviours displayed by mice in the elevated plus-maze test.

METHOD

Animals and Drugs

Subjects were 10- to 12-week-old adult male DBA/2 mice (Biomedical Services, University of Leeds, UK), housed in groups of 10 (cage size: 45 × 28 × 13 cm) for at least 4 weeks before testing. They were maintained under a 12 L : 12 D cycle (lights off at 0800 h) in a temperature (21 ± 1°C) and humidity (50 ± 5%) controlled environment. Food and drinking water were freely available with the exception of the brief testing period. All mice were experimentally naive. (±)7-OH-DPAT hydrobromide (Tocris Cookson, Bristol, UK) was dissolved in a physiologic saline vehicle and administered intraperitoneally (IP) (10 ml/kg) 20 min before testing. Doses cited (0.01-10 mg/kg) refer to the salt.

Apparatus

The elevated plus-maze was a modification of that validated for mice by Lister (26), and comprised a plus-shaped configuration (like arms opposite) with two open arms (30 × 5 cm) and two enclosed arms (30 × 5 × 15 cm) extending from a common central platform (5 × 5 cm). The entire apparatus was elevated to a height of 60 cm above the floor level. The maze floor was made from black Plexiglas; the side and end walls of the enclosed arms were constructed from clear Plexiglas. As previously reported [e.g., (38)], open-arm activity was encouraged by the inclusion of a slight raised edge (0.25 cm) around the perimeter of the open arms and by testing under dim red light (4 × 60 W, indirect).

Procedure

All testing was conducted during the mid-dark phase of the light–dark cycle (i.e., 1000–1300 h). To facilitate adaptation, animals were transported the short distance from the holding facility to the laboratory at least 1 h before testing. Subjects were randomly assigned to five treatment conditions (n = 9-10; saline, 0.01, 0.1, 1.0, and 10.0 mg/kg 7-OH-DPAT), and tested in a counterbalanced order. Testing commenced by placing an animal onto the centre platform of the maze facing an open arm. A 5-min test duration was employed; between subjects, the maze was thoroughly cleaned with damp and dry cloths. Test sessions were recorded by a videocamera (positioned above and at about 50° to the maze) that was linked to a monitor and VCR in an adjacent room where, to avoid unnecessary disturbance to the animals, the experimenter remained during testing.

Behavioural Analysis

Tapes were scored by a trained observer who remained blinded to treatment conditions until all data had been collected. Measures comprised conventional plus-maze indices together with a range of specific acts and postures related to the defensive repertoire of the mouse (ethological measures). Conventional measures were: number of open, closed, and total arm entries (arm entry = all four paws into an arm), total rears, and time spent on the different sections of the maze (including the centre platform). The spatial and temporal distribution of behaviour was additionally calculated as percent totals both for frequency (i.e., percent open entries) and duration (i.e., percent time spent on open, centre, and closed sections) data. The ethological measures included entry latency [time taken (s) at start of session to move from the centre platform into an arm], nonexploratory behaviour (NEB) [combined duration (s) of immobility and grooming], and head-dipping (exploratory scanning over the sides of the maze). In addition, several behaviours related to risk assessment (7,8,36-38) were recorded: stretched attend postures (SAP) (forward elongation of the head and shoulders followed by retraction to original position) and closed-arm returns (exiting a closed arm with forepaws only and then returning or doubling back into the same arm). Both head-dipping and SAP were differentiated by location as protected (i.e., occurring from the relative safety of the closed arms or centre platform) or unprotected (i.e., occurring on or from an open arm). Analogous to calculations for open entries and open time, data for head-dipping and SAP are presented both as totals and percent protected values (i.e., protected/total × 100).

Statistical Analysis

Data were analyzed by single-factor (drug) or two-factor (drug × location; repeated measures on location) analyses of

variance (ANOVA). Where indicated (by significant or near-significant F values), further comparisions were performed by Dunnett's t-tests.

RESULTS

Conventional Measures

Data are summarized in Fig. 1. ANOVA revealed significant effects of 7-OH-DPAT treatment on total entries [$F(4, 43) = 20.78$, $p < 0.001$; open entries, $F(4, 43) = 4.42$, $p < 0.001$; closed entries, $F(4, 43) = 27.97$, $p < 0.001$; and rearing, $F(4, 43) = 12.16$, $p < 0.001$]. Follow-up tests confirmed significant reductions in total and closed-arm entries over the entire dose range tested (0.01–10.0 mg/kg; $p < 0.05$–0.005), reductions in rearing at 1.0 and 10.0 mg/kg ($p < 0.005$), and an inhibition of open-arm entries at the highest dose tested ($p < 0.005$).

7-OH-DPAT also affected the percentage of open entries [$F(4, 39) = 9.15$, $p < 0.001$ (note: the lower error df is due to zero arm entries in four animals tested in the high-dose condition], percent time centre [$F(4, 43) = 9.31$, $p < 0.001$], and percent time closed [$F(4, 43) = 27.2$, $p < 0.001$]. However, drug treatment did not alter the percentage of time open [$F(4, 43) = 1.37$, NS]. Further comparisons with saline control indicated a significant increase in the percentage of open entries at 10 mg/kg ($p < 0.005$), with increases in time centre and decreases in time closed at 1.0 and 10.0 mg/kg ($p < 0.005$). The apparent reduction in closed time observed at 0.1 mg/kg (Fig. 1) just failed to reach an acceptable level of statistical significance. These apparent alterations in the spatiotemporal distribution of behaviour were confirmed by a two-factor ANOVA. Consistent with general findings from our laboratory [e.g., (38)], this analysis confirmed that mice preferred the enclosed arms over the centre platform over the open arms [$F(2, 86) = 65.35$, $p < 0.001$]. 7-OH-DPAT altered this profile [$F(8, 86) = 17.53$, $p < 0.001$], with changed spatiotemporal preferences evident in both the 1.0-mg/kg (centre > closed > open) and 10.0-mg/kg (centre > open > closed) conditions.

Ethological Measures

Data are summarized in Fig. 2. ANOVA revealed significant drug effects for entry latency [$F(4, 43) = 9.96$, $p < 0.001$], nonexploratory behaviour [$F(4, 43) = 6.13$, $p < 0.001$], closed-arm returns [$F(4, 43) = 3.88$, $p < 0.01$], head-dips [$F(4, 43) = 10.70$, $p < 0.001$], percent protected head-dips [$F(4, 38) = 4.23$, $p < 0.01$], and SAP [$F(4, 43) =$

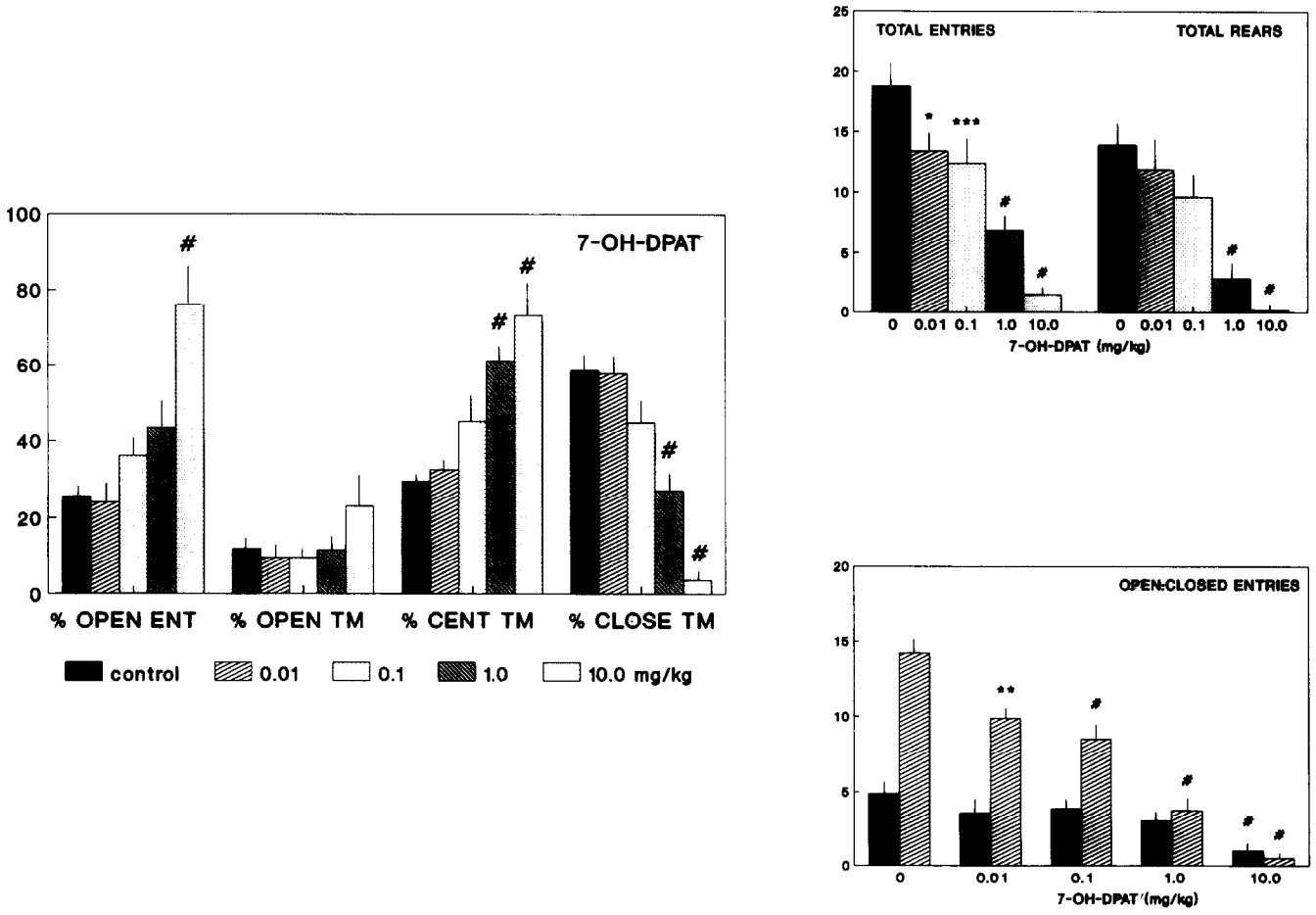

FIG. 1. Effects of (±)7-OH-DPAT HBr (0.01–10.0 mg/kg, IP) on conventional behavioural parameters in the murine elevated plus-maze test. For the open:closed entries chart, black bars = open; hatched bars = closed. *$p < 0.05$, **$p < 0.025$, ***$p < 0.01$, #$p < 0.005$ vs. saline control. See Fig. 2 for complementary data.

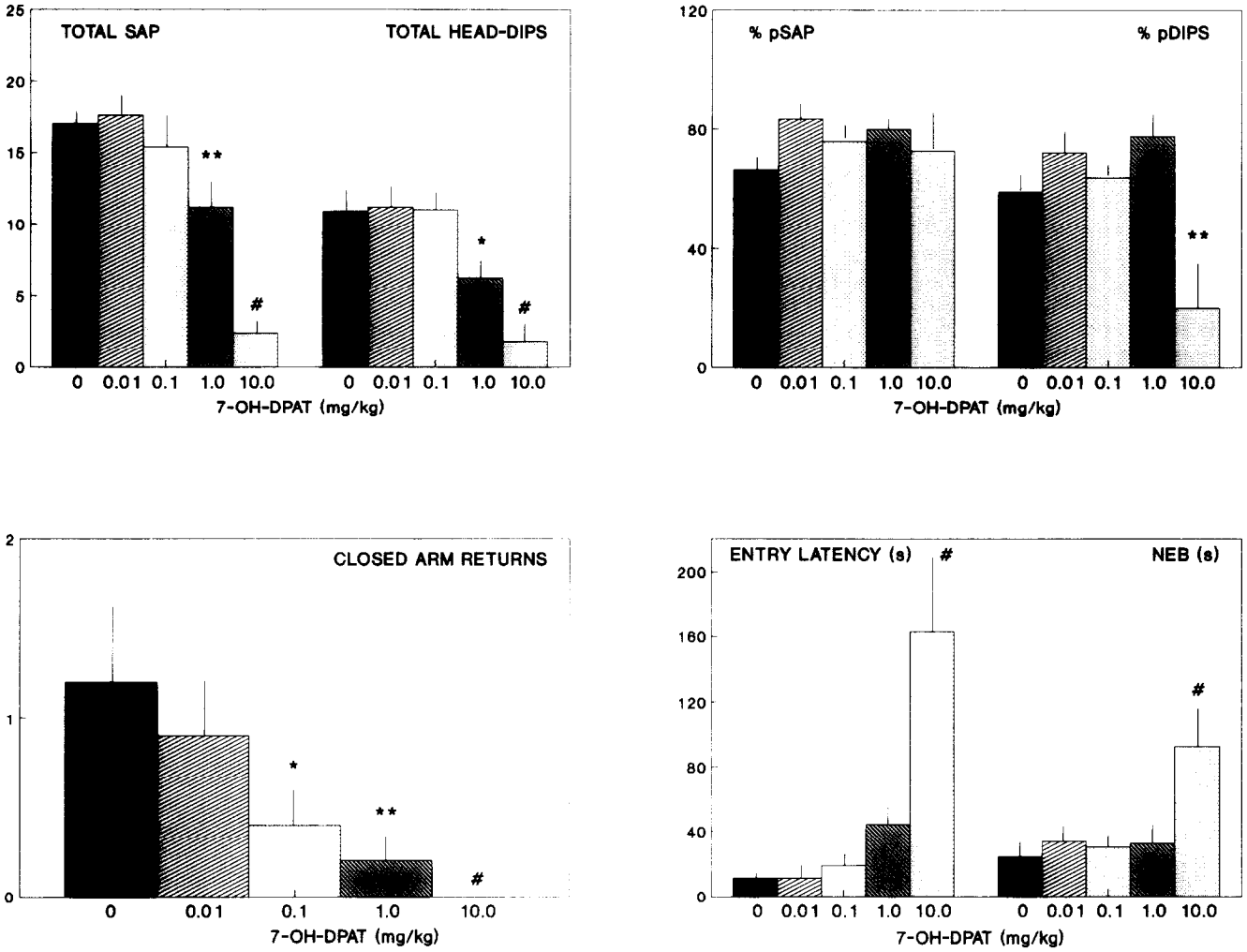

FIG. 2. Effects of (±)7-OH-DPAT HBr (0.01–10.0 mg/kg, IP) on ethological parameters in the murine elevated plus-maze test. SAP = stretched attend postures; NEB = nonexploratory behaviour; %p (SAP; Dips) = protected/total × 100. $*p < 0.05$, $**p < 0.025$, $***p < 0.01$, $\#p < 0.005$ vs. saline control. See Fig. 1 for complementary data.

19.02, $p < 0.001$]. However, the percentage of protected SAP was unaffected by treatment [$F(4, 40) = 0.71$, NS]. Dunnett's tests confirmed significant decreases in closed-arm returns at 0.1–10.0 mg/kg ($p < 0.05$–0.005), head-dipping, and SAP at 1.0–10.0 mg/kg ($p < 0.05$–0.005) and percent protected head-dipping at 10 mg/kg ($p < 0.025$). Entry latencies and nonexploratory behaviour were both increased at the highest dose tested ($p < 0.005$). In view of their high variance, entry latency data were reanalyzed by nonparametric methods; this yielded an essentially identical pattern to the parametric ANOVA, with Kruskal-Wallis $H = 19.00$, $p < 0.001$ and Mann-Whitney comparisons confirming that only the high dose of 7-OH-DPAT differed significantly from control ($U = 6.5$, $p < 0.002$).

DISCUSSION

The present study used an ethological approach to assess the effects of the preferential D_3-receptor agonist 7-OH-DPAT on the behaviour of mice in the elevated plus-maze test. Typically, in this test, antianxiety effects are indicated by increases in percent open-arm entries and time, and decreases in various risk-assessment measures such as stretched attend postures and closed-arm returns (7,8,38). Conversely, proanxiety effects are revealed by reductions in percent open entries and time, and/or increases in risk assessment (36). In each instance, the issue of behavioural selectivity may be addressed by examining treatment effects on other aspects of the behavioural profile, including closed-arm entries, rearing, head-dipping, and nonexploratory behaviour. In an earlier study on the effects of DA-receptor ligands on plus-maze behaviour (38), we reported that the D_1 partial agonist SKF 38393 was devoid of behavioural activity over the dose range studied (2.5–20.0 mg/kg), whereas the D_1 antagonist SCH 23390 produced global behavioural suppression at the highest doses tested (0.1–0.2 mg/kg). In contrast, the D_2/D_3-receptor antagonist sulpiride yielded a behaviourally selective anxiolytic-like profile whereas under identical test conditions, earlier work had shown that another D_2 antagonist, haloperidol, merely disrupted ongoing behaviour (8). Because the D_2-receptor ago-

nist quinpirole produced a pattern of behavioural change also indicative of behavioural disruption, the aim of the present study was to determine whether this overall pharmacological profile might be accounted for by variable activity at the D_3 receptor. 7-OH-DPAT, a preferential D_3-receptor agonist (25), is one of the few pharmacologic tools currently available for studies of this type.

Our results show that at the highest dose tested (10 mg/kg), 7-OH-DPAT increased the percentage of open-arm entries, and at 1 and 10 mg/kg, altered the temporal distribution of behaviour on the maze such that mice spent much less time in the enclosed arms of the maze compared with controls. At first glance, and had we been using only percent entry and percent time data (unfortunately, not uncommon in the literature), this profile might suggest an anxiolytic-like action, an interpretation partially supported by the (nonsignificant) increase in percent open time. Furthermore, and also in line with anxiety reduction, risk-assessment behaviours (such as stretched attend postures and closed-arm returns) were dose dependently reduced across the dose range studied. However, these behavioural effects were accompanied by a profound suppression of general activity and directed exploration (i.e., closed-arm entries, head-dipping, and rearing), coupled with high-dose increases in entry latencies and nonexploratory behaviour. Indeed, the behavioural profile of 7-OH-DPAT is one of profound dose-dependent behavioural suppression culminating, at the highest dose tested, in animals remaining on the centre platform (where they were placed at the start of the session) until at least halfway through the test period (entry latency and percent time data) and spending approximately one third of the test in nonexploratory behaviour (typically immobile). Although this profile might also be considered to be consistent with drug-induced freezing, mice treated with 10 mg/kg 7-OH-DPAT were observed to have relaxed muscle tone when taken from the holding cages and placed on the maze, and did not show an exaggerated startle reaction upon initial capture or when removed from the maze. Furthermore, while showing markedly increased latencies to leave the centre platform at the start of the session, these animals continued to display head movements and some active behaviours such as stretched attend postures and head-dipping.

Previous behavioural work with 7-OH-DPAT indicated a biphasic effect on locomotor activity in rats, with low doses (0.01–0.1 mg/kg) producing hypoactivity and higher doses (0.3–10.0 mg/kg) resulting in either a return to control levels or locomotor stimulation (1,11,46). Although the compound has been reported to be without effect on locomotor activity in mice up to 0.3 mg/kg (45), our data indicate that in this species, 7-OH-DPAT (0.01–10.0 mg/kg) produces a monophasic suppression of locomotor activity. More specifically, it is generally agreed that the most reliable measure of locomotor activity in the plus-maze is the frequency of closed-arm entries [e.g., (37)], and on this measure (Fig. 1), 7-OH-DPAT produced a clear dose-dependent reduction with even the lowest dose (0.01 mg/kg) significantly active vs. saline control. This apparent species difference requires independent confirmation and further study.

Overall, the behavioural effects observed with 7-OH-DPAT in the elevated plus-maze test bear a striking similarity to those seen with quinpirole under identical test conditions (38). This finding may not be too surprising in that whereas some reports suggest that quinpirole is a preferential D_2 agonist [e.g., (41)], others have found it to be equipotent at D_2 and D_3 receptors [e.g., (46)] or even to have greater affinity for D_3 sites (25). Furthermore, close similarities in the behavioural (6) and electrophysiological (27) effects of these two dopamine agonists have previously been noted. In view of such considerations, it may be parsimonious to conclude, as have others (27), that 7-OH-DPAT is sufficiently potent at D_2 receptors that it cannot resolve D_2- from D_3-mediated responses in behavioural systems. As such, the question of D_3-receptor involvement in anxiety, and in the anxiolytic-like effects of sulpiride, also remains unresolved. Future studies will attempt to resolve this issue by using "silent" doses of a D_2 antagonist to isolate D_3 effects of 7-OH-DPAT, and by studying the intrinsic and interactive effects of selective D_3-receptor antagonists such as S-14297 (28).

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