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BRIEF COMMUNICATION

Effect of Oxiracetam on Scopolamine-Induced Amnesia in the Rat in a Spatial Learning Task

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PITSIKAS, N. AND S. ALGERI. *Effect of oxiracetam on scopolamine-induced amnesia in the rat in a spatial learning task*. PHARMACOL BIOCHEM BEHAV 43(3) 949–951, 1992.—The effects of the nootropic agent 4-hydroxy-2-oxo-pyrrolidinoacetamide (oxiracetam) on memory and performance impairments induced by scopolamine were evaluated in the Morris water maze task. No effect was seen on the performance of rats when treated with oxiracetam (30 mg/kg, IP) alone. Task performance of scopolamine (0.2 mg/kg, SC)-treated rats was impaired as compared to that of control animals. The behavioral deficits expressed in the task by scopolamine treatment were attenuated by the same dose of oxiracetam.

Oxiracetam Nootropic drugs Scopolamine Spatial learning Morris water maze

EVIDENCE is available that the nootropic drug 4-hydroxy-2-oxo-pyrrolidinoacetamide (oxiracetam) improves cognitive functions in memory-impaired animals by utilizing different behavioral paradigms in which discrete or working memory were assessed (1,6,18,19). Oxiracetam enhances learning also in normal and aged rodents (8,17).

That scopolamine disrupts acquisition of spatial navigation tasks is well known (2,4,20). These tasks evaluate spatial reference memory, which is different from the discrete or working memory assessed in avoidance or radial-arm maze paradigms (12). Deficits in spatial memory are commonly found in studies of aged human subjects (15).

The aim of the present study was to investigate whether oxiracetam may counteract scopolamine-induced learning deficits in rats in a spatial reference memory task. For this purpose, the Morris water maze task has been chosen (10).

METHOD

Animals

Thirty-two male CD-COBS rats (Charles River, Calco, Italy) weighing about 200–220 g were used in this study. Animals were randomly divided into four experimental groups based upon their pharmacological treatment: control-saline (SAL; $n = 8$), oxiracetam (OXI; $n = 8$), scopolamine (SCOP; $n = 8$), and scopolamine + oxiracetam (SCOP + OXI; $n = 8$). Rats were housed in Makrolon cages (35 × 45 × 20 cm), four rats per cage, and maintained on a 12 L:12 D cycle, with free access to water and food.

Drug Administration

Drugs were freshly prepared each day. Animals were injected every day before starting the behavioral procedure. Control rats were treated with vehicle (NaCl, 0.9%) IP 60 min before starting the test. Scopolamine HBr (Sigma Chemical Co., St. Louis, MO) was dissolved in saline and injected SC 30 min before beginning the behavioral training at the dose of 0.2 mg/kg. Oxiracetam (a gift from I.S.F., Trezzano sul Naviglio, Italy) was dissolved in saline and delivered IP 60 min before starting the experiment at the dose of 30 mg/kg.

Morris Water Maze Task

The apparatus was extensively described before (13). Each trial involved placing the rat in the pool, close to and facing the wall in one of the four equally spaced quadrants. Rats were allowed to swim freely until they found the escape platform. If a rat failed to find the escape platform within 120 s, it was placed on it by the observer. The intertrial interval was 30 s, during which the animal remained on the platform. Each rat did four trials for 4 consecutive days. During this period of test acquisition, the platform was located in a fixed position

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midway between the center and the edge of the pool (in the middle of quadrant 4). The time to reach the platform (latency) and the swimming path length taken were recorded. These two parameters were averaged for each block of trials and for each rat, whose daily performance was thus characterized. On day 5, animals performed a spatial probe trial. This trial consisted of removing the platform from the tank and allowing the rat to swim for 60 s in search of it. The distance swum in each of the four quadrants of the pool was calculated as a percentage over 60 s. If the animal showed a persistent preference during this trial to swim in the pool quadrant where the platform had previously been placed, this was taken to indicate that the rat had acquired the spatial task and remember it (3).

Statistical Analysis

The effects of drugs on daily performance (escape latency and swimming path length) during task acquisition were calculated by an analysis of variance (ANOVA) with a split-plot design (between-within subjects) (5). Spatial probe trial data were analyzed by the nonparametric test of Friedman followed by the Newman-Keuls test (16). For comparing the animal's persistence of swimming on the previously reinforced quadrant, a Kruskal-Wallis test was used (5).

RESULTS

Differences in distances traveled were perfectly superimposable to differences in latencies so only the former are reported (Fig. 1). Rats treated either with SAL or OXI acquired similarly well the task and reached the asymptotic on day 3, $F(3, 42) = 48.4$, $p < 0.01$, for the latency, and $F(3, 42) = 32.3$, $p < 0.01$ for the swimming path length. Rats treated with SCOP also improved their performance significantly over trials, $F(3, 42) = 14.4$, $p < 0.01$, for the latency, $F(3, 42) = 6.6$, $p < 0.01$ for the distance. Overall, performance of SCOP-treated rats was poorer as compared to that of SAL-treated rats, $F(1, 14) = 33$, $p < 0.01$, for the latency, and $F(1, 14) = 11.1$, $p < 0.01$ for the swimming distance.

Rats that received SCOP+OXI were less efficient to resolve this spatial task than rats that received OXI alone, $F(1, 14) = 11$, $p < 0.01$, for the latency, and $F(1, 14) = 16.7$, $p < 0.01$ for the swimming path length. These animals' overall task performance however, was significantly better than that of SCOP-treated animals, $F(1, 14) = 5.32$, $p < 0.05$, for the latency, and $F(1, 14) = 4.4$, $p < 0.05$, for the distance.

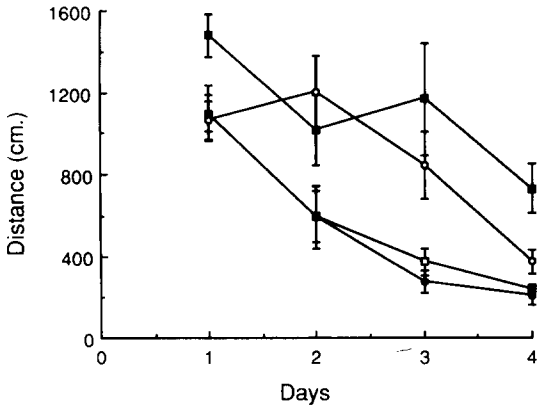

FIG. 1. Length of the swimming path to find the escape platform by control (-●-), oxiracetam (-□-)-, scopolamine (-■-)-, and oxiracetam + scopolamine (-○-)-treated rats. Each point represents the mean group performance in successive daily blocks of trials and vertical bars indicate SEM.

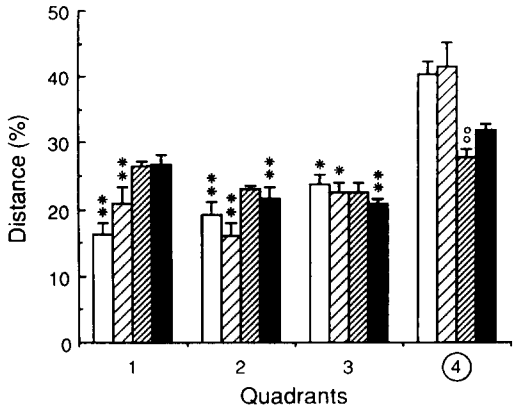

FIG. 2. Mean percentage of total distance swum in each pool quadrant by control (-□-), oxiracetam (-▨-)-, scopolamine (-▨-)-, and oxiracetam + scopolamine (-■-)-treated rats. Data are mean ± SEM. During the period of acquisition, the platform was located in the center of quadrant 4 (solid ring). *$p < 0.05$, **$p < 0.01$ vs. fourth quadrant. °°$p < 0.01$ between scopolamine group vs. control and oxiracetam groups on the same quadrant.

Figure 2 shows the results of the spatial probe trial. SAL- and OXI-treated rats swam significantly longer in quadrant 4, where the platform was previously placed during the training trials, than in the other three remaining quadrants (Friedman test followed by Newman-Keuls test $p < 0.01$ vs. quadrants 1 and 2, and $p < 0.05$ vs. quadrant 3).

Rats treated with SCOP did not swim preferentially in the pool quadrant where the platform was previously located (Friedman test, not significant), whereas SCOP + OXI-treated animals swum significantly more in the previously reinforced quadrant as compared to quadrants 2 and 3 (Friedman test, $p < 0.01$, but not vs. quadrant 1).

The percentage of the total distance swum by SCOP-treated rats in quadrant 4, where the platform had been located during the acquisition trials, was significantly lower than for SAL- or OXI-treated rats: (Kruskal-Wallis test, $\chi^2 = 21.8$, $p < 0.01$). No differences in this parameter were revealed when the percentage of swimming distance of the SCOP + OXI group was compared to both the control populations.

DISCUSSION

Control and oxiracetam-treated rats acquired the task well. No effect on performance of rats was observed when treated with oxiracetam alone. According to other reports, animals treated with scopolamine were impaired acquiring this place navigation task and were unable to locate the site of the platform during the spatial probe trial (4,20). Treatment with oxiracetam seems to attenuate this scopolamine-induced amnesia. Rats that received both oxiracetam and scopolamine improved their behavioral parameters recorded over trials and demonstrated a higher preference for the previously reinforced quadrant of the platform compared to scopolamine-treated rats. Performance of these rats, however, was less efficient during task acquisition compared to that of control animals.

Our results are in line with previous findings in which, by utilizing various amnestic animal models and assessing different types of memory, the efficacy of oxiracetam was reported (1,6,17–19). For the first time, the effect of a nootropic drug was observed in a spatial reference memory task such as the Morris water maze (10). That spatial memory tasks are predictive models for studying animal cognition is well documented and probably may be more appropriate to support the clinical relevance of the animal models for assessing nootropics than the avoidance tasks. Moreover, the clinical efficacy of this drug is not clear and needs further evaluation (11).

Whether oxiracetam acts on memory formation by increasing attention or by a more direct effect on cognition requires investigation (11). The pharmacological profile of this compound is also not clearly documented (11). The stimulatory effect of oxiracetam on central glutamatergic (7,14) and central cholinergic transmission (18,19), and the possible involvement of steroids (9) in its mechanism of action, are some of the hypotheses advanced.

In conclusion, our results suggest that oxiracetam attenuates scopolamine-induced amnesia in the rat in a spatial learning task.

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