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Effects of the Serotonin Agonists 8-OH-DPAT, Buspirone, and DOI on Water Maze Performance

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KANT, G. J., R. M. WYLIE, K. CHU AND S. GHOSH. *Effects of the serotonin agonists 8-OH-DPAT, buspirone, and DOI on water maze performance.* PHARMACOL BIOCHEM BEHAV **59**(3) 729–735, 1998.—We have previously reported that the serotonin 5-HT_{1A} agonist 8-OH-DPAT and the 5-HT_{2C} agonist TFMPP impair performance on a water maze. In the present report we extended those studies by examining a second 5-HT_{1A} agonist, buspirone, to see whether its effects paralleled those of 8-OH-DPAT, and by testing the effects of the 5-HT_2 agonist DOI. Unlike the open pool Morris water maze, the maze used in these experiments has alleys and doorways. The maze can be easily reconfigured to present rats with both previously learned or new maze challenges. Performance is assessed by time to reach the maze exit platform and the number of wrong doorways entered (errors). At doses that did not affect performance in a previously learned maze, the 5-HT_{1A} agonists 8-OH-DPAT (0.1 mg/kg) and buspirone (1 mg/kg) slowed acquisition of a new maze configuration as measured by both swim time to the exit platform and errors committed. A higher dose of buspirone (10 mg/kg) completely blocked acquisition of a novel maze. In contrast, DOI slowed performance as assessed by swim time on both a well-learned maze as well as acquisition of a new maze, but did not affect error rate on either task, suggesting that this 5-HT_2 agonist impaired performance by depressing motor activity. These experiments demonstrate that serotonin agonists, especially the 5-HT_{1A} subtype, can impair learning. © 1998 Elsevier Science Inc.

8-OH-DPAT Buspirone DOI Serotonin receptors Water maze Learning 5-HT_{1A}, 5-HT_2

THE recent therapeutic focus on serotonin selective reuptake inhibitors (SSRI) for the treatment of depression coupled with the identification of numerous serotonin receptor subtypes have provided both the interest and the means for elucidating more of the behavioral effects attributable to specific serotonin receptor sites (4,5,13,15,21,24,27,29,30).

Our laboratory has characterized a useful water maze for evaluating the effects of drugs on both learning and memory (17–20). This maze has alleyways and doors similar to traditional land-based mazes, rather than the more commonly used Morris water maze in which rats traverse an open pool to find a submerged platform (8,26,28). In our maze task, the performance of the rats is measured both by the speed with which they reach the exit platform and the number of errors committed along the swim path. Different maze paths can be easily reconfigured, and rats can be repeatedly tested for acquisition of new mazes as well as performance on a well-learned configuration. Drugs known to affect learning or memory such as MK-801, diazepam, triazolam (Halcyon®), or amphetamine, impair performance on this maze (17–20). Placing the maze in water rather than using a land-based food rewarded maze has the advantage of removing the influence of a drug on appetite, which may then affect performance. Because serotonergic drugs have been shown to affect food intake (2,3,7,9,23), a water maze is especially appropriate for testing the effects of these drugs on learning, memory, and performance.

In a recently published study we reported that 8-OH-DPAT, a 5-HT_{1A} agonist, impaired performance on the water maze task, increasing both the time required to reach the exit platform and the number of errors committed (19). In contrast TFMPP, a 5-HT_{2C} agonist, only increased the time required to reach the platform, a finding consistent with reports that TFMPP decreases locomotor activity (19,22). In the present series of experiments, we extended our previous work by examining additional serotonergic agonists in the same

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paradigm utilized previously to facilitate comparisons among drugs and receptor subtypes.

METHOD

Subjects

Two separate studies were performed using two different groups of subjects. Both groups of male Sprague–Dawley rats were purchased from Charles River and housed in the Institute vivarium in individual cages with rat chow and water freely available. Lights were on from 0600 to 1800 h each day. Testing was conducted during the light hours (between 0800 and 1500 h). At the end of initial maze training, prior to the first drug administration experiment in each study, rats in the first group (8-OH-DPAT, buspirone) had an average weight of 513 g; rats in the second group (DOI) weighed an average of 501 g.

Maze

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. Some of the maze configurations used in these experiments are shown in Fig. 1. The maze was located in the animal facility next to the rats' cages. Objects were hung on the walls as spatial cues. The room was well lit from overhead fluorescent fixtures. Tap water (27 ± 3°) filled the maze to a depth of 25 cm.

Drugs

8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin) hydrobromide, buspirone (8-[4-[4-(2-pyrimidynl)-1-piperazinyl]-butyl]-8-azaspiro[4,5]decane-7,9-dione hydrochloride, and DOI (±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride were purchased from RBI (Natick, MA). These drugs were dissolved in saline immediately prior to use. Drugs were administered based on drug weight (calculated as the salt) and injected IP in a volume of 1 ml/kg rat weight 30 min prior to maze testing. Drug doses were selected based on reported scientific studies using these drugs, not on equimolar quantities. For comparison purposes, 1 mg of 8-OH-DPAT HBr = 3.0 M, 1 mg buspirone HCl = 2.3 M, and 1 mg of DOI HCl = 2.8 μM.

Experimental Procedures

During these studies rats were tested both on well-learned and novel maze configurations. These comparative data were then used to help elucidate whether impairments were primarily cognitive in nature (characterized by normal performance on a well-learned maze and poor performance in acquiring a new maze) or primarily due to nonspecific effects of the drug (anxiety, motivation, general motor activity) that might affect swim maze performance. Nonspecific effects were considered to similarly impair well-learned and novel maze performances.

In each of the two studies described below, several different phases of training and testing were performed. In both studies, maze configuration A (Fig. 1) was the first maze configured and used for initial maze training. Rats were placed at the "start" 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 behind with a paddle and guided through the correct path until they reached the platform.

Study 1: Buspirone and 8-OH-DPAT

Rats in the first study were trained on maze A (23–25 trials) without administration of drugs and then divided into three groups, each counterbalanced for performance. The three groups were randomly assigned to receive 8-OH-DPAT, buspirone, or saline. Rats were first given a retest on maze A following 0.25 mg/kg 8-OH-DPAT, 2.5 mg/kg buspirone, or saline. On the next daily trial, no drugs were administered. On the third retest day, rats were administered 0.5 mg/kg 8-OH-DPAT, 5 mg/kg buspirone or saline. On the fourth retest, no drugs were administered. On the fifth retest

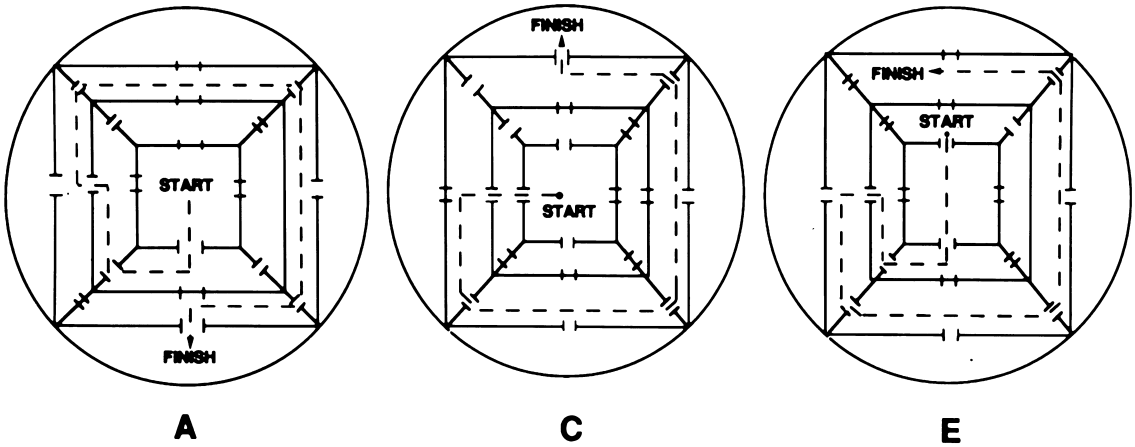

FIG. 1. Maze configurations. Straight unbroken lines represent the white plastic walls with removeable doorways. The dotted line represents the optimum swim path from start to finish. All rats were first trained on maze A. An out-of-the-water platform (double stacked test tube racks) was placed at the "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.

TABLE 1
EFFECTS OF 8-OH-DPAT AND BUSPIRONE ON MAZE A

Group	Test Day 1	Test Day 3	Test Day 5
Time seconds			
Saline	43.2 ± 11.1	24.4 ± 2.7	29.2 ± 3.5
8-OH-DPAT	45.3 ± 12.6	68.7 ± 29.7	25.0 ± 3.7
	(0.25 mg/kg)	(0.5 mg/kg)	(0.1 mg/kg)
Buspirone	29.0 ± 7.3	21.7 ± 4.2	32.0 ± 6.9
	(2.5 mg/kg)	(5.0 mg/kg)	(10.0 mg/kg)
Errors			
Saline	1.4 ± 0.9	0.11 ± 0.24	0.0 ± 0.0
8-OH-DPAT	1.9 ± 0.9	2.1 ± 1.0	0.4 ± 0.2
	(0.25 mg/kg)	(0.5 mg/kg)	(0.1 mg/kg)
Buspirone	1.9 ± 1.2	0.4 ± 0.2	1.2 ± 0.7
	(2.5 mg/kg)	(5.0 mg/kg)	(10.0 mg/kg)

Values represent the mean of nine rats ± SEM. Each drug dose was tested on a separate day with one trial per rat. Test days 2 and 4 were no-drug injection days (data not shown).

day, rats were administered 0.1 mg/kg 8-OH-DPAT, 10 mg/kg buspirone or saline.

Rats were then challenged to learn a new maze configuration, maze C (Fig. 1) in 14 daily training trials preceded by administration of saline, 0.25 mg/kg 8-OH-DPAT, or 10 mg/kg buspirone. Buspirone-treated rats were unable to learn maze C; therefore, all rats were then briefly retrained on maze A with no drug administration and then retested on maze A with 0.25 and 0.1 mg/kg of 8-OH-DPAT or 10 mg or 1.0 mg/kg buspirone or saline over 2 days.

A second drug acquisition training period followed, on maze configuration E (Fig. 1) with 10 daily training trials preceded by 0.1 mg/kg 8-OH-DPAT or 1.0 mg/kg buspirone. Finally, all rats used in the study were challenged to learn still another new maze configuration, H (not shown) without any drug administration.

Study 2: DOI

Following 23 trials of training in maze A, the rats were divided into three groups of 10 rats each counterbalanced for performance. Rats were then retested daily (one trial per day) for 4 days. Group one (control) rats received saline, saline, no injection and saline 30 min prior to testing on each of the 4 days. Group two (low-dose DOI) rats were injected with 0.1, 0.25, no injection, and 0.1 mg/kg over the 4 test days. Group 3 (high-dose DOI) rats received 1.0 mg/kg, 0.5 mg/kg, no injection, and 0.25 mg/kg DOI IP 30 min prior to testing for the 4 test days.

In the third phase of the experiment, the rats were challenged to learn maze E with a single daily trial 30 min following administration of saline, 0.1 mg/kg DOI or 0.25 mg/kg DOI. Sixteen trials were conducted during this acquisition task.

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. Data were analyzed by two-way parametric ANOVA for the main effects of trial and drug. Group differences were considered to be significant at $p < 0.05$.

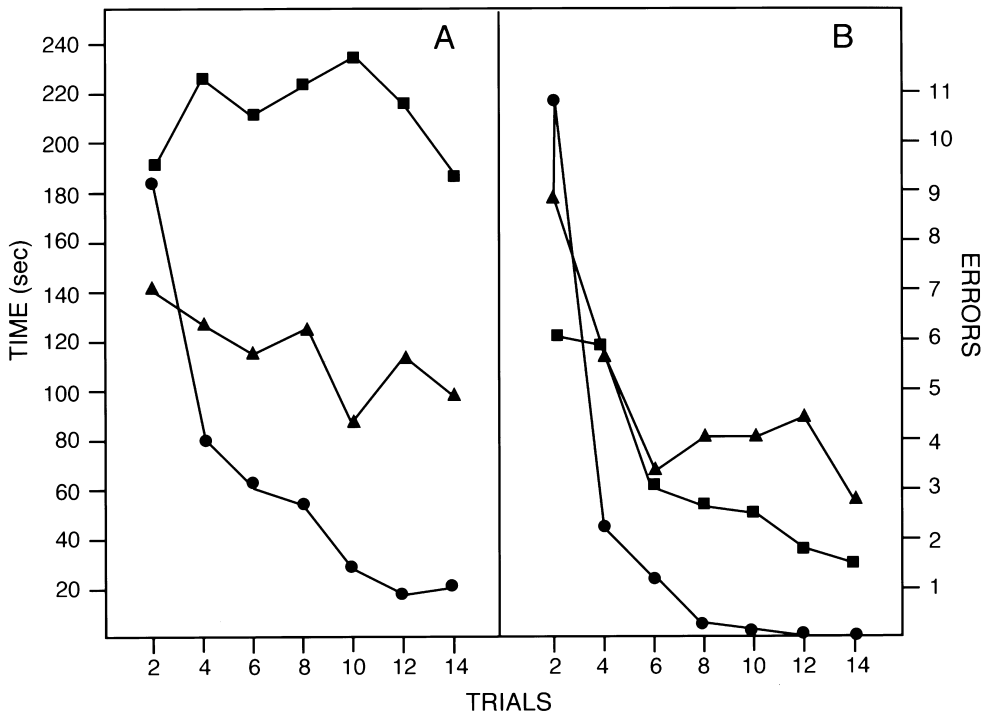

FIG. 2. Effects of 8-OH-DPAT (0.25 mg/kg, triangles) and buspirone (10 mg/kg, squares) on acquisition of maze C. Saline-treated rats are circles.

RESULTS

Study 1: 8-OH-DPAT and Buspirone, 5-HT_1A Agonists

After 25 training trials on maze A, rats were averaging 27 s swim times with less than one error per trial. As shown in Table 1, retesting on maze A following administration of 0.1, 0.25, or 0.5 mg/kg of 8-OH-DPAT or 2.5, 5.0, or 10 mg/kg of buspirone, resulted in no statistically significant changes in swim time or errors committed, although a nonsignificant increase in swim time and errors was seen at the highest 8-OH-DPAT dose.

In the second phase of this study rats were tested for acquisition of maze C in daily trials preceded by injection of saline, 8-OH-DPAT (0.25 mg/kg) or buspirone (10 mg/kg). These doses were chosen based on their lack of effect on performance on the well-learned maze A. As shown in Fig. 2, saline-injected rats learned the new maze quickly, but acquisition was markedly impaired in both the 8-OH-DPAT and buspirone treated groups [time: $F(2, 357) = 79$, $p < 0.0001$; errors $F(2, 357) = 14.6$, $p < 0.0001$]. Therefore, rats were refamiliarized with maze A for 4 days with no drug injections. On the first day, rats previously injected with 8-OH-DPAT or buspirone took longer to reach the swim platform, but there were no statistically significant differences among the groups for swim time over the pooled 4-day trials (data not shown). Rats were then retested on 2 separate days on maze A after drug administration. On the first drug retest day, rats were given saline, 0.25 mg/kg 8-OH-DPAT or 10 mg/kg buspirone, as had been administered in the aquisition of maze C experiment. Both drugs at these doses significantly increased swim times, $F(2, 24) = 9$, $p < 0.01$, unlike the original drug testing on maze A conducted prior to the maze C acquisition study. On the second maze A drug retest day, rats were administered lower doses of the two test drugs—0.1 mg/kg 8-OH-DPAT or 1.0 mg/kg buspirone—or saline prior to maze A testing. At these lower doses, performance on maze A was not statistically different among groups [time: $F(2, 24) = 2.44$, $p = 0.11$; errors: $F(2, 24) = 0.94$, $p = 0.40$]. Therefore, these doses were administered in the second acquisition study in which rats were challenged to learn new maze E in daily trials preceded by saline, 0.1 mg/kg 8-OH-DPAT or 1 mg/kg buspirone. As shown in Fig. 3, rats were less affected by these lower drug doses and were able to learn maze E, but performance, especially on the early trials, was impaired in both drug groups, as judged by swim time, compared to saline-injected rats [time: $F(2, 255) = 22.5$, $p < 0.0001$]. Although the drug-treated rats appeared to decrease errors more slowly than saline animals, this difference was not statistically significant [errors $F(2, 255) = 1.73$, $p = 0.18$]. Finally, all rats were challenged to learn new maze H with no drug administration. All groups rapidly learned maze H averaging approximately 20 s swim times and less than one error within five trials (data not shown). There were no significant differences among groups based on prior drug experience.

Study 2: DOI, a 5-HT_2 Agonist

After 23 training trials on maze A, rats were averaging 36 s swim times to reach the platform with zero or one error committed. The rats were then divided into three groups counterbalanced so that performance among the groups prior to drug testing was similar. On each of 4 successive days, the control rats received saline, saline, no injection, and saline. The low-dose DOI group received 0.1 mg/kg DOI, 0.25 mg/kg, no in-

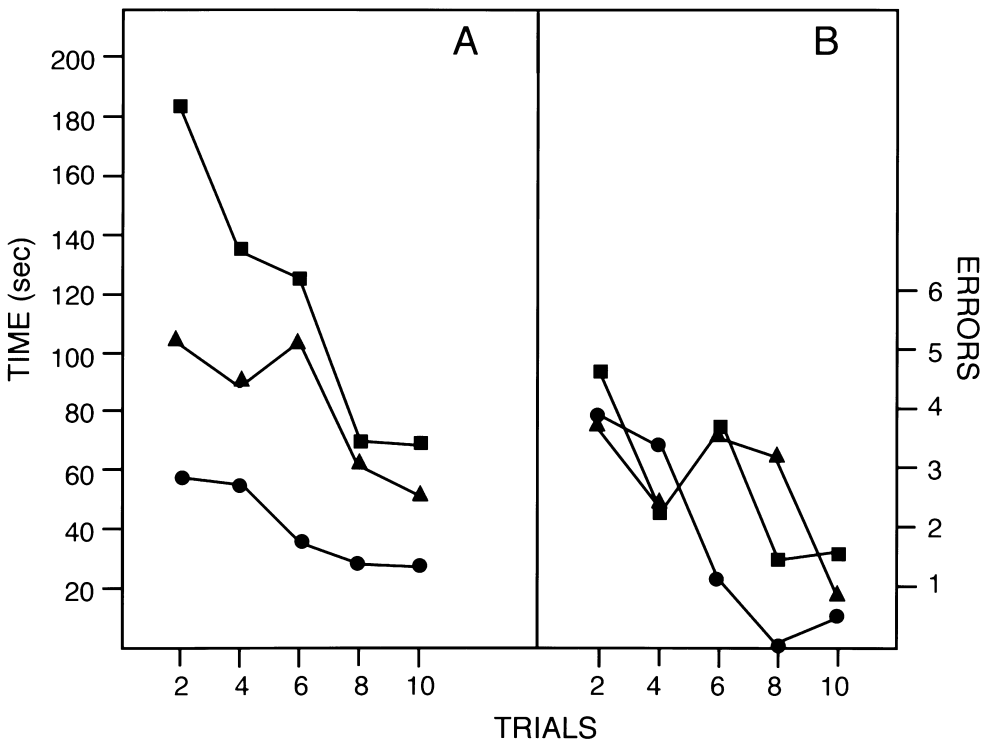

FIG. 3. Effects of 8-OH-DPAT (0.1 mg/kg, triangles) and buspirone (1 mg/kg, squares) on acquisition of maze E. Saline-treated rats are circles.

jection, and 0.1 mg/kg, and the high-dose DOI received 1 mg/kg, 0.5 mg/kg, no injection, and 0.25 mg/kg. For analyses, performance data was combined by drug dose not by high- vs. low-DOI group (e.g., both groups received 0.25 mg/kg DOI on different days; these data were combined). One-way ANOVA across six groups (noninjected, saline-injected, 0.1 mg/kg DOI, 0.25 mg/kg DOI, 0.5 mg/kg DOI, and 1.0 mg/kg DOI showed a significant effect of group [time: $F(5, 114) = 3.71$, $p < 0.01$], but did not demonstrate an effect on errors [errors: $F(5, 114) = 1.92$, $p > 0.05$]. Time and (errors) for noninjected, saline, 0.1, 0.25, 0.5, and 1.0 mg/kg DOI were 41 s (0.33 errors), 36 s (0.40 errors), 77 s (0.35 errors), 78 s (0.60 errors), 119 s (1.6 errors), and 94 s (0.50 errors).

Rats were then challenged to learn maze E (Fig. 1) in one trial per day after receiving saline, 0.1 mg/kg or 0.25 mg/kg of DOI. As shown in Fig. 4, DOI increased swim times but had no effect on error rate [time: $F(2, 431) = 20.0$, $p < 0.0001$; errors $F(2, 431) = 1.7$, $p = 0.19$]. The improvement over trials appeared similar in saline and DOI groups.

DISCUSSION

Although there have been reports linking serotonergic neurotransmission with learning processes (1,8,16,28), studies of the effects of subtypes of serotonin agonists have been relatively few. In our previous study (19) of the effects of 8-OH-DPAT and the 5-HT_{2C} agonist TFMPP on performance in a water maze, we were somewhat surprised by the potent effects of 8-OH-DPAT on this task in comparison to glutaminergic, cholinergic, and benzodiazepine compounds, which are known to affect learning and memory and which we have previously studied using the same maze paradigm (17,18,20). The impairment of maze acquisition caused by 8-OH-DPAT in our reported study was greater than we previously found for atropine and similar to what we reported for MK-801 and diazepam using the same maze. The effects of TFMPP in the maze were less dramatic and appeared to be due to the known depression of motor activity caused by this compound (22). The purpose of the present experiments was to compare the effects of 8-OH-DPAT with those of another 5-HT_{1A} agonist, buspirone, and to examine the effects of the 5-HT_2 agonist DOI on performance of this task.

Buspirone is of considerable interest clinically as an anxiolytic and antidepressant (4,12,14,15). In rats, buspirone increases licking in the Vogel conflict procedure, a classic test for anxiolytic activity, in a dose range of 1 to 20 mg/kg (33). Buspirone also decreases anxiety in the anxiety/defense test battery (6), increases social interaction time in the social interaction test, and increases open arm exploration in the elevated plus maze (10). It also decreases immobility in the forced swim test, a screen for antidepressant activity (32).

One of the potential clinical advantages of buspirone and related drugs compared to benzodiazepines is their purported reduced impairment of memory (25).

In the present experiments, doses of 8-OH-DPAT (0.25 mg/kg) and buspirone (10 mg/kg) that did not significantly affect performance on a well-learned maze greatly impaired acquistion of a new maze task, leading us to the conclusion that the primary impairment was cognitive. Rats injected with 8-OH-DPAT gradually reduced swim times and errors during training trials on the new maze, albeit at a slower rate than the saline-treated rats.

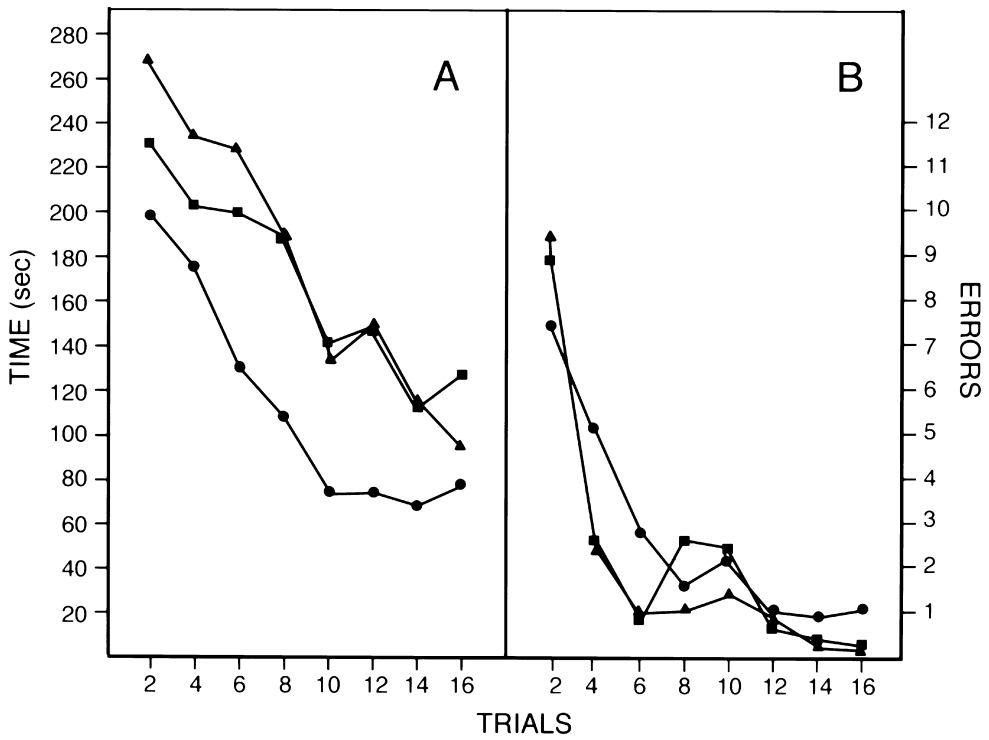

FIG. 4. Effects of DOI on acquisition of a new maze (E). Circles are saline-treated rats, triangles are DOI (0.1 mg/kg), and squares are DOI (0.25 mg/kg)-treated. Ten rats/group. (A) Swim times and (B) errors.

Buspirone-treated rats (10 mg/kg) did not learn a new maze in the 14-trial test period, as judged by swim time to the platform. Although the error rate decreased over trials, this decrease appeared to be due primarily to rats that simply did not swim anywhere, thus committing zero errors. Because error rate was not commensurate with swim times, we believe that this deficit was primarily motivational or motoric. Unlike 8-OH-DPAT, which has been reported to increase locomotor activity, buspirone has been shown to decrease locomotor activity (11), possibly as a result of its affinity for dopamine D_2 receptors.

In the second acquisition experiment with 8-OH-DPAT and buspirone, conducted at lower doses of 0.1 and 1 mg/kg, respectively, drug-treated animals learned the new maze, but required longer swim times and committed more errors than saline-treated rats. These deficits seem similar to those reported by us for the benzodiazepines diazepam and triazolam (20) and suggest that buspirone might have similar adverse side effects in humans, despite the different receptor affinities of these drugs.

In contrast to the effects of the 5-HT_{1A} agonists, DOI, a prototypical 5-HT_2 agonist, did not seem to affect learning per se, but did increase swim times without affecting error rate. Both 0.1 mg/kg and 0.25 mg/kg DOI increased swim times on the first trial of the new maze. Swim times then decreased at the same rate for DOI and saline-treated rats over subsequent trials. The number of errors committed by the saline and drug groups decreased similarly over trials. That DOI decreases general motor activity has been previously reported (31). The decreases in motor activity are similar to those seen after TFMPP, another 5-HT_2 agonist (27).

These data extend the findings of our first report describing different effects of the 5-HT_1A drug 8-OH-DPAT vs. the 5-HT_{2C} agonist TFMPP to another 5-HT_{1A} agonist buspirone and a second 5-HT_2 agonist, DOI. Again we find that 5-HT_1A agonists appear to affect cognition, as evidenced by selective difficulty with novel mazes as opposed to well-learned configurations, while 5-HT_2 agonists seem to affect only swim speed.

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