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8-Hydroxy-2-(di-n-propylamino)tetralin impairs spatial learning in a water maze: role of postsynaptic 5-HT_{1A} receptors

M. Carli & [1]R. Samanin

Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milan, Italy

1 The effect of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), a 5-HT_{1A} receptor agonist, on place navigation was studied by use of two spatial tasks in a water maze.

2 In the first experiment, rats treated subcutaneously with 100 and 300 (but not 30) $\mu g\,kg^{-1}$ 8-OH-DPAT were impaired in their ability to locate a hidden platform. The probe test confirmed the impairment of spatial navigation but the effect (time spent in the training quadrant) was quantitatively different, depending on whether 8-OH-DPAT was administered only before each training session, only before the probe test or in both conditions.

3 In the second experiment, rats received 150 μg 5,7-dihydroxytryptamine (5,7-DHT) intracerebroventricularly to destroy 5-hydroxytryptamine (5-HT)-containing neurones and 24 days later were examined for choice accuracy in a two-platform spatial discrimination task.

4 At 100 (but not 30) $\mu g\,kg^{-1}$ 8-OH-DPAT impaired rats' accuracy with no effect on latency and no errors of omission. In 5,7-DHT-treated rats, this dose had a greater effect, including errors of omission. Sham-operated rats injected with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT were markedly impaired in accuracy but they had longer latencies and made more errors than controls. All the effects were increased in 5,7-DHT treated rats.

5 The results suggest that, at doses causing no apparent changes in motor behaviour or motivation, 8-OH-DPAT impairs spatial navigation by stimulating postsynaptic 5-HT_{1A} receptors in the rat brain.

Keywords: 8-OH-DPAT; 5-HT_{1A} receptors; spatial discrimination; rat

Introduction

Several studies suggest that stimulation of 5-HT_{1A} receptors in the brain causes various effects such as hypotension (Fozard *et al.*, 1987), hypothermia (Goodwin & Green, 1985), changes in motor behaviour and hyperphagia (Dourish *et al.*, 1985; Bendotti & Samanin, 1986), antidepressant-like (Cervo & Samanin, 1987) and anxiolytic-like activity (Engel *et al.*, 1984; Carli & Samanin, 1988). There is little information on the role of this 5-hydroxytryptamine (5-HT) receptor type in learning and memory processes. High densities of 5-HT_{1A} binding sites have been found in the hippocampus (Pazos *et al.*, 1988), an area traditionally linked to cognitive functions, particularly spatial memory (O'Keefe & Nadel, 1978; Morris *et al.*, 1982).

Post-training infusion of 5-HT in the hippocampus was reported to impair retention in a Y-maze brightness discrimination task (Wetzel *et al.*, 1980). In agreement with these findings, Altman *et al.* (1990) recently reported that 5-hydroxytryptaminergic deafferentiation of the hippocampus facilitated learning of a positively reinforced spatial discrimination task. These studies suggest that 5-HT in the hippocampus has a negative influence on memory processes but do not clarify which 5-HT receptor type is involved. 5-HT_{1A} receptors apparently exert a predominant inhibitory influence on the electrical activity of hippocampal pyramidal cells (Andrade & Nicoll, 1987; Sprouse & Aghajanian, 1988) but other 5-HT receptor types in the hippocampus have electrophysiological effects opposite to those of 5-HT_{1A} receptors (Colino & Halliwell, 1987; Chaput *et al.*, 1990).

The density of 5-HT_{1A} receptor binding is high in the nucleus raphe dorsalis (DR) (Pazos *et al.*, 1988). Stimulation of these receptors reduces the firing of 5-HT cells (Sprouse & Aghajanian, 1986) and diminishes the release of 5-HT in various terminal regions (Sharp *et al.*, 1989). There is no information on the role of presynaptic 5-HT_{1A} receptors on learning and memory. Electrical stimulation of the DR disrupts memory in a passive avoidance task by a 5-HT-dependent mechanism (Fibiger *et al.*, 1978). Therefore stimulation of pre- and postsynaptic 5-HT_{1A} receptors by appropriate agonists may affect rats' performance in learning and memory tasks.

8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), a specific agonist at 5-HT_{1A} receptors, was recently reported to reduce the efficiency of rats in a radial maze at 300 and 500 $\mu g\,kg^{-1}$ (Winter & Petti, 1987). These relatively high doses, however, cause profound changes in the animals' motor behaviour (Evenden & Angeby-Moller, 1990) making it difficult to assign the effects observed to specific disruption of memory processes. Recently 100 $\mu g\,kg^{-1}$ 8-OH-DPAT, administered before or immediately after the training trial, was found to impair rats' performance in a one-trial passive avoidance task; 30 $\mu g\,kg^{-1}$ 8-OH-DPAT administered before the training trial also impaired their performance (Carli *et al.*, 1992). These studies suggest that relatively low doses of 8-OH-DPAT interfere with mechanisms related to the acquisition and storage of memory of recent events. Spatial learning in the Morris water maze task was impaired by 200 $\mu g\,kg^{-1}$ 8-OH-DPAT while 60 $\mu g\,kg^{-1}$ had no effect (Hunter & Roberts, 1988). The dose and the test may therefore be critical to reveal the memory disruptive effect of 8-OH-DPAT.

In the present study we examined the effects of various doses of 8-OH-DPAT (starting from 30 $\mu g\,kg^{-1}$) in a Morris swim maze in which rats are required to learn the location of a spatially fixed platform. One purpose of this study was also to distinguish effects on acquisition from those on performance by administering 8-OH-DPAT at different times during the task.

To reduce the problems associated with drug effects on rats' performance, the effects of 8-OH-DPAT were also examined in a two-platform spatial discrimination task in the water maze, in which choice accuracy and latency can be measured

[1] Author for correspondence.

separately (Hagan *et al.*, 1987). In order to clarify whether pre- or postsynaptic 5-HT$_{1A}$ receptors were involved in the effect of 8-OH-DPAT, this task was conducted in rats that had received 5,7-dihydroxytryptamine (5,7-DHT) intracerebroventricularly to destroy 5-HT-containing neurones.

Methods

Male albino rats (CD-COBS, Charles River, Italy), weighing 200–250 g, were housed in pairs and kept in a room at constant temperature (21 ± 1°C) and relative humidity (60%), with a regular light/dark schedule (07 h 00 min–19 h 00 min). Food (Altromin pellets for rats) and water were available *ad libitum*. All animals were handled for 2–3 days before starting the experiments.

Injection of 5,7-dihydroxtryptamine (5,7-DHT)

The rats, anaesthetized with Equithesin, were immobilized in a Kopf stereotaxic instrument. 5,7-Dihydroxytryptamine creatinine sulphate (5,7-DHT) 150 μg (calculated as a free base) was dissolved in 20 μl of ascorbic acid solution (1 mg ml^{-1}) and administered into the right lateral ventricle. Control animals received only the ascorbic acid solution (vehicle). To protect noradrenaline-containing neurones from the action of 5,7-DHT (Baumgarten *et al.*, 1973), 30 min before the injection of 5,7-DHT the rats were given desipramine 25 mg kg^{-1} intraperitoneally (i.p.), an inhibitor of noradrenaline uptake into nerve endings (Breese & Cooper, 1975). After surgery, animals were allowed to recover for 24 days during which time they were accustomed to being handled.

Forty-eight hours after the end of the experiments, rats treated with 5,7-DHT and their controls were killed by decapitation and their brains were rapidly removed for assay of 5-HT according to Achilli *et al.* (1985).

Morris water-maze

A circular 'swimming pool' measuring 1.5 m in diameter, 0.5 m high was used. The pool was filled to a depth of 0.29 m with water (26 ± 1°C) which was rendered opaque by the addition of a food dye (coffee color, Bayo, Italy). The water was changed daily. The pool was located centrally in a large room and was surrounded by various visual cues: a blackened window with a big white cross, a white wall with a big black cross, a long table, a door and a picture-covered wall with a rack for cages. The site of the objects could be occluded, when required, by black curtains around the maze. When open, the curtains were collected together at one corner of the room, so forming a prominent visual cue in themselves. The room was illuminated by a light bulb (100 W) located in the centre of the ceiling or by two overhead lamps (each 60 W) positioned and directed in such a way as to give diffuse illumination of the room.

The rats were placed in the pool and left to swim around until they found the single escape platform (11 × 11 cm) the top of which was made of transparent perspex, 'hidden' 1.5–2.0 cm below the water surface.

The pool surface was divided into four quadrants (training quadrant; adjacent left; adjacent right and opposite quadrant). There were four starting positions from which the rats were put into the water, arbitrarily designated by the cardinal points North, East, South and West (N, E, S, and W) around the circumference of the pool. Three concentric equal-area zones from the pool centre and separated by radii 0.58 PR (PR = pool radius) and 0.82 PR were defined on the pool surface.

The rat's behaviour was monitored by an overhead video camera (CCD, Sitel, Italy) linked to the VP112 scanning unit (HVS Image, U.K.) which in turn was connected to a Amstrad PC 1512 computer.

For all rats, training consisted of four trials each day for five days. The platform was fixed in one of the four quadrants throughout training. A training trial began with the experimenter lowering the animal into the pool, its head facing and close to the side wall, at position N, E, S or W. The timer was started (by a remote control connected to the computer) and the time the animal took to escape from the water onto the platform (escape latency) was recorded. If the animal did not find the platform in 120 s, it was picked up by the experimenter and put onto the platform. The rat remained on the platform for 15 s before being picked up and put in a holding cage for a 4–8 min inter-trial interval.

Twenty-four hours after the last training day, a probe test was done to assess the spatial bias of all trained animals. The hidden platform was removed from the pool and the rat was placed in it for a single 60 s period. The rats were placed in the pool from the starting point opposite their training quadrant. A record was made of the paths the animals followed searching for the platform. The software (HVS Image, U.K.) used by our monitoring set-up gave a precise measure of the path length swum, latency to reach the platform, speed and the % time swum by the rat in each quadrant and in each equal-area zone.

Escape latency (s), swimming distance (m), speed (m s^{-1}) were analysed by analysis of variance with factors: drug (between subjects) and days (within subjects), and *post hoc* comparisons between groups were analysed by Tukey's test. Probe test performance (swimming speed, % time swum in the training quadrant and % time swum in the outer equal-area zone) were analysed by analysis of variance and *post hoc* comparison with the controls (saline) by Dunnett's *t* test.

Two-platform spatial discrimination task

The apparatus was the same as in the place navigation task. Two visible platforms were used. The fixed one protruded 1.5–2.0 cm above the water surface. Its top was square (11 × 11 cm) and made of Perspex. The second platform was identical to the first and also protruded 1.5–2.0 cm above the water. It was made of the same material but was filled with expanded polystyrene. It was 'anchored' with thread to a solid movable base placed on the bottom of the pool. Thus one platform was rigid and provided support, the other sank when the rats attempted to climb on it. These platforms were both flat grey.

The rats were trained to swim to one grey escape platform while avoiding the second grey floating platform. For all rats, the rigid escape platform (correct) was always in the same location at the centre of one of the four quadrants. The floating platform (incorrect) was positioned, over successive trials, in a quasirandom sequence of eight locations around the pool, subject to the constraint that the spatial relationship between the platforms and starting positions did not consistently reward either right or left turning tendencies. The rigid platform was equally often the closest to the starting point as the one farthest away. They were sometimes close together, while in other trials they were far apart.

All rats were trained for 12 consecutive days, doing 10 trials each day. A trial began with the rat being placed in the pool while held at, and facing, the side wall. Eight possible starting locations were used in quasirandom sequence across trials. A trial ended when the rat escaped onto the rigid platform, where he was allowed to sit for 15 s before being returned to a holding cage before the next trial. The rats were trained in squads of four. Trials were run spaced with an inter-trial interval of approximately 2–4 min. Each rat's daily testing lasted approximately 30 min. The criterion was reached when performance had to average at least 80% correct over two days. A correct trial was one in which the rats climbed onto the rigid platform without touching the floating platform with

their forepaws or snout. The occasional incident of brushing past the floating platform in passing was not considered an error. If the rat did not choose to escape on either platform (correct or incorrect) in 60 s it was taken out of the pool and an omission error was scored. We measured (1) the first choice in each trial (correct/incorrect), (2) the latency to escape (s), and (3) the number of omissions.

Treatment schedules

In the Morris swim maze, in one experiment 8-OH-DPAT hydrobromide (R.B.I. Wayland, Massachusetts, U.S.A.) was dissolved in saline and injected subcutaneously (s.c.) 30 min before each acquisition training session and before the probe test. In order to distinguish effects on acquisition from those on performance, in another two experiments 8-OH-DPAT was administered before acquisition training sessions only or before the probe test only.

In the experiment in which choice procedure was used, sham-operated and 5,7-DHT-treated rats were injected s.c., starting 24 days after intracerebroventricular injection of 5,7-DHT, with saline or 8-OH-DPAT 30 min before each acquisition training session.

Statistics

Data, percentages of correct choices and latency to escape (s) from vehicle and 5,7-DHT groups were analysed separately by analysis of variance (two-way ANOVA with factors) days (within subject) and drug (between subject) and *post hoc* comparisons between groups were done with Tukey's test. Lesioned and unlesioned rats were also compared at each dose separately using a two-factor (days × lesion) ANOVA. The number of omissions on the first day of training was analysed by two-way analysis of variance and the *post hoc* comparisons by Tukey's test.

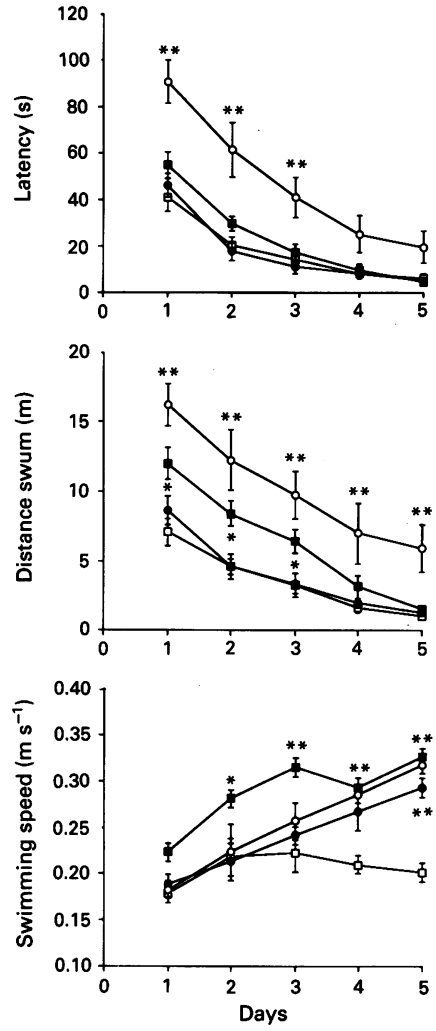

Figure 1 Acquisition of familiarity with the Morris swim maze by rats treated with 0 (□), 30 (●), 100 (■) or 300 (○) $\mu g\,kg^{-1}$ 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). The animals received 8-OH-DPAT subcutaneously 30 min before each training session. Each value is the mean of 8 rats per group; vertical bars show s.e.means.
* $P < 0.05$; ** $P < 0.01$ vs. controls (Tukey's test).

Results

Morris water maze acquisition

All animals improved their performance over the trials as shown by the progressive reduction in latency and distance swum to reach the platform (latency: $F_{4,112} = 90.2$, $P < 0.001$; distance: $F_{4,112} = 57.5$, $P < 0.001$). Administration of 8-OH-DPAT before each session dose-dependently affected rats' performance (latency: $F_{3,28} = 12.8$, $P < 0.001$; distance: $F_{3,28} = 13.8$, $P < 0.001$; speed: $F_{3,28} = 7.7$, $P < 0.001$). Animals treated with 8-OH-DPAT 300 $\mu g\,kg^{-1}$ swam significantly more than controls ($P < 0.01$; Tukey's test) for the whole period of training while in animals treated with 100 $\mu g\,mg^{-1}$ the effect was seen only on days 1, 2 and 3 ($P < 0.05$; Tukey's test). The impairment (days × group interaction, $F_{12,112} = 3.7$ $P < 0.01$) was less evident on measuring the latency to reach the platform; 300 $\mu g\,kg^{-1}$ 8-OH-DPAT caused a significant increase only on days 1, 2 and 3 ($P < 0.01$, Tukey's test) and 100 $\mu g\,kg^{-1}$ produced no effect. This can be explained by the fact that rats injected with 100 $\mu g\,kg^{-1}$ 8-OH-DPAT had a higher swimming speed from the first days and by the end of training all 8-OH-DPAT-treated animals swam faster than controls (significant days × group interaction $F_{12,112} = 2.9$, $P < 0.01$).

Morris water maze probe test

Figure 2a shows the results with animals which had received 8-OH-DPAT before each training session and before the probe test. The acquisition data for this group are shown in Figure 1. Only those treated with 300 $\mu g\,kg^{-1}$ were unable to locate the training quadrant ($F_{3,27} = 5.8$, $P < 0.01$). They spent significantly less time in the training quadrant than the other experimental groups ($P < 0.01$; Dunnett's t test). These animals tended to swim close to the side walls ($F_{3,27} = 4.7$, $P < 0.01$) as shown by the significantly higher time they spent in the outer zone of the pool ($P < 0.05$; Dunnett's t test). The swimming speed ($F_{3,27} = 9.5$, $P < 0.01$) of the animals treated with 100 and 300 $\mu g\,kg^{-1}$ 8-OH-DPAT was significantly higher than controls ($P < 0.01$; Dunnett's t test).

When 8-OH-DPAT was administered only before the probe test (Figure 2b), all the doses significantly ($F_{3,28} = 6.9$, $P < 0.01$) reduced the time spent in the training quadrant ($P < 0.05$ for 30 $\mu g\,kg^{-1}$ and $P < 0.01$ for 100 and 300 $\mu g\,kg^{-1}$; Dunnett's t test). Only rats treated with 300 $\mu g\,kg^{-1}$ spent significantly more time than controls in the outer zone ($F_{3,28} = 6.2$, $P < 0.01$; $P < 0.01$ Dunnett's t test), whereas swimming speed ($F_{3,28} = 16.6$, $P < 0.001$) was higher in animals injected with 100 and 300 $\mu g\,kg^{-1}$ 8-OH-DPAT ($P < 0.05$ and $P < 0.01$ respectively, Dunnett's t test).

Figure 2c shows the results of the experiment in which the animals received 8-OH-DPAT only before each training session. The effects of 8-OH-DPAT on acquisition were not

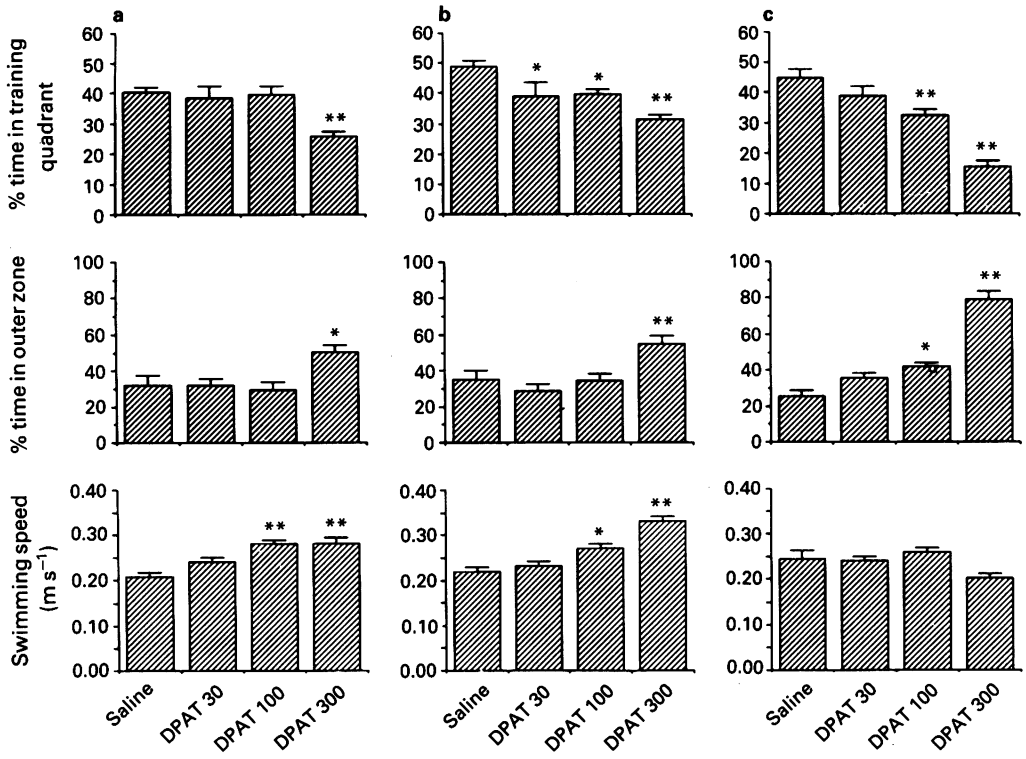

Figure 2 Behaviour in the probe test of rats given 0, 30, 100 and 300 $\mu g\,kg^{-1}$ 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) subcutaneously 30 min before each training session and before the probe test (*a*), only before the probe test (b) or only before each training session (c). Each value is the mean of 8 rats per group; s.e.mean shown by vertical bars.
* $P < 0.05$; ** $P < 0.01$ vs. controls (Tukey's test).

different from those shown in Figure 1. Animals' performance during the probe test was impaired after doses of 100 and 300 $\mu g\,kg^{-1}$ given only before each training session, (% time in training quadrant: $F_{3,27} = 28.4$, $P < 0.001$; % time in outer zone: $F_{3,27} = 55.0$, $P < 0.001$; $P < 0.01$, Dunnett's test). The time the animals treated with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT spent in the training quadrant was markedly reduced ($P < 0.01$, Dunnett's *t* test) and they spent about 80% of their time in the outer zone of the pool ($P < 0.01$, Dunnett's *t* test). These effects were less marked but still significant with 100 $\mu g\,kg^{-1}$ ($P < 0.05$; Dunnett's *t* test) whereas the lowest dose caused no effect. No effect on swimming speed was seen with any dose in this condition ($F_{3,27} = 1.9$ NS).

Two-platform spatial discrimination task

The accuracy of controls improved over the days and approached asymptote on day 4 (Figure 3). 5,7-DHT lesion by itself did not significantly modify swim maze acquisition (days × lesion: $F_{11,165} = 1.4$, $P > 0.05$). 8-OH-DPAT significantly reduced the percentage of correct choices (accuracy) in vehicle- and 5,7-DHT-treated rats (days × drug: $F_{33,352} = 2.0$ and $F_{33,330} = 1.9$; $P < 0.01$ for vehicle and 5,7-DHT, respectively). Rats treated with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT before each session made significantly more errors ($P < 0.01$; Tukey's test) than controls from day 3 to day 9 but by days 10–12 they did not differ from controls. In 5,7-DHT-treated rats, 300 $\mu g\,kg^{-1}$ 8-OH-DPAT caused more errors throughout the whole of training ($P < 0.01$; Tukey's test). A similar but less marked pattern of effects was seen with 100 $\mu g\,kg^{-1}$ 8-OH-DPAT ($P < 0.05$ and $P < 0.01$; Tukey's test). Animals treated with 100 $\mu g\,kg^{-1}$ showed more errors only on days 3 ($P < 0.01$) and 4 ($P < 0.05$ Tukey' test) in vehicle and days 1–7 in 5,7-DHT-treated animals (days 1, 6 and 7, $P < 0.05$; days 2–5, $P < 0.01$ Tukey's test).

A comparison between lesioned and unlesioned animals showed a significant days × lesion interaction at 300 ($F_{11,165} = 1.4$, $P < 0.05$) and 100 $\mu g\,kg^{-1}$ ($F_{11,176} = 2.0$, $P < 0.05$). No effect at any time or condition was seen with 30 $\mu g\,kg^{-1}$ 8-OH-DPAT.

Animals treated with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT showed significantly higher latencies for most of the training time in vehicle (days × drug: $F_{33,352} = 3.1$, $P < 0.01$) and 5,7-DHT-treated animals (days × drug: $F_{33,330} = 2.5$, $P < 0.01$), whereas 100 $\mu g\,kg^{-1}$ significantly increased latencies only in 5,7-DHT-treated animals on days 1 and 2 ($P < 0.05$; Tukey's test) (Figure 3).

The animals treated with 300 $\mu g\,kg^{-1}$ tended to swim close to the side wall and made significantly more errors of omission on day 1 than controls (saline) in vehicle and 5,7-DHT-treated animals (treatment × drug: $F_{3,61} = 2.5$, $P < 0.05$); 100 $\mu g\,kg^{-1}$ caused more errors only on day 1 for 5,7-DHT treated animals ($P < 0.01$; Tukey's test).

The results on omissions by the various experimental groups on day 1 are shown in Table 1. At all doses, the incidence of errors of omission essentially disappeared from day 2

Table 1 Spatial discrimination task: errors of omission caused by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in vehicle and 5,7-dihydroxytryptamine (5,7-DHT)-treated rats

Drug	$\mu g\,kg^{-1}$	*Vehicle*	*5,7-DHT*
Saline	0	0.4 ± 0.1	0.6 ± 0.2
8-OH-DPAT	30	0.9 ± 0.2	0.9 ± 0.2
8-OH-DPAT	100	1.6 ± 0.5	3.7 ± 0.7**
8-OH-DPAT	300	3.7 ± 1.2**	6.3 ± 0.7**††

Values are mean ± s.e.mean of 7–9 rats per group.
The animals were injected intracerebroventricularly with 5,7-DHT (150 μg in 20 μl) or vehicle (ascorbic acid 0.1%) 24 days before the experiments.
** $P < 0.01$ vs. vehicle + saline or 5,7-DHT + saline (Tukey's test).
†† $P < 0.01$ vs. vehicle + 8-OH-DPAT 300 $\mu g\,kg^{-1}$ (Tukey's test).

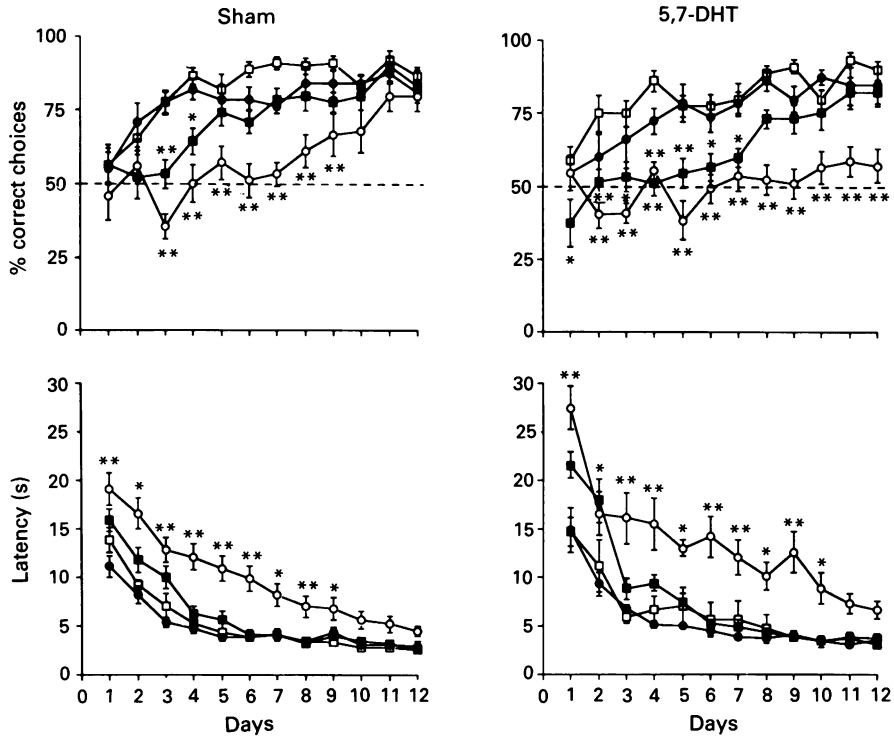

Figure 3 Spatial discrimination task: the effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on the percentage of correct choices and latency of rats injected intercerebroventricularly with vehicle (Sham) or 5,7-dihydroxytryptamine (5,7-DHT). 5,7-DHT (150 μg in 20 μl) or vehicle (ascorbic acid 0.1%) were administered 24 days before the beginning of the experiments. The animals received 0 (□), 30 (●), 100 (■) or 300 (○) $\mu g\,kg^{-1}$ 8-OH-DPAT subcutaneously 30 min before each acquisition session. Each value is the mean of 7–9 rats per group; vertical bars show s.e.means.
* $P < 0.05$; ** $P < 0.01$ vs. controls (Tukey's test).

in vehicle-treated animals while 5,7-DHT-treated animals given 300 $\mu g\,kg^{-1}$ 8-OH-DPAT still had about 20% omissions until day 4.

Brain levels of 5-HT were markedly lower (about 10% of controls) in 5,7-DHT-lesioned rats. Levels of 5-HT ($ng\,g^{-1}$; mean ± s.e.mean) were: vehicle + saline 471 ± 18; 5,7-DHT + saline 56 ± 6. No dose of 8-OH-DPAT significantly changed 5-HT levels in vehicle- or 5,7-DHT-treated rats (data not shown).

Discussion

8-OH-DPAT at doses of 100 and 300 $\mu g\,kg^{-1}$ administered 30 min before training sessions dose-dependently impaired place navigation in the Morris swim maze while 30 $\mu g\,kg^{-1}$ had no such effect. In rats given 300 $\mu g\,kg^{-1}$ 8-OH-DPAT, distances taken to reach the hidden platform were longer than those of controls for the whole period of training but latencies were significantly increased only in the initial sessions. Rats treated with 100 $\mu g\,kg^{-1}$ showed a significant increase in distance swum on days 1, 2 and 3.

The lack of effect of 100 $\mu g\,kg^{-1}$ 8-OH-DPAT on latencies may be explained by the higher swimming speed of these animals in the early sessions. By day 5, all the animals treated with 8-OH-DPAT showed a higher swimming speed with no significant effect on latency. At this time only rats treated with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT swam longer distances. The results suggest that the distance swum is a more accurate measure of performance impairment during acquisition of a swim maze task when there are changes in animals' swimming speeds. All the animals treated with 8-OH-DPAT, like controls, clearly improved their performance over the trials. It is difficult, however, to establish whether the improvement was due to true spatial localization or alternative strategies which the animals used to reach the platform.

The probe test confirmed that 300 $\mu g\,kg^{-1}$ 8-OH-DPAT impaired spatial navigation since the animals spent significantly less time in the training quadrant. However, the drug was even more active when administered only before the probe test. Even 30 $\mu g\,kg^{-1}$ produced a significant effect in this condition. This raises the question whether acute effects of 8-OH-DPAT on motor performance were involved in the effect in the probe test. This is likely in view of the fact that visual inspection of their behaviour revealed that particularly rats treated with 300 $\mu g\,kg^{-1}$ tended to swim very close to the side walls. These animals also spent more time than the other experimental groups in the outer zone of the pool. An additional confounding variable was that animals receiving 100 and 300 $\mu g\,kg^{-1}$ before acquisition and before the probe test or only before the probe test swam faster than controls.

To clarify how the effects of 8-OH-DPAT during acquisition influenced animals' behaviour in the probe test, one group of rats received 8-OH-DPAT only before each training session and was tested in the probe test 24 h later. Animals treated with 100 and 300 $\mu g\,kg^{-1}$ remained in the training quadrant less than controls, spent more time in the outer zone of the pool and showed no change in their swimming speed during the probe test. Thus the effect on swimming speed seems related to the acute effects of 8-OH-DPAT, whereas the tendency to swim around in large circles, already observed in the early training sessions, is probably part of the strategy the animals adopt to improve their performance during acquisition.

The effects in the probe test in animals which had received 100 and 300 $\mu g\,kg^{-1}$ only during the acquisition stage, suggest that spatial localization was impaired in animals treated with 8-OH-DPAT.

Obviously, the effects observed in the Morris swim maze cannot be interpreted exclusively in terms of changes in learning and memory processes since sensory-motor abnormalities or changes in motivation could be involved in the effect of

8-OH-DPAT on latencies, distances swum or rats' behaviour during the probe test.

In a second experiment therefore we used a recently described procedure in which choice accuracy and latency could be measured separately (Hagan *et al.*, 1987). Moreover, motivational effects could be revealed by the number of omissions. In order to clarify whether pre- or postsynaptic 5-HT$_{1A}$ receptors were involved in the effect of 8-OH-DPAT on choice accuracy, this study was conducted in animals which had received 5,7-DHT intracerebroventricularly to destroy 5-HT-containing neurones.

Rats treated with 100 and 300 $\mu g\,kg^{-1}$ 8-OH-DPAT before each session made significantly more errors than saline-treated animals. That memory processes were disrupted is suggested by the fact that at 100 $\mu g\,kg^{-1}$ 8-OH-DPAT impaired the rats' accuracy with no effect on omissions or latencies in vehicle-treated animals. Moreover, 300 $\mu g\,kg^{-1}$ 8-OH-DPAT caused significantly more omissions in vehicle treated rats only on day 1 while accuracy was impaired until day 10. Animals treated with 300 $\mu g\,kg^{-1}$ 8-OH-DPAT also showed increased latencies. This effect could not be attributed to a reduction in motor activity since swimming speed was actually increased. As mentioned above, the animals treated with 300 $\mu g\,kg^{-1}$ tended to swim close to the side walls and this may have influenced the paths they used to reach the platform.

The effect of 8-OH-DPAT on choice accuracy was significantly potentiated in rats treated with 5,7-DHT. The greater effect of 100 $\mu g\,kg^{-1}$ 8-OH-DPAT in 5,7-DHT-treated rats could not be attributed only to sensory-motor disturbances or changes in motivation since the number of omissions was increased only on day 1, latencies were longer on days 1 and 2 but choice accuracy was impaired significantly until day 7. 5,7-DHT-treated rats, given 300 $\mu g\,kg^{-1}$ 8-OH-DPAT instead, showed not only longer latencies but also more omissions for most of the training period, suggesting that abnormalities in motor behaviour or motivation could have contributed to the results.

The results in the two-platform spatial discrimination task confirm that at 100 $\mu g\,kg^{-1}$, 8-OH-DPAT specifically interferes with the mechanisms involved in spatial learning. Although the lack of specific 5-HT$_{1A}$ receptor antagonists prevented us trying to prove it more directly, the fact that relatively low doses of 8-OH-DPAT were active and its relative specificity as a 5-HT$_{1A}$ receptor agonist (Hoyer, 1988) suggest that the compound impairs spatial navigation by an action on 5-HT$_{1A}$ receptors.

That 8-OH-DPAT may interfere with mechanisms related to the acquisition and storage of memory of recent events is also suggested by a recent study showing that 8-OH-DPAT affected rats' performance in a passive avoidance task by a mechanism which could be separated from effects on pain perception, general activity or emotional behaviour (Carli *et al.*, 1992).

High densities of 5-HT$_{1A}$ binding sites are found in the hippocampus, raphe nuclei and some layers of the cerebral cortex in the rat brain (Pazos *et al.*, 1988). The fact that 5,7-DHT treatment did not reduce but actually potentiated the effect of 8-OH-DPAT suggests that postsynaptic 5-HT$_{1A}$ receptors are involved in the ability of 8-OH-DPAT to impair spatial navigation. In view of the important role of hippocampus in the processes involved in spatial learning (O'Keefe & Nadel, 1978; Morris *et al.*, 1982), it is likely that 5-HT$_{1A}$ receptors in this region are involved in the effect of 8-OH-DPAT. Various studies suggest that supersensitivity of postsynaptic 5-HT receptors, including the 5-HT$_{1A}$ type, develops after 5,7-DHT (Nelson *et al.*, 1978; Zemlan *et al.*, 1983; Goodwin *et al.*, 1987). Although the density of hippocampal 5-HT$_{1A}$ binding sites is not increased in rats treated with 5,7-DHT (and may actually be reduced in the CA2/CA3 region) (Vergé *et al.*, 1986; Hensler *et al.*, 1991), a supersensitivity of some hippocampal 5-HT$_{1A}$ receptors following 5,7-DHT lesions of 5-hydroxytryptaminergic terminals cannot be excluded. Experiments on inhibition of forskolin-stimulated adenylate cyclase by 5-HT$_{1A}$ receptor agonists (De Vivo & Maayani, 1986) may help clarify this.

In conclusion, the present study indicates that 8-OH-DPAT, a specific 5-HT$_{1A}$ receptor agonist, impairs spatial learning by a mechanism which may involve postsynaptic 5-HT$_{1A}$ receptors, probably in the hippocampus. Measures aimed at changing the activity of postsynaptic 5-HT$_{1A}$ receptors in the hippocampus more directly will be necessary to clarify their role in spatial memory in rodents and, in general, in learning and memory processes in various tasks and species.

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