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Role of 5-HT_{1A} Receptors in a Mouse Passive Avoidance Paradigm

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ABSTRACT—The effect on memory processes of modulation of 5-HT_{1A} receptor subtype was investigated in the mouse passive avoidance test. The administration of 5-HT_{1A}-receptor antagonists NAN-190 (1-(2-methoxyphenyl)-4-[4-2-phthalimmido)butyl]piperazine) and WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide) produced a dose-dependent amnesic effect comparable to that obtained with the well-known amnesic agents scopolamine and dicyclomine. Pretreatment with the 5-HT_{1A}-receptor agonists 8-OH-DPAT ((±)-8-hydroxy-dipropylaminotetralin) and 5-CT (5-carboxamidotryptamine) dose-dependently prevented the amnesia induced by 5-HT_{1A} antagonists, scopolamine, dicyclomine and exposure to an hypoxic environment. The antiamnesic effect exerted by 5-HT_{1A}-receptor agonists was comparable to that produced by the nootropic drug piracetam and cholinesterase inhibitor physostigmine. At effective doses, neither 5-HT_{1A}-receptor agonists nor 5-HT_{1A}-receptor antagonists produced any impairment of mouse motor coordination (rota-rod test), spontaneous motility (Animex apparatus) and inspection activity (hole board). These results indicate that modulation of 5-HT_{1A}-receptors appears to play an important role in the regulation of cognitive processes.

Keywords: Learning, Memory, 5-HT_{1A}-receptor, Amnesia, Central serotoninergic system

The serotoninergic system has been implicated in physiological and pathophysiological mechanisms (1), among them learning and memory (2, 3), but the specific role of 5-HT-receptor subtypes in cognitive processes is still unclear (4). Several 5-HT types (5-HT_{1-7}) and subtypes (5-$HT_{1A/1B/1D/1F}$, 5-$HT_{2A/2B/2C}$ and 5-$HT_{5A/5B}$) of receptors have been characterized in mammalian species; these have been divided into families based on their differential affinities for agonist and antagonist drugs, involvement of different second messenger systems and/or gene structures (5, 6).

The 5-HT pathways project to brain areas (7, 8) involved in learning and memory (9), and there is evidence suggesting that 5-HT and its receptors might have a role in these processes (2, 10 – 12), including 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3 receptors (2, 4, 10, 13, 14).

The role of 5-HT_{1A}-receptors in learning and memory processes is still controversial. There are studies reporting that 5-HT_{1A}-receptor agonists enhance learning, others have failed to show such improvement, and others that have observed impairment (15 – 18). Furthermore, the effects produced by 5-HT_{1A}-receptor antagonists are not yet established. The administration of WAY-100635 has been observed to produce ameliorative activity on marmoset memory processes (19), whereas NAN-190 has been reported to impair rat working memory (20).

On the basis of the above-mentioned literature data, we thought it worthwhile to further investigate the role of 5-HT_{1A}-receptors in learning and memory processes. To this purpose, we evaluate the effects produced by both 5-HT_{1A} agonists (8-OH-DPAT, 5-CT) and antagonists (NAN-190, WAY-100635) in the mouse passive avoidance paradigm.

MATERIALS AND METHODS

Animals

Male Swiss albino mice (24 – 26 g) from Morini (San Polo d'Enza, Italy) were used. Fifteen mice were housed per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. The animals were fed a standard laboratory diet and tap water ad libitum and kept at 23 ± 1°C with a 12-h light/dark cycle, light at 7 a.m.

I.c.v. injection technique

Intracerebroventricular (i.c.v.) administration was per-

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formed under ether anesthesia with isotonic saline as solvent, according to the method described by Haley and McCormick (21). During anesthesia, mice were grasped firmly by the loose skin behind the head. A hypodermic needle (0.4-mm external diameter) attached to a 10-μl syringe was inserted perpendicularly through the skull and no more than 2 mm into the brain of the mouse, where 5 μl of solution were then administered. The injection site was 1 mm to the right or left from the midpoint on a line drawn through to the anterior base of the ears. Injections were performed randomly into the right or left ventricle. To ascertain that the drugs were administered exactly into the cerebral ventricle, some mice were injected with 5 μl of diluted 1:10 India ink, and their brains were examined macroscopically after sectioning. The accuracy of the injection technique was evaluated with 95% of injections being correct.

Passive avoidance

The test was performed according to the step-through method described by Jarvik and Kopp (22). The apparatus consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. Mice, as soon as they entered the dark compartment, received a punishing electrical shock (0.5 mA, 1 s). The latency times for entering the dark compartment were measured in the training test and after 24 h in the retention test. The maximum entry latency allowed in the training and retention session was 60 and 180 s, respectively.

In order to provoke hypoxia-induced amnesia, groups of five mice, after individual training for the passive-avoidance test, were introduced into the cage and gassed for 7 min with pure nitrogen at a constant rate of 2 l/min. Since the training of each mouse took about 15 s, a maximum of 2 min elapsed for training all five mice. Hypoxia was therefore started just after training of the fifth mouse and a maximum of 2 min after the training of the first one.

Hole-board test

The hole board test consists of a 40 cm square plane with 16 flush-mounted cylindrical holes (diameter 3 cm) distributed 4 by 4 in an equidistant, grid-like manner. Mice were placed on the centre of the board one by one and left to move about freely for a period of 5 min each. Two electric eyes, crossing the plane from midpoint to midpoint of opposite sides, thus dividing the plane into four equal quadrants, automatically signalled the movement of the animals on the surface of the plane (locomotor activity). Miniature photoelectric cells, in each of the 16 holes, recorded the exploration of the holes (head plunging activity) by the mice (exploratory activity).

Rota-rod test

The apparatus consisted of a base platform and a rotating rod of 3-cm diameter with a non-slippery surface. The rod was placed at a height of 15 cm from the base. The rod, 30 cm in length, was divided into five equal sections by 6 disks. Thus up to 5 mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 rpm. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s according to Vaught et al. (23). The performance time was measured before and 15, 30 and 45 min after the beginning of the test.

Spontaneous activity meter (Animex)

Locomotor activity in mice was quantified using an Animex activity meter Type S (LKB, Farad, Sweden) set to maximum sensitivity. Every movement of the mice, which were placed on the top of the Animex activity meter, produced a signal due to variation in inductance and capacity of the apparatus resonance circuit. Then signals were automatically converted to numbers. On the day of the experiment, the mice were treated and then the cage, containing 5 mice, was put on the measuring platform. Activity counts were made every 15 min for 45 min starting immediately after injection of the drug. Because of the arbitrary scale adopted to quantify movements, drug-treated mice were always compared with saline-treated ones.

Drugs

The following drugs were used: scopolamine hydrobromide, NAN-190 (1-(2-methoxyphenyl)-4-[4-2-phthalimmido) butyl]piperazine) hydrobromide, 8-OH-DPAT ((±)-8-hydroxy-dipropylaminotetralin) hydrobromide, physostigmine hemisulphate, piracetam (Sigma Tau, Milan, Italy); dicyclomine hydrochloride (Le Petit, Rome, Italy); D-amphetamine (De Angeli, Milan, Italy); WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide), 5-CT (5-carboxamidotryptamine) maleate (RBI, Milan, Italy). Other chemicals were of the highest quality commercially available. Drugs were dissolved in isotonic (0.9% NaCl) saline solution immediately before use. Drug concentrations were prepared so that the necessary dose could be administered in a volume of 5 μl per mouse by intracerebroventricular (i.c.v.) injection and 10 ml/kg by intraperitoneal (i.p.) injection.

Statistical analyses

All experimental results are given as the means ± S.E.M. An analysis of variance (ANOVA), followed by Fisher's Protected Least Significant Difference (PLSD) procedure for post-hoc comparison, was used to verify the significance of differences between two means. Data were analyzed with the StatView software for the Macintosh (1992).

RESULTS

Amnesic effect of 5-HT$_{1A}$ antagonists

The effect of the 5-HT$_{1A}$ antagonists NAN-190 and WAY-100635 on memory processes was evaluated in the mouse passive avoidance test. NAN-190 (0.001 – 0.5 μg per mouse, i.c.v.) produced a dose-dependent reduction of the entrance latency into the dark compartment, reaching its maximum effect at 0.5 μg (Fig. 1). Similarly, WAY-100635 (0.001 – 1 μg per mouse, i.c.v.) induced a dose-dependent amnesia (Fig. 1). The intensity of the 5-HT$_{1A}$-antagonist amnesia was comparable to that obtained by treating animals with well-known amnesic drugs such as scopolamine (1 mg/kg, i.p.) and dicyclomine (2 mg/kg, i.p.). No difference in the reduction of the entrance latency into the dark compartment produced by the two effective doses of WAY-100635 was revealed (Fig. 1). Therefore, higher doses of 5-HT$_{1A}$ antagonists were not investigated. Amnesic drugs were administered immediately after the training session since the time-course study indicated that the maximum amnesic effect was reached at this time (data not shown). Pretreatment with the 5-HT$_{1A}$ antagonists did not modify the entrance latency into the dark compartment in comparison with control animals (data not shown).

Prevention of amnesia by 5-HT$_{1A}$ agonists

The amnesia induced by both NAN-190 (0.5 μg per mouse, i.c.v.) and WAY-100635 (0.1 μg per mouse, i.c.v.) was prevented, in the mouse passive avoidance test, by pretreatment with the 5-HT$_{1A}$ agonists 8-OH-DPAT (1 – 3 μg per mouse, i.c.v.) and 5-CT (10 μg per mouse, i.c.v.) injected 20 min before training session (Fig. 2). Both compounds enhanced the entrance latency to the dark compartment up to a value comparable to that produced by control animals (Fig. 2). 5-CT at the dose of 1 μg per mouse, i.c.v. was completely ineffective on preventing amnesia induced by either NAN-190 or WAY-100635.

No difference among the entrance latencies of every group in the training session of the passive avoidance test was observed (Fig. 3). 5-HT$_{1A}$ agonists were administered 20 min before the training session since the time-course study indicated that the maximum amnesic effect was reached at this time (data not shown).

8-OH-DPAT (3 μg per mouse, i.c.v.) and 5-CT (5 – 10 μg per mouse, i.c.v.) were also able to completely prevent scopolamine (1 mg/kg, i.p.; Fig. 3) and dicyclomine (2 mg/kg, i.p.; Fig. 4) induced deficits in passive avoidance behavior, showing an antiamnesic effect comparable to that exerted by the nootropic drug piracetam and the cholinesterase inhibitor physostigmine (Fig. 4).

Exposure to a hypoxic environment produced deficits in passive avoidance behaviour that was completely prevented by pretreatment with the two 5-HT$_{1A}$ agonists 8-OH-DPAT and 5-CT at the doses of 10 μg per mouse, i.c.v. (Fig. 5). The antiamnesic effect produced by i.c.v. injection of 8-OH-DPAT and 5-CT was comparable to that produced by the well-known nootropic drug piracetam (30 mg/kg, i.p.) and the cholinesterase inhibitor physostigmine (0.2 mg/kg, i.p.) as illustrated in Fig. 5.

Doses of 8-OH-DPAT and 5-CT higher than 10 μg per mouse, i.c.v. were not investigated because a complete prevention of 5-HT$_{1A}$ antagonist-, scopolamine-, dicyclomine-

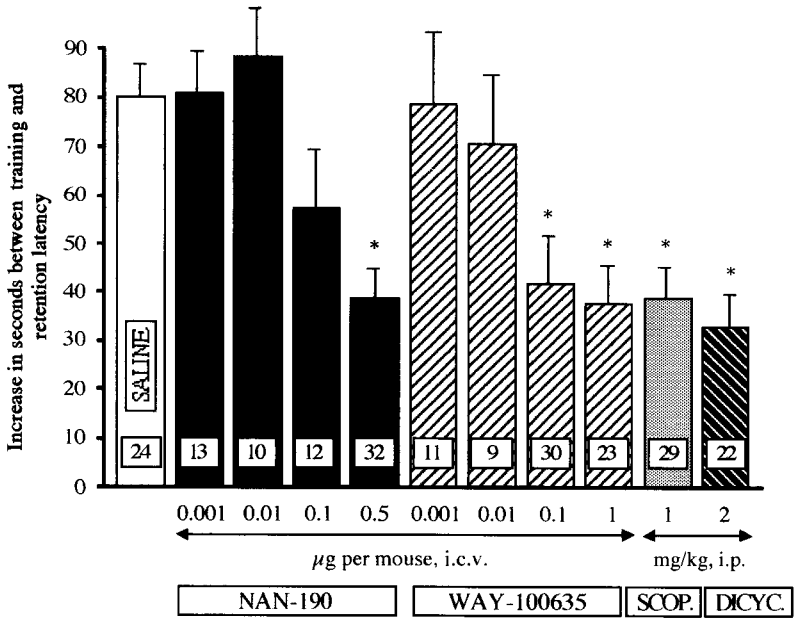

Fig. 1. Effect of NAN-190 and WAY-100635 in comparison with scopolamine (SCOP.) and dicyclomine (DICYC.) in mouse passive avoidance test. NAN-190 and WAY-100635 were injected i.c.v., and scopolamine and dicyclomine were administered i.p. immediately after punishment. The number of mice is given inside the column. *P<0.01, in comparison with saline-treated mice.

and hypoxia-induced deficits in the passive avoidance behavior used was already reached.

8-OH-DPAT and 5-CT, when given alone, at the highest doses used, had no effect on mouse passive avoidance test in comparison with saline-treated mice. No statistically significant difference among in-the-entrance latencies for each compound tested in the training session of the passive avoidance test was observed (data not shown).

Effect of 5-HT$_{1A}$ modulators on Animex, rota-rod and hole-board tests

Mice pretreated with 5-HT$_{1A}$ agonists 8-OH-DPAT (10 μg per mouse, i.c.v.) and 5-CT (10 μg per mouse, i.c.v.), and antagonists NAN-190 (0.5 μg per mouse, i.c.v.) and WAY-100653 (0.1 μg per mouse, i.c.v.), were evaluated for motor coordination, spontaneous motility and inspection activity by use of the rota-rod, Animex and hole-board tests (data not shown). All behavioral tests were carried out

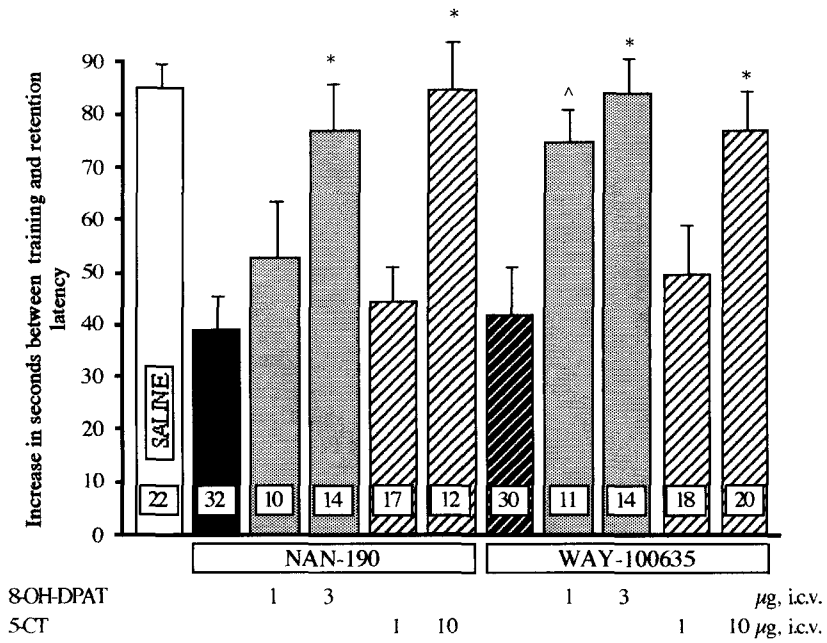

Fig. 2. Effect of 8-OHDPAT and 5-CT on amnesia induced by both NAN-190 (0.5 μg per mouse, i.c.v.) and WAY-100635 (0.1 μg per mouse, i.c.v.) in mouse passive-avoidance test. 8-OH-DPAT and 5-CT were administered 20 min before the training session, and NAN-190 and WAY-100635 were injected immediately after punishment. All drugs were injected i.c.v. The number of mice is given inside the column. $^P<0.05$, $*P<0.01$, in comparison with mice treated with NAN-190 and WAY-100635.

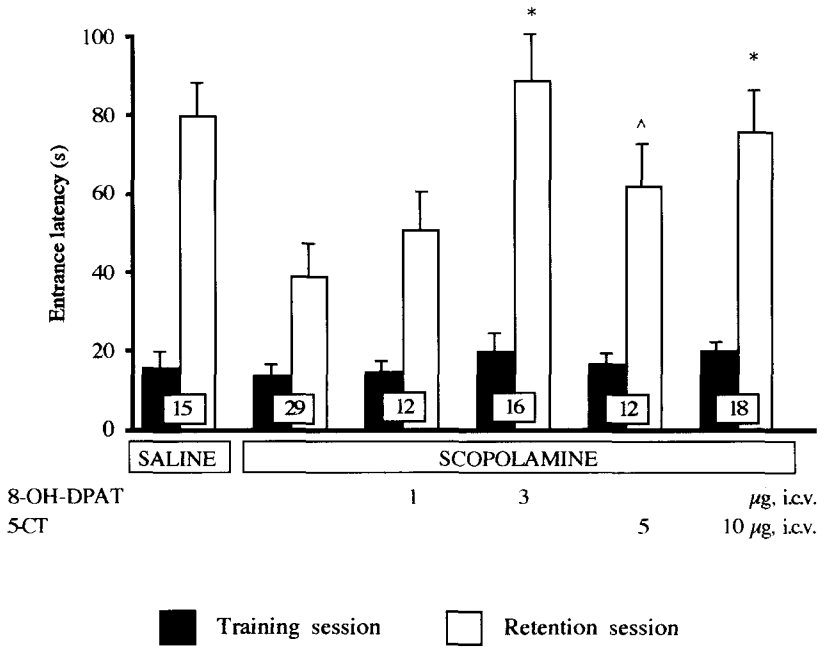

Fig. 3. Effect of 8-OH-DPAT and 5-CT on amnesia induced by scopolamine (1 mg/kg, i.p.) in the mouse passive avoidance test. 8-OH-DPAT and 5-CT were administered 20 min before the training session. The number of mice is given inside the column. $^P<0.05$, $*P<0.01$, in comparison with mice treated with scopolamine.

15 min after administration. The motor coordination of animals pretreated with both 5-HT_{1A} agonists and antagonists, which was evaluated using the rota-rod test, was not significantly impaired in comparison with saline-treated mice (data not shown). Each group progressively reduced its number of falls since mice learned how to balance on the rotating rod.

The spontaneous motility and inspection activity of mice was unmodified by pretreatment with all investigated 5-HT_{1A} modulators at the highest effective doses as revealed by the Animex apparatus and the hole-board test (data not shown) in comparison with saline-treated mice. In the experimental conditions used to perform the hole-board test, D-amphetamine (2 mg/kg, s.c.) increased both evaluated parameters.

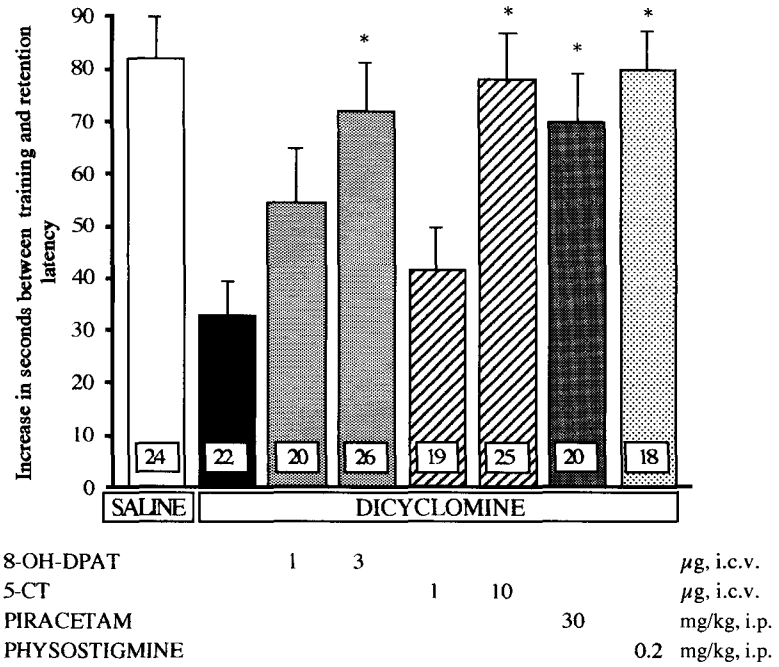

Fig. 4. Effect of 8-OH-DPAT and 5-CT in comparison with both piracetam and physostigmine on amnesia induced by dicyclomine (2 mg/kg, i.p.) in the mouse passive avoidance test. 8-OH-DPAT, 5-CT, piracetam and physostigmine were administered 20 min before the training session, and dicyclomine was injected immediately after punishment. The number of mice is given inside the column. *$P<0.01$, in comparison with dicyclomine-treated mice.

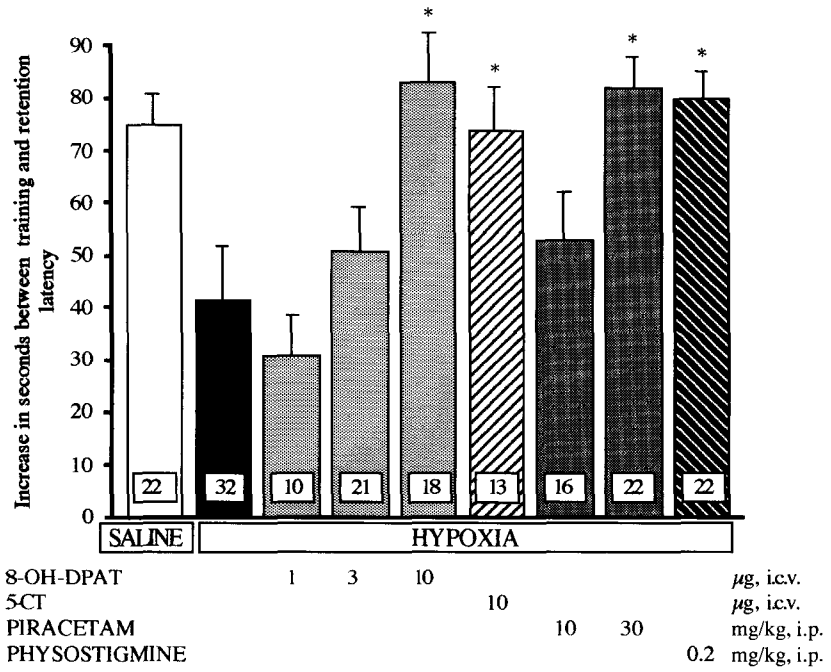

Fig. 5. Effect of 8-OH-DPAT and 5-CT in comparison with both piracetam and physostigmine on amnesia induced by hypoxia (O_2 5% + N_2 95%) in the mouse passive avoidance test. 8-OH-DPAT, 5-CT, piracetam and physostigmine were administered 20 min before training. Mice were submitted to hypoxia immediately before punishing. The number of mice is given inside the column. *$P<0.01$, in comparison with mice subjected to hypoxia.

DISCUSSION

5-HT_{1A}-receptors appear to be involved in the regulation of cognitive processes in mice. Our results demonstrate that the administration of 5-HT_{1A}-receptor antagonists (NAN-190 and WAY-100635) provoke amnesia in the mouse passive avoidance test of severity to a level comparable to that induced by the amnesic drugs scopolamine and dicyclomine. There are some controversial data on the effect of NAN-190 on memory processes in the literature. Controversial results have been obtained in not only the induction of amnesia, but also the absence of any effect in various behavioral tasks (17, 20, 24, 25). The present results elucidate the effects produced by blockade of 5-HT_{1A}-receptors. The amnesic activity of NAN-190 was, in fact, confirmed and, by extending the investigation to another 5-HT_{1A}-receptor antagonist (WAY-100635), we assessed that the induction of amnesia was a general effect obtained by blockade of 5-HT_{1A}-receptors.

In the present study, an improvement of memory processes by activation of by 5-HT_{1A}-receptor was also observed. The 5-HT_{1A}-receptor agonists (8-OH-DPAT and 5-CT) prevented the amnesia induced not only by 5-HT_{1A}-receptor antagonists, but also by antimuscarinic drugs and exposure to a hypoxic environment. Previous data, demonstrating that the stimulation of 5-HT_{1A}-receptors reverse the impairment of memory processes caused by scopolamine in a spatial learning paradigm in rats (26) as well as in an operant delayed matching to position task (17), are in agreement with our results. Furthermore, it has been reported that 8-OH-DPAT enhances learning when administered 15, 20 and 30, but not 40 and 120 min before the training session (27 – 29).

However, there are also some studies in which an impairment of memory processes induced by stimulation of 5-HT_{1A} receptors is reported. The injection of 8-OH-DPAT into the hippocampal CA1 region impairs acquisition and retention in a spatial discrimination task which is blocked by spiroxatrine (30, 31). By contrast, *p*-clorophenylalanine, a serotonin depletor, had no effect (2, 32), indicating that postsynaptic 5-HT_{1A}-receptors may mediate the impairment induced by 8-OH-DPAT. There are also some reports indicating that the effects on learning and memory produced by 8-OH-DPAT are eliminated by pretreatment with *p*-clorophenylalanine (20, 33, 34) suggesting that both pre- and post-synaptic 5-HT_{1A} receptors participate in the modulation of memory processes, even if by producing different effects.

The discrepancy might be due to the wide-spread presence of 5-HT_{1A}-receptors in various brain regions. In contrast to the synaptic release of 5-HT, pharmacological application of an agonist will activate or inhibit various polysynaptic loops that affect memory or other behavioural features in a synergistic or opposite way.

The antiamnesic effect produced by 8-OH-DPAT and 5-CT might indicate that, in our experimental condition and in the range of concentrations used in the present study, the two 5-HT_{1A}-receptor agonists act presynaptically. It has been reported that activation of 5-HT_{1A}-receptors increases ACh release in freely moving guinea pigs (35) and in conscious rats (36). Since it has long been known that the stimulation of the cholinergic system improves cognitive processes (37), the facilitatory effect induced by 5-HT_{1A} agonists 8-OH-DPAT and 5-CT could be due, at least in part, to activation of the cholinergic system. To further support this hypothesis, it should be observed that both 5-HT_{1A} agonists prevent amnesia induced by the antimuscarinic drugs scopolamine and dicyclomine. Moreover, 8-OH-DPAT and 5-CT prevent amnesia induced by exposure to a hypoxic environment, a condition of impaired memory in which ACh releasers show antiamnesic properties (38).

The 5-HT_{1A} receptor agonists have been reported to be endowed with analgesic properties (39). In our experimental conditions, these compounds were administered before receiving the punishing stimulus in correspondence with their maximum antinociceptive activity. It is, however, unlikely that their analgesic effect may have influenced the results obtained. Analgesic drugs, by reducing the perception of the punishing stimulus (electric shock), may produce a false amnesic effect. 8-OH-DPAT and 5-CT, even at the highest doses used, were always able to prevent amnesia, indicating that the degree of antinociception produced was insufficient to reduce the perception of the electric shock applied.

The 5-HT_{1A}-receptor agonists and antagonists, at the highest doses used, did not modify the animals' gross behavior. Nor did these compounds impair motor coordination as revealed by the rota rod test or modify locomotor and inspection activity as indicated by the hole board and Animex tests. We can, thus, suppose that the effects produced by 5-HT_{1A}-receptor modulators were not imputable to compromised viability. Higher doses of all compounds were not investigated since the maximum amnesic (NAN-190, WAY-100635) and antiamnesic (8-OH-DPAT, 5-CT) effect was already reached.

In conclusion, these results confirm the important role played by 5-HT_{1A}-receptors in the regulation of memory processes.

Acknowledgments

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