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Different Effects of Tropisetron and Ondansetron in Learning and Memory Paradigms

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PITSIKAS, N. AND F. BORSINI. *Different effects of tropisetron and ondansetron in learning and memory paradigms.* PHARMACOL BIOCHEM BEHAV **56**(4) 571–576, 1997.—The effects of the 5-HT_3 receptor antagonists tropisetron (ICS 205-930) and ondansetron on memory and performance impairments induced by scopolamine were tested in a passive avoidance procedure and in the Morris water maze task. Pretreatment with ondansetron (0.01 and 1 μg/kg IP) but not with tropisetron (1, 10, and 30 μg/kg IP) reversed scopolamine-induced memory deficits in the step-through passive avoidance task. When the effects of these 5-HT_3 receptor antagonists on cognition were assessed in the Morris water maze, ondansetron (0.01, 1, and 10 μg/kg IP) did not antagonize scopolamine-induced spatial navigation deficits. On the contrary, pretreatment with tropisetron (10 and 30 μg/kg, and to some extent also with 1 μg/kg IP) counteracted the learning and memory impairment due to scopolamine treatment. The findings suggest that it could be worthwhile to investigate whether or not different subtypes of the 5-HT_3 receptor may underlie the different effects on cognition displayed by compounds that belong to the same pharmacological class. © 1997 Elsevier Science Inc.

Tropisetron (ICS 205-930) Ondansetron 5-HT_3 receptor Scopolamine Learning Memory Passive avoidance Morris water maze

SEROTONIN (5-HT) seems to play a crucial role in learning and memory processes (1,17). There is accumulating evidence that serotonergic modulation of the cholinergic system may underlie these cognitive implications (6). Multiple 5-HT receptor subtypes have been identified in the central nervous system (25). In particular, the involvement of 5-HT_3 receptors in learning and memory function has been proposed. In fact, blockade of the 5-HT_3 receptor was found to attenuate cognitive deficits (3,4,7,9,13,22,23). It has also been reported, however, that 5-HT_3 antagonists did not always counteract memory dysfunctions (5,14) or visual attention deficits (20). Moreover, recent experimental evidence suggests the existence of different subtypes of the 5-HT_3 receptor (11,18,26).

Thus, in view of these controversial effects on cognition and the probability that 5-HT_3 receptors may exist in different splice variants, we wanted to evaluate the effects of ondansetron and tropisetron, which are 5-HT_3 receptor antagonists, on cognition abilities in the young rat. The efficacy of these compounds in antagonizing the effects induced by treatment with scopolamine was assessed in two different memory paradigms that involve different memory mechanisms: the step-through passive avoidance procedure (16) and the Morris water maze task (19).

MATERIALS AND METHODS

Procedures involving animals and their care were conducted in conformity with institutional guidelines, in compliance with national and international laws and policies (EEC Council Directive 86/609,-J L 358, 1, December 12, 1987; *NIH Guide for Care and Use of Laboratory Animals*, NIH publication no. 85-23, 1985).

Animals

Male CD-COBS rats (Charles River, Calco, Italy) weighing 200–220 g were housed in Makrolon cages (35 × 45 × 20 cm), four per cage, in a regulated environment (21 ± 1°C, 50–55% relative humidity, 12 L:12 D cycle, lights on at 0700 h) with free access to food and water. Experiments were carried out in the room where only these animals were housed, and took place between 0900 and 1300 h.

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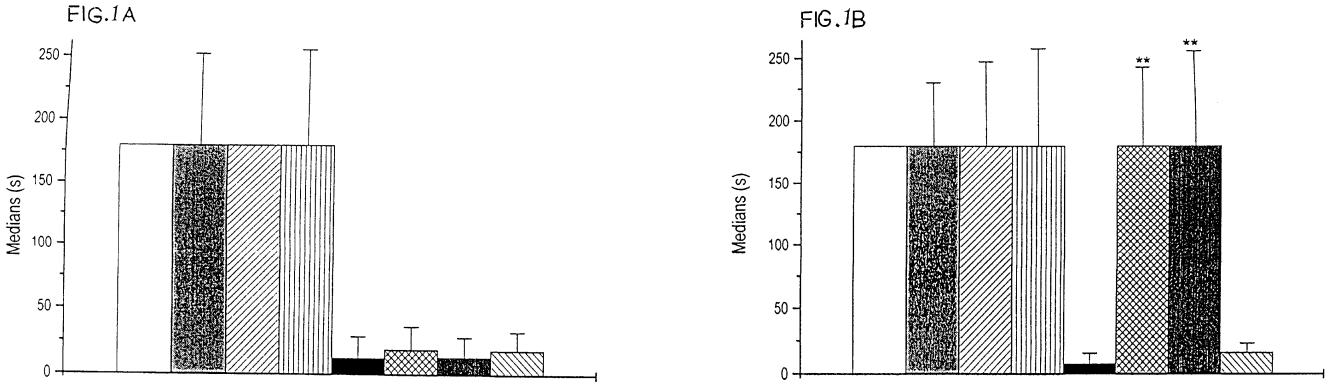

FIG. 1. (A) Retention latency to enter the dark chamber in the step-through passive avoidance task expressed by rats treated with vehicle + vehicle (□), vehicle + 1 μg/kg tropisetron (■), vehicle + 10 μg/kg tropisetron (▨), vehicle + 30 μg/kg tropisetron (▥), vehicle + 0.75 mg/kg scopolamine (■), scopolamine + 1 μg/kg tropisetron (▩), scopolamine + 10 μg/kg tropisetron (■), and scopolamine + 30 μg/kg tropisetron (▧). (B) Retention latencies to enter the dark chamber in the step-through passive avoidance task expressed by rats treated with vehicle + vehicle (□), vehicle + 0.01 μg/kg ondansetron (■), vehicle + 1 μg/kg ondansetron (▨), vehicle + 10 μg/kg ondansetron (▥), vehicle + 0.75 mg/kg scopolamine (■), scopolamine + 0.01 μg/kg ondansetron (▩), scopolamine + 1 μg/kg ondansetron (■), and scopolamine + 10 μg/kg ondansetron (▧). Each value represents the median and the interquartile range for 10 rats. $^{**}p < 0.01$ vs. vehicle + scopolamine-treated animals.

Drug administration

Drugs were freshly prepared daily. Control rats were treated with vehicle (NaCl, 0.9%). Scopolamine HBr (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in saline and injected SC. Tropisetron [ICS 205-930: (3-α-tropanyl)1H-indole-3-carboxylic acid ester] and ondansetron [GR38032F: 1,2,3,9-tetrahydro-9-methyl-3-((2-methyl-1H-imidazol-1-yl)-methyl)-4H-carbazol-4-one, $HCl{\cdot}2H_2O$] (both synthesized by Boehringer Ingelheim Italia) were dissolved in saline and administered IP.

Step-Through Passive Avoidance Experiments

Method. The apparatus has been described elsewhere (15). In the training session (first day), each rat was gently placed in the light chamber and 10 s later the guillotine door was opened. When the rat moved into the dark compartment, the door was shut and a 1.6-mA foot shock was applied for 1 s. Following the shock, the rat was removed immediately and replaced in its home cage. Retention testing of the noxious stimulus was performed 24 h later. The rat was again placed in the illuminated chamber facing away from the open guillotine door. The latency to enter the dark chamber with all four paws was recorded as step-through latency. If a rat did not enter the dark chamber within 180 s, it was removed and assigned a score of 180 s.

Experimental design and drug treatment. The effects of tropisetron and ondansetron on scopolamine-induced memory impairment were tested separately in two different experiments with the same experimental design. Animals were randomly divided into eight experimental groups ($n = 10$ rats per group) as follows: vehicle + vehicle, vehicle + tropisetron 1 μg/kg, vehicle + tropisetron 10 μg/kg, vehicle + tropisetron 30 μg/kg, vehicle + scopolamine, scopolamine + tropisetron 1 μg/kg, scopolamine + tropisetron 10 μg/kg, and scopolamine + tropisetron 30 μg/kg. Control rats were treated with the vehicle 45 min and 30 min, IP and SC, respectively, before receiving the electric foot shock. Scopolamine (0.75 mg/kg) was administered SC 30 min before animals received the noxious stimulus. The dose of scopolamine was selected on the basis of our prior experience (4). Tropisetron was given IP 45 min before starting the training session of the test. The experimental design was replicated with naive rats to study the effects of ondansetron. Ondansetron was administered at doses of 0.01, 1, and 10 μg/kg IP 45 min before starting the training session. Doses of compounds are expressed as bases.

Statistical analysis. The model of Cox for the analysis of survival data was applied on the complete experimental model: the main factors were the presence or absence of scopolamine, the three doses of the drugs, and their interactions. Post hoc analysis was done by calculating the hazard ratios and the relative 95% confidence interval (8).

Morris Water Maze Experiments

Method. The apparatus has been described extensively (21). Many extramaze cues such as a lamp, a table, animal cages, and pictures on the walls surrounded the environment. These were kept in fixed positions with respect to the swimming tank to allow the rat to locate the escape platform hidden below the water surface. Each trial involved placing the rat in the pool, close to and facing the wall in one of the four equal quadrants into which the pool was divided. Animals were allowed to swim freely until they found the escape platform. If a rat failed to find the landmark within 60 s, it was placed on it by the experimenter. The intertrial interval was 30 s, during which time the rat remained on the platform. Each rat performed a daily session of four trials for four consecutive days. During this training period, the escape platform was located in a fixed position in the middle of quadrant number 1. The time required to reach the platform (latency), the swimming path length (distance), and the swimming speed were recorded. These parameters were averaged for each daily block of trials and for each rat, whose daily performance was thus characterized. On day 5, rats performed a spatial probe trial. This trial consisted of removing the platform from the pool and allowing the rat to swim for 60 s in search of it. The time spent in each of the four quadrants of the tank was calculated as a percentage over 60 s. If the rat demonstrated a persistent preference during the trial to navigate in the pool quadrant where the escape platform had previously been placed, this was taken to indicate that the animal had acquired the spatial task and remembered it (12). Data for all the

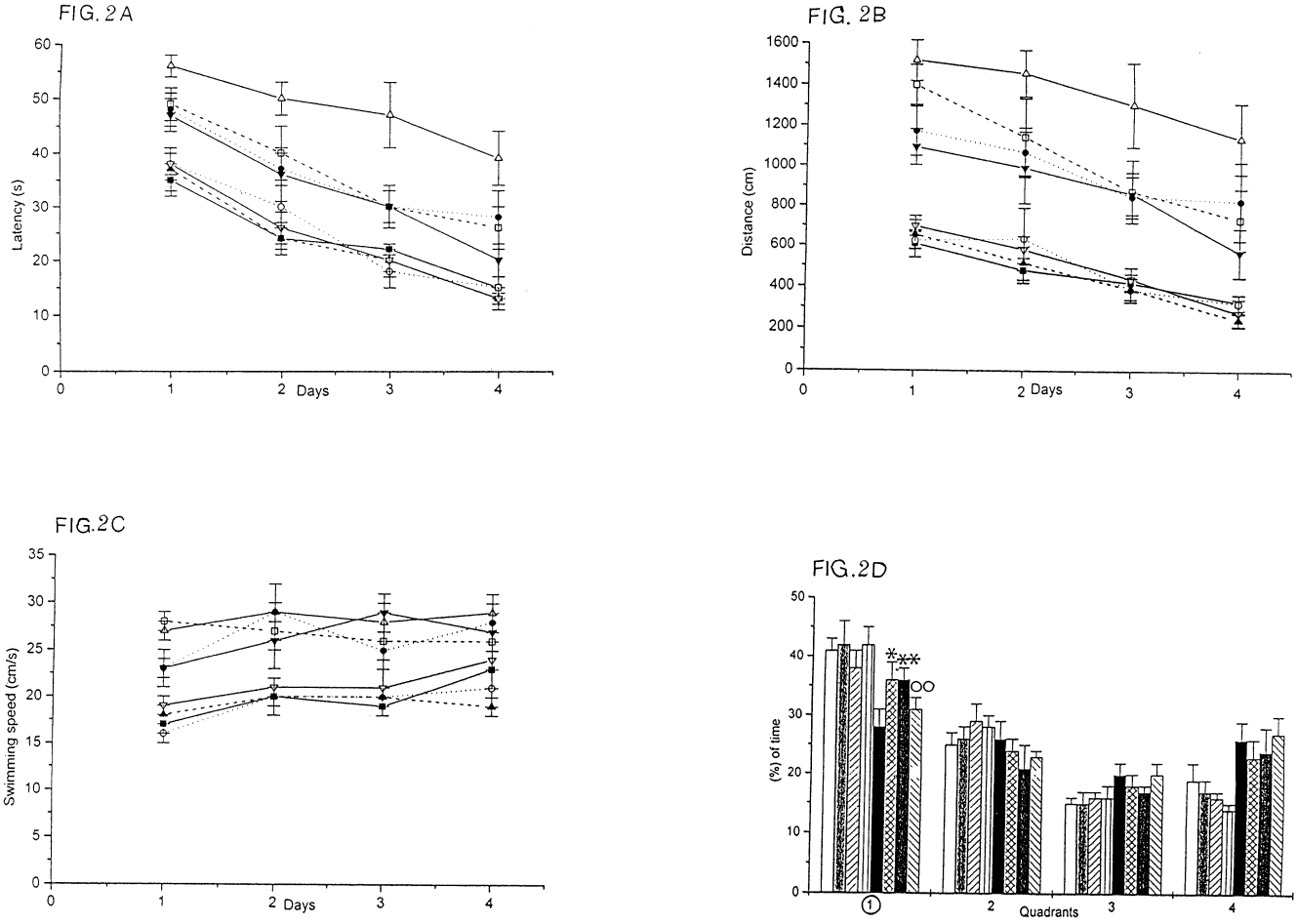

FIG. 2. (A) Mean latency, (B) mean distance, and (C) mean swimming speed expressed by rats treated with vehicle + vehicle (-■-), vehicle + 1 μg/kg tropisetron (-○-), vehicle + 10 μg/kg tropisetron (-▲-), vehicle + 30 μg/kg tropisetron (-▽-), vehicle + 0.2 mg/kg scopolamine (-△-), scopolamine + 1 μg/kg tropisetron (-□-), scopolamine + 10 μg/kg tropisetron (-▼-), and scopolamine + 30 μg/kg tropisetron (-●-). Each point represents the mean group performance in successive daily blocks of trials, and vertical bars indicate SEM. (D) Mean percentage of total time spent in each pool quadrant by rats treated with vehicle + vehicle (□), vehicle + 1 μg/kg tropisetron (■), vehicle + 10 μg/kg tropisetron (▨), vehicle + 30 μg/kg tropisetron (▥), vehicle + 0.2 mg/kg scopolamine (■), scopolamine + 1 μg/kg tropisetron (▩), scopolamine + 10 μg/kg tropisetron (■), and scopolamine + 30 μg/kg tropisetron (▧). Data are mean ± SEM. During the training period, the platform was located in the centre of quadrant number 1 (solid ring). *$p < 0.05$, **$p < 0.01$ vs. second, third, and fourth quadrants; ○○$p < 0.01$ vs. second and third quadrants.

parameters assessed in the Morris water maze task were calculated as mean ± SEM. Data were recorded by an HVS image analyzing system (VP 112, HVS Image, Hampton, UK).

Experimental design and drug treatment. The effects of tropisetron and ondansetron on scopolamine-induced memory deficits were tested separately in two different experiments with the same experimental design. Similar to the passive avoidance studies, the animals were randomly divided into the same eight experimental groups ($n = 10$ rats per group). The rats were injected each day before undertaking the behavioral procedure. Control animals were treated with the vehicle IP 45 min and SC 30 min before starting the test. Scopolamine was administered SC at a dose of 0.2 mg/kg 30 min before beginning the behavioral training. The selection of this dose of scopolamine was based on our previous studies (21,23). Tropisetron (1, 10, and 30 μg/kg) and ondansetron (0.1, 1, and 10 μg/kg), were administered IP 45 min before starting the experiment. Doses of compounds are expressed as bases.

Statistical analysis. The effects of drugs on daily performance (escape latency, swimming path length, and swimming speed) during task acquisition were calculated by analysis of variance (ANOVA) with a split-plot design (between–within subjects) (16). Post hoc analyses were made by Tukey's test. For comparing the animal's persistence of swimming in the previously reinforced quadrant (number 1) versus the three remaining quadrants during the spatial probe trial, the nonparametric test of Friedman followed by the Newman–Keuls test was used (24).

RESULTS

Effects of Tropisetron in the Passive Avoidance Test

Data are plotted in Fig. 1A. Pretreatment with tropisetron failed to counteract scopolamine-induced amnesia in this test. The probability that animals treated with scopolamine would enter the dark chamber during the retention trial was 5.5 times

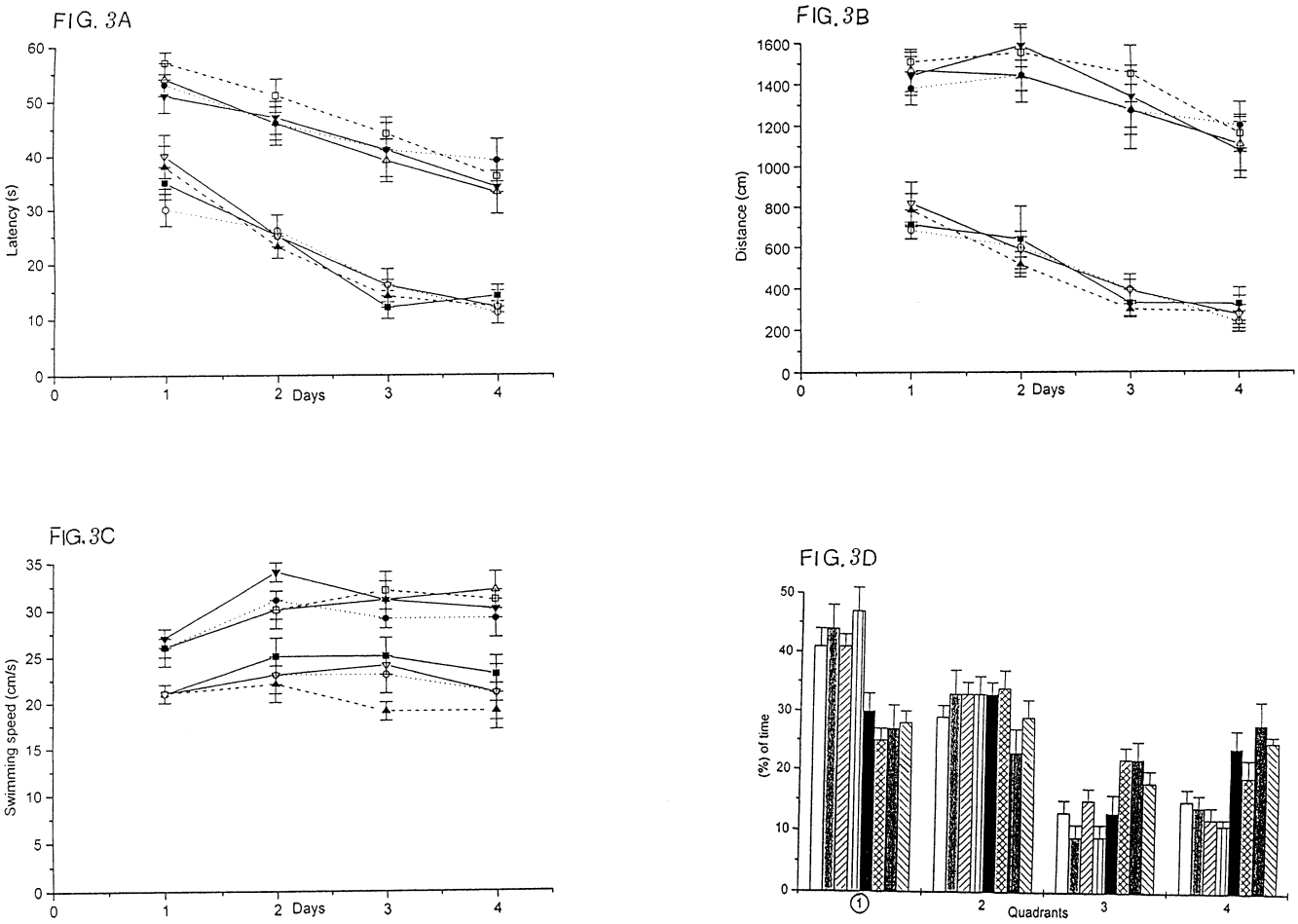

FIG. 3. (A) Mean latency, (B) mean distance, and (C) mean swimming speed expressed by rats treated with vehicle + vehicle (-■-), vehicle + 0.01 μg/kg ondansetron (-○-), vehicle + 1 μg/kg ondansetron (-▲-), vehicle + 10 μg/kg ondansetron (-▽-), vehicle + 0.2 mg/kg scopolamine (-△-), scopolamine + 0.01 μg/kg ondansetron (-□-), scopolamine + 1 μg/kg ondansetron (-▼-), and scopolamine + 10 μg/kg ondansetron (-●-). Each point represents the mean group performance in successive daily blocks of trials, and vertical bars indicate SEM. (D) Mean percentage of total time spent in each pool quadrant by rats treated with vehicle + vehicle (□), vehicle + 0.01 μg/kg ondansetron (▩), vehicle + 1 μg/kg ondansetron (▨), vehicle + 10 μg/kg ondansetron (▥), vehicle + 0.2 mg/kg scopolamine (■), scopolamine + 0.01 μg/kg ondansetron (▩), scopolamine + 1 μg/kg ondansetron (▩), and scopolamine + 10 μg/kg ondansetron (▧). Data are mean ± SEM. During the training period, the platform was located in the centre of quadrant number 1 (solid ring).

higher as compared with the control rats (hazard ratio and 95% confidence interval: 5.5, 2.73–11.43). An effect of the drug given alone was not revealed.

Effect of Ondansetron in the Passive Avoidance Test

The results are illustrated in Fig. 1B. Pretreatment with 0.01 and 1 μg/kg (but not with 10 μg/kg) of ondansetron significantly counteracted the scopolamine-induced amnesia ($p < 0.01$ for both doses). Ondansetron given alone did not affect performance of the control rats.

Effects of Tropisetron in the Morris Water Maze Task

Scopolamine produced a severe deficit in the performance of treated rats as compared with that of vehicle-treated animals [$F(1, 18) = 39.7$, $p < 0.01$, for latencies, Fig. 2A; $F(1, 18) = 43.4$, $p < 0.01$, for swimming distances, Fig. 2B].

Rats treated with 1 μg/kg tropisetron + scopolamine were also impaired as compared with their controls [$F(1, 18) = 9.3$, $p < 0.01$, for latencies; $F(1, 18) = 14.5$, $p < 0.01$, for swimming distances], but their performance was slightly better than that of rats treated with scopolamine [$F(1, 18) = 5.8$, $p < 0.05$, for escape latencies]. Animals that received 10 or 30 μg/kg tropisetron + scopolamine exhibited a significantly higher overall performance than their counterparts treated with scopolamine + vehicle [$F(1, 18) = 11.1$, $p < 0.01$, for latencies, and $F(1, 18) = 9$, $p < 0.01$, for distances (10 μg/kg tropisetron); $F(1, 18) = 8$, $p < 0.01$, for latencies, and $F(1, 18) = 4.6$, $p < 0.05$, for distances (30 μg/kg tropisetron)]. Escape latencies and distances displayed by these rats, however, were poorer as compared with their control animals [$F(1, 18) = 10$, $p < 0.01$, for latencies, and $F(1, 18) = 21.6$, $p < 0.01$, for distances (10 μg/kg tropisetron); $F(1, 18) = 16.9$, $p < 0.01$, for latencies, and $F(1, 18) = 16.2$, $p < 0.01$, for distances (30 μg/kg tropisetron)].

Scopolamine produced a consistent increase of the swimming speeds in all the rats as compared with the control animals, which was not counteracted by treatment with tropise-

tron (Fig. 2C). During the spatial probe trial (Fig. 2D), control animals and rats treated with tropisetron alone preferentially swam in the previously reinforced quadrant (number 1) as compared with the remaining three quadrants ($p < 0.01$). Scopolamine-treated rats did not show preference for any pool quadrant (Friedman test, $\chi^2 = 4.8$, not significant). Conversely, rats treated with scopolamine + tropisetron swam significantly more in the previously reinforced quadrant (number 1) as compared with the three remaining quadrants (Friedman test, $\chi^2 = 7.7$, $p < 0.05$; $\chi^2 = 13.1$, $p < 0.01$; $\chi^2 = 11.7$, $p < 0.01$, for rats treated with scopolamine + 1, 10, or 30 μg/kg tropisetron, respectively).

Effects of Ondansetron in the Morris Water Maze Test

Escape latencies and length of the swimming path displayed by scopolamine-treated rats were poorer as compared with their controls [$F(1, 18) = 52.6$, $p < 0.01$, for latencies; $F(1, 18) = 62$, $p < 0.01$, for swimming distances (Fig. 3A and 3B, respectively)]. Ondansetron did not reverse the effects of scopolamine at any dose given. Moreover, the escape latencies and the swimming distances displayed by the scopolamine + ondansetron-treated animals were significantly worse than those of the vehicle + ondansetron-treated rats. Administration of scopolamine induced a significant increment of the swimming speed of the rats as compared with their relative controls, which was not counteracted by treatment with ondansetron (Fig. 3C). During the spatial probe trial (Fig. 3D), control rats and animals treated with ondansetron alone spent significantly more time in the previously reinforced quadrant as compared with the remaining three quadrants ($p < 0.01$). In contrast, scopolamine produced a dramatic impairment in this parameter that was not attenuated by treatment with ondansetron.

DISCUSSION

It was found that ondansetron and tropisetron exhibited different effects on cognition. In the step-through passive avoidance procedure, ondansetron, but not tropisetron, reversed the memory deficits due to scopolamine treatment. Contrariwise, spatial navigation impairments induced by scopolamine were successfully antagonized by tropisetron but not by ondansetron. In both tasks, a per se effect of the drugs was not observed. Our results with ondansetron are in line with a previous study in which this compound failed to antagonize scopolamine-induced memory and performance deficits in a complex task, the Stone maze (5). Tropisetron did not reverse the scopolamine-induced memory deficit in the passive avoidance test as was reported in a previous study (7). However, this is probably due to the dissimilar experimental conditions (different foot shock intensities) and to different aspects of cognition evaluated in the different protocols [retrieval in the study of Chugh et al. (7) vs. retention in our experiments]. Similar to another 5-HT_3 receptor antagonist, itasetron (DAU 6215) (23), tropisetron antagonized scopolamine-induced spatial navigation impairment in a rather complex spatial memory task, the Morris water maze procedure.

What the mechanisms are that underlie the different behavioral profiles displayed by these 5-HT_3 receptor antagonists still remains unknown. It could be worthwhile to investigate whether or not the affinity of some compounds shown at the 5-HT_4 receptor (itasetron, tropisetron) is critical for exerting their beneficial effects on memory (10). Moreover, there is now some experimental evidence for the existence of two splice variants of 5-HT_3 receptors (11,18,26). Thus, the possible existence of other 5-HT_3 receptor subtypes might help to explain the different behavioral effects of ondansetron, tropisetron, and itasetron. These receptors, however, so far have not been sufficiently characterized to show significant pharmacological differences between them.

It is noteworthy that [^{3}H]zacopride and [^{3}H]granisetron bind to different sites on the 5-HT_3 receptor (2), suggesting that other 5-HT_3 receptor antagonists might also bind differently to the receptor. When the 5-HT_3 receptor subtypes are better characterized, it will be worthwhile correlating behavioral effects of the drugs with their effects on the different receptor subtypes.

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