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Effects of the Serotonin Receptor Agonists 8-OH-DPAT and TFMPP on Learning as Assessed Using a Novel Water Maze[1]

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KANT, G. J., G. R. MEININGER, K. R. MAUGHAN, W. L. WRIGHT, T. N. ROBINSON, III AND T. M. NEELY. *Effects of the serotonin receptor agonists 8-OH-DPAT and TFMPP on learning as assessed using a novel water maze.* PHARMACOL BIOCHEM BEHAV **53**(2) 385–390, 1996. – We evaluated the effects of two drugs active at serotonin receptors, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, a 5-HT_{1A} agonist) and N-3-trifluoromethylphenyl)piperazine hydrochloride (TFMPP, a 5-HT_{2C} agonist) on learning using a novel water maze previously characterized in our laboratory. The water maze utilized is a traditional type of maze with alleyways and doors through which the rats learn to swim to reach a platform, unlike the open pool Morris water maze task. Performance is assessed by swim time required to reach the platform and errors committed. Following initial training on maze configuration A, rats were assigned to saline, TFMPP and 8-OH-DPAT treatment groups and tested for performance once per dose, 30 min after administration of drug (0.25. 0.5, and 1.0 mg/kg IP). Swim times were significantly increased as compared to saline for all doses for both drugs. The error rate was increased for 8-OH-DPAT at all doses, while TFMPP had no effect on error rate at any dose. Next, rats were challenged to learn new mazes following daily administration of 0.25 or 0.5 mg/kg of each drug 30 min prior to each daily swim trial. Rats given 0.25 mg/kg of 8-OH-DPAT learned new maze C more slowly than saline-treated rats, while TFMPP had no effect at this dose. At the higher dose of 0.5 mg/kg, tested on new maze B, TFMPP administration significantly increased swim times but not errors, while this dose of 8-OH-DPAT markedly increased both swim time and errors. Finally, rats from all groups were tested on maze E after drug administration was discontinued, and there were no performance differences among groups. These data suggest that serotonin$_{1A}$ receptors may inhibit learning.

Serotonin agonists Water maze Learning Memory Rat 8-OH-DPAT TFMPP
5-HT_{1A} receptor 5-HT_{2C} receptor

INTRODUCTION

THE recent identification of numerous serotonin receptor subtypes (11,12,23,28,29), and the increasing availability of specific agonists and antagonists for some of these receptors have made it possible to investigate the role of specific serotonin receptors in various behaviors (10,18,25). Behavioral models of anxiety or depression have been of particular interest because of the current interest in serotonergic drugs to treat these conditions in humans (3,5,16,19,20,36). Agonists at serotonin$_{1A}$ receptors such as 8-OH-DPAT have been shown to greatly increase punished responding, particularly in pigeons (4), suggesting that this drug is anxiolytic. 8-OH-DPAT has also been shown to inhibit potentiated startle, increase feeding, increase locomotor activity, and decrease body temperature (9,25,30,31,33). TFMPP appears to be less selective than 8-OH-DPAT. It is currently described primarily as a 5-HT_{2C} agonist [the 5-HT_{1C} receptor has recently been reclassified as a

[1] The views of the author(s) do not purport to reflect the position of the Department of the Army or the Department of Defense (para 4-3, AR 360-5). Research was conducted in compliance with the Animal Welfare Act, and other Federal statutes and regulations relating to animals and experiments relating to animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NIH publication 86-23.

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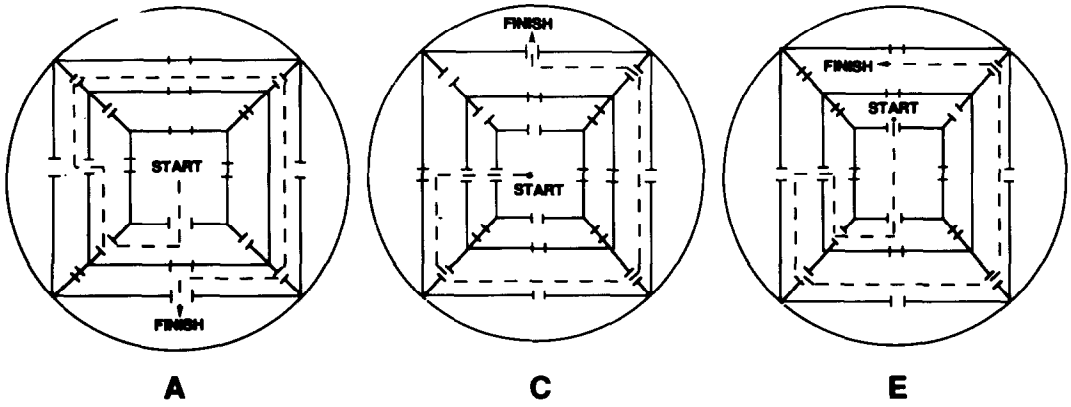

FIG. 1. Maze configurations. Straight unbroken lines represent the white plastic walls with removeable doorways. The dotted line represents the optimum swim path from start to finish. All rats were first trained on maze A. Maze B is the reverse of maze A (same path, start, and finish reversed). An out-of-the-water platform (double stacked test tube racks) was placed at the finish. Rats were placed at the start and given a maximum of 5 min to swim to the platform. Whole body entries through doors not on the correct path were counted as errors.

5-HT_{2C}, see (12)], but also as a partial agonist or antagonist at other 5-HT receptors (10,12,23). TFMPP has been reported to decrease food intake, decrease locomotion, decrease REM sleep, and decrease body temperature (2,15,17,25,27). Rats trained to discriminate 8-OH-DPAT do not generalize to TFMPP, supporting different receptor profiles for these two drugs (18,22,34).

Relatively few studies have examined the role of specific serotonin agonists in paradigms of learning and memory; however, a recent report found that 8-OH-DPAT impaired performance in a open Morris maze task (8). The present study was performed to extend these findings to a different type of water maze task and to compare the effects of 8-OH-DPAT with a serotonergic drug with different receptor affinity. A water maze task is especially appropiate for studying serotonergic drugs, which have been reported to affect appetite (2,6,9,15,18), because food is not used to motivate task performance.

TABLE 1

EFFECTS OF TFMPP AND 8-OH-DPAT ON WELL-LEARNED MAZE A

Group Dose	Saline	TFMPP	8-OH-DPAT
Time (s)			
0.25 mg/kg	33.3 ± 15.0	40.5 ± 7.3*	61.4 ± 11.5*
0.50 mg/kg	13.6 ± 1.3	26.1 ± 4.1*	73.5 ± 28.8*
1.0 mg/kg	36.2 ± 20.5	94.4 ± 31.8*	192 ± 32*
Errors			
0.25 mg/kg	2.1 ± 1.4	1.3 ± 0.2	3.3 ± 0.7*
0.50 mg/kg	0.7 ± 0.2	0.9 ± 0.3	3.6 ± 2.0*
1.0 mg/kg	0.22 ± 0.15	2.4 ± 1.4	6.5 ± 1.4*

Values represent the mean of 9-11 rats ± SEM.

*Significantly different than saline-treated rats tested on the same day. Data analysis by nonparametric Kruskal-Wallis ANOVA, $p < 0.05$. Each drug dose was tested on a separate day with one trial per rat. Drug or saline (1 ml/kg) was injected 30 min prior to testing.

METHOD

Subjects

Male rats (Sprague-Dawley from Charles River), weighing between 445 and 559 g at the end of initial maze training (beginning of drug treatment), were used as subjects. Rats were housed in the animal housing area in individual cages with food and water freely available. Lights were on from 0700 to 1900 h.

Drugs

8-Hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT) and N-3-trifluoromethylphenyl)piperazine HCl (TFMPP) were purchased from Research Biochemicals Inc (Natick, MA). Drugs were prepared fresh daily and dissolved in saline. Drugs were injected IP 30 min prior to maze testing. Equal weights of each drug (calculated as the salt) were administered rather than equimolar amounts, but the molecular weights of the two drugs are similar. Slightly more TFMPP (1 mg = 3.8 μM) was administered on a molar basis than 8-OH-DPAT (1 mg = 3.0 μM).

Water Maze Testing

The maze consisted of concentric squares set inside a 6 ft diameter child's swimming pool. The maze walls (50 cm high) were white opaque plastic and the alleys between the walls were 16 cm wide. Removeable doorways set in the center of each of the walls allowed for different maze configurations. The maze configurations used in these experiments are shown in Fig. 1 (maze B is the same as maze A, but with the start and finish reversed). The maze was located in an open laboratory with overhead lighting and numerous available spatial room cues including laboratory equipment. Tap water (15-20°) filled the maze to a depth of 25 cm. Maze A was the first maze configured. Rats were placed into the center of the maze and given a maximum of 5 min to find the out-of-the water exit platform located at the finish. Both the time required and the number of errors (whole body entries through doorways not leading to the exit platform) were recorded for each trial. Rats not reaching the platform in 5 min were gently pushed from

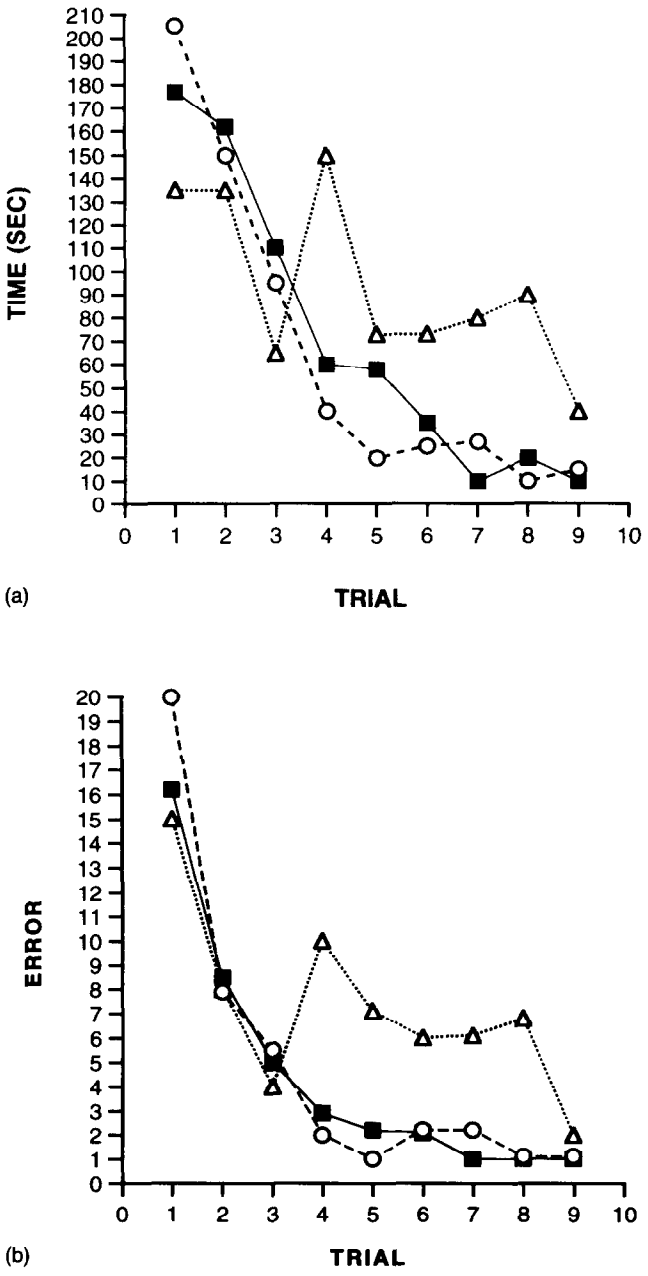

FIG. 2. Effects of 0.25 mg/kg of drug on learning a new maze (C). Open circles are saline-treated rats; open triangles are 8-OH-DPAT-treated, and black squares are TFMPP-treated (9–11 rats/group). (A) Swim times and (B) errors.

behind with a paddle and guided through the correct path until they reached the platform. Following initial training in maze A (20 trials), the rats were divided into three groups such that maze performance was approximately equal among groups. The rats were then retested five times over 9 days (only one test trial on any given day with 4 days of no test trials) in the order: one trial of 1.0 mg/kg drug or saline, one trial with no drug injection, 3 days of no testing, one trial of 0.25 mg/kg drug or saline, one trial of no drug injection, no test, one trial of 0.5 mg/kg drug or saline.

In the third phase of the experiment, the rats were challenged to learn a new maze (C) with a single daily trial 30 min following administration of 0.25 mg/kg 8-OH-DPAT, TFMPP, or saline. Nine trials were conducted at this dose.

After five no-test days, rats were challenged to learn another maze (B) over 14 daily trials following administration of 0.5 mg/kg of drug. Finally, three no test days preceded final testing on new maze E for seven trials without any drug administration.

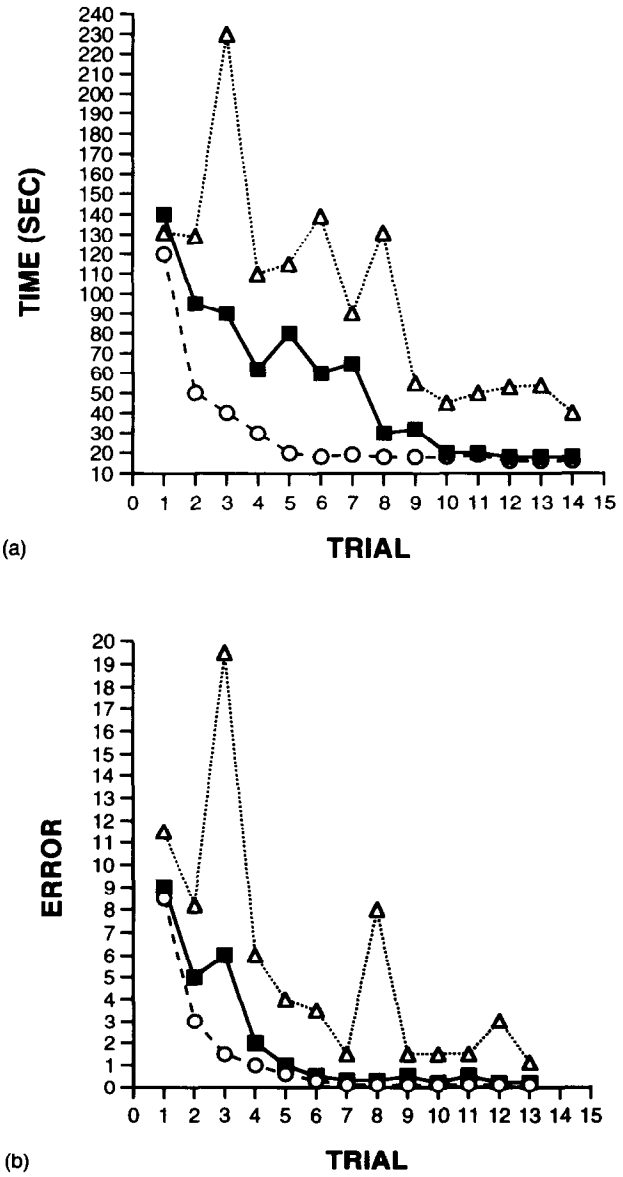

FIG. 3. Effects of 0.5 mg/kg of drug on learning a new maze (B). Open circles are saline-treated; open triangles are 8-OH-DPAT-treated, and black squares are TFMPP-treated (9–11 rats/group). (A) Swim times and (B) errors.

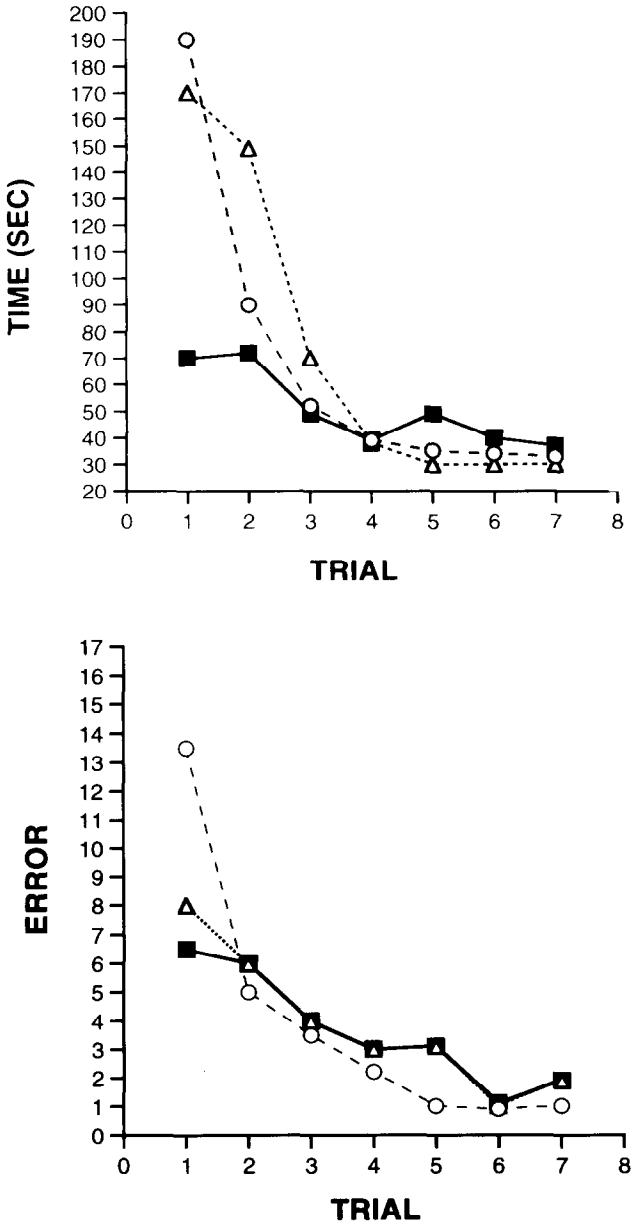

FIG. 4. Learning a new maze with no drugs administered. Open circles are rats from the previously saline-treated; open triangles are rats from the previously 8-OH-DPAT-treated, and black squares are rats from the previously TFMPP-treated (9–11 rats/group). (A) Swim times and (B) errors.

Data Analysis

Swim time required to reach the platform and errors committed for each day's trial were recorded, entered into a database, and analyzed by the BMDP statistical software. For the initial single trial testing of each drug dose on performance of previously learned maze A, each dose trial was analyzed by one-way nonparametric ANOVA (Kruskal–Wallis), due to the presence of outliers. For analyzing the effects of drug on learning new mazes, data were analyzed by two-way parametric ANOVA for the main effects of trial and drug. Group differences were considered to be significant at $p < 0.05$.

RESULTS

Effects of 8-OH-DPAT and TFMPP on Performance of Well-Learned Maze

Following initial training on maze A and division of the rats into three groups, swim times to reach the platform in all groups averaged approximately 20 s with less than one error. The rats were then retested on maze A for memory performance on separate days following administration of 0.25, 0.5, or 1.0 mg/kg of 8-OH-DPAT, TFMPP, or saline. Because the performance of rats in the saline-treated group appeared to vary appreciably over days, each test day was analyzed separately using a between-drug design. Because of the presence of a number of outliers, a nonparametric ANOVA was performed. As shown in Table 1, the ANOVA showed significant effects on swim times for all doses of both drugs as compared to saline, and significant effects on error rates at all doses of 8-OH-DPAT. Errors were not affected by any dose of TFMPP. For 8-OH-DPAT vs. saline, 0.25 mg/kg time ($p = 0.030$) and errors ($p = 0.041$); 0.5 mg/kg time ($p = 0.0024$) and errors ($p = 0.024$); 1.0 mg/kg time ($p = 0.001$) and errors ($p = 0.0002$). For TFMPP vs. saline, 0.25 mg/kg time ($p = 0.030$) and errors ($p = 0.377$); 0.5 mg/kg time ($p = 0.006$) and errors ($p = 1.0$); 1.0 mg/kg time ($p = 0.0087$) and errors ($p = 0.166$).

Effects of 8-OH-DPAT or TFMPP on Learning a New Maze

In the second study, the effects of 0.25 mg/kg 8-OH-DPAT or TFMPP on learning a new maze (C) were assessed. Each day, 30 min prior to the single swim trial, 8-OH-DPAT or TFMPP or saline was injected. As shown in Fig. 2, the saline- and TFMPP-treated rats learned the maze more quickly than the 8-OH-DPAT-treated rats. The 8-OH-DPAT-treated rats were significantly impaired compared to the saline group as assessed by either swim time ($F = 5.3$, $p < 0.02$) or errors ($F = 6.1$, $p < 0.02$), while the TFMPP group was not significantly different than saline.

Five days after completion of the 0.25 mg/kg study, rats were treated with 0.5 mg/kg of TFMPP, 8-OH-DPAT, or saline and tested on a new maze configuration (B). Rats were given a single trial, each day for 14 days. As shown in Fig. 3, both drugs significantly impaired learning maze B compared to the saline group with respect to swim time, but only 8-OH-DPAT significantly increased the error rate: 8-OH-DPAT swim times ($F = 75$, $p < 0.0001$); 8-OH-DPAT errors ($F = 38$, $p < 0.0001$); TFMPP swim times ($F = 18$, $p < 0.0001$); TFMPP errors ($F = 2.3$, $p > 0.05$).

Long-Term Effects of 8-OH-DPAT or TFMPP on Learning

Finally, when drug treatment was discontinued, and rats were tested on new maze E after 3 days of no testing, there were no differences in learning due to previous drug regimen (Fig. 4); time ($F = 1.52$, $p > 0.05$); errors ($F = 0.4$, $p > 0.05$).

DISCUSSION

The effects of cholinergic, glutaminergic, and benzodiazepine compounds on learning and memory have been studied and reported much more frequently than that of serotonergic drugs [e.g., (7,13,21,24,35)]. Yet, as the present experiments demonstrate, some serotonergic compounds have marked ef-

fects on these processes. The acquisition impairment found in this study with 8-OH-DPAT is greater than we previously reported for atropine and similar to what we have previously reported for the *N*-methyl-D-aspartate antagonist MK-801 and the benzodiazepine diazepam at similar doses with this water maze task (13,14). Furthermore, it appears that learning and memory are affected by similar doses of this drug as have been reported to cause other behavioral effects in rodents (9,25, 32,33). The results of the present study are complementary to those demonstrating improved learning following depletion of central or hippocampal serotonin (1).

Performance of the water maze task can be affected by motivational, sensory, motor, or cognitive impairments. For 8-OH-DPAT, we believe that the impairment is primarily cognitive, because swim time increased together with error rate. The rats required more time to reach the platform because more errors were committed, resulting in more distance to be swum, suggesting that cognition more than motivation was the cause of the poor performance. Also, performance of the 8-OH-DPAT treated rats was generally similar to that of saline controls for the initial trials in a new maze. As trials continued, the saline rats improved their performance more quickly than the 8-OH-DPAT-treated rats, suggesting that cognitive learning more than motivation or sensorimotor performance was impaired. Similar results were reported by Carli and Saminin (8) using the open Morris water maze task. These investigators were able to separate swim speed from spatial navigation and found that swim speed was actually increased by 8-OH-DPAT, but rats required more time to locate the platform. Using food-rewarded tasks, Ohno et al. (26) similarly concluded that 8-OH-DPAT, at doses similar to those used in the present report, significantly increased the number of working memory errors but not reference memory errors in a three-panel runway task. Winter and Petti (37) found that 8-OH-DPAT decreased efficiency of responding at lower doses than it affected response rate on a radial maze.

Although the anxiolytic properties of 8-OH-DPAT could affect motivation by reducing the aversiveness of the water and thereby impair performance, we do not believe this was a significant factor in the present experiments. All rats in the present study swam many trials on the water maze task before any drug administration, the water temperature was moderate, and we have found in previous experiments that rats habituate to the task such that stress hormones markedly attenuate with repeated trials (unpublished data).

For TFMPP, the identical arguments cannot be made because swim times seemed to be more affected than error rates for this drug. TFMPP has been reported to reduce locomotor activity, and the increased swim times seen in the present experiment may be a related effect (25). On the radial maze task used by Winter and Petti, 1.0 mg/kg of TFMPP produced a significant decrease in response rate and a nonsignificant decrease in response efficiency. With the reported nonselectivity of TFMPP for receptor subtypes, it is also difficult to ascribe a definite site as the mediator of TFMPP's effects.

Thus, there seems to be both a quantitative and qualitative difference in the effects of the two drugs tested that is most likely due to the different subtype receptor specificity of these drugs. It appears that stimulation of the 5-HT_{1A} receptor impairs learning. The marked effects of 8-OH-DPAT seen in the present report suggests that 5-HT_{1A}-based anxiolytic drugs may have some unanticipated adverse side effects on learning or memory similar to those seen for the benzodiazepines.

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