Pharmacology Biochemistry and Behavior, Vol. 63, No. 2, pp. 221–227, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00229-9

Combined Action of Thioperamide Plus Scopolamine, Diphenhydramine, or Methysergide on Memory in Mice

LUIGI MOLINENGO,[1] GIOVANNI DI CARLO AND PIERA GHI

Dipartimento di Anatomia, Farmacologia e Medicina Legale, Sezione di Farmacologia, Via Giuria 9 10125 Torino, Italy

Received 10 February 1998; Revised 10 November 1998; Accepted 10 November 1998

MOLINENGO, L., G. DI CARLO AND P. GHI. *Combined action of thioperamide plus scopolamine, diphenhydramine, or methysergide on memory in mice*. PHARMACOL BIOCHEM BEHAV **63**(2) 221–227, 1999.—The aim of the present experiments was to test the role played by the interaction of the selective H_3 receptor antagonist, thioperamide, with the cholinergic, histaminergic, and serotonergic systems in modifying memory. The behavioral tests used (open-field and passive-avoidance repetition) were selected on the basis of the action displayed by thioperamide in these behavioral situations. Posttrial administration of thioperamide (5 mg/kg) resulted in an improvement in memory consolidation, as tested in the repetition of the open-field test, but repeated posttrial administration of thioperamide (2 or 5 mg/kg) had no effect in the repetition of passive avoidance test. Scopolamine (2 mg/kg) caused a deterioration in the memory processes in both tests; this effect was blocked by 2 mg/kg of thioperamide, which was itself ineffective in the test. These results may suggest that both the improvement in memory due to thioperamide and its antagonism of the amnestic effects of scopolamine are determined by activation of central cholinergic systems, due to thioperamide inhibition of H_3 heteroreceptors. Diphenhydramine (2 or 10 mg/kg) was itself ineffective in the tests, but counteracted the memory improvement caused by thioperamide in the repetition of the open-field test. The effect of diphenhydramine is discussed in terms of interactions between histaminergic and cholinergic systems. Methysergide counteracted the effect of thioperamide in the open-field test only at a high dosage (50 mg/kg). The possible implication of serotonergic systems on the effects of the methysergide–thioperamide interaction in the memory process is discussed. © 1999 Elsevier Science Inc.

Memory process Open field Passive avoidance Thioperamide Scopolamine Diphenhydramine Methysergide

THERE is evidence that the interaction of drugs with H_3 receptors modifies animal behavior in cognitive tests. Thioperamide, a selective H_3 receptor antagonist (3), improves short-term memory and reversal learning (5), improves learning and memory in SAM-P/8 mice (21), blocks the decay of memory storage seen in controls (23), and improves memory consolidation in rats tested in the habituation of exploratory activity (11). The H_3 receptor agonists, (R)-alfa methyl histamine and imetit, impair object recognition and the passive avoidance response (4).

H_3 receptor activation inhibits histamine release in the CNS, and the H_3 antagonist, thioperamide, causes a histamine release (3,14). Intracerebral administration of histamine results in memory facilitation on step-down inhibitory avoidance behavior (7), and Kamei et al. (19) observed that the decrease in CNS histamine content caused by administration of alfa fluoro methyl histidine, a histidine decarboxylase inhibitor, is correlated with a reduction in the acquisition of avoidance responses in the rat.

Thus, the improvement in cognitive processes seen with thioperamide may be caused by the increase in CNS histamine levels as a result of H_3 receptors inhibition. However, it should be noted that H_3 receptors also function as presynaptic heteroreceptors controling the release of serotonin (9), acetylcholine (6), and several other neurotransmitters (29,30).

The present study was designed to evaluate the role played by the cholinergic, histaminergic, and serotonergic systems in the cognitive effects induced by thioperamide. The results

[1]Requests for reprints should be addressed to L. Molinengo, Universita Degli Studi Di Torino, Sezione di Farmacologia, Dipartimento di Anatomia, Farmacologia e Medicina Legale, Via Giuria 9, 10125 Torino, Italy.

may contribute to a better evaluation of the physiological significance of the effects of thioperamide on memory processes.

METHOD

Subjects

A total of 700 male albino mice (25–30 g) were used. The animals were obtained from Morini Laboratories (San Polo d'Enza, Italy) in groups of 100, and were not used for experiments for at least 10 days following their arrival. The mice were housed 10 per cage and allowed free access to food and water. The animal experiments were conducted in conformity with our institution's guidelines, which conform to national and international laws and policies (EEC Council Directive 86/609,OJL 358 1 December 12, 1987).

Behavioral Tasks

Habituation of exploratory activity. An open field was used, consisting of a rectangular base (72 × 5 cm), surrounded by a 30 cm-high wall, the floor of the field being divided into 9-cm squares. Illumination was provided by a 100-watt lamp, suspended 500 cm above the center of the field. The observer sat at a desk at the edge of the field and recorded the total number of squares crossed in the 3 min the experiment lasted.

Each mouse was tested twice in the open field on successive days. Drugs were given intraperitoneally within 1 min after the end of the first test performed. To evaluate the modifications caused by test repetition, the percentage difference between the number of squares crossed on the first and second days was calculated. No less than 10 mice per group were used.

Passive avoidance. The procedure described by Meguro et al. (21) was followed with minor modifications.

The step-through passive-avoidance response was examined between 0900 and 1100 h on each day. The apparatus consisted of two compartments, one (15 × 25 cm, height 25 cm) being illuminated by a 60-W and the other (30 × 30 cm, height 25 cm, with a grid floor) not illuiminated. The two compartments were separated by a guillotine door (5 × 5 cm). When the mice were placed in the illuminated compartment, they escaped into the dark compartment, and when all four paws were on the grid, a constant current (0.08 mA, constant voltage 120 V, 50 Hz) was delivered through a scrambler (Grason & Stadler Co.) to the grid for 3 s. The mice were then returned to their home cages.

The passive-avoidance learning test was repeated on the second, third, and fourth days, and the response latency before entering the dark compartment measured in seconds. The latency value of 300 s was assigned when animals did not enter the dark compartment within 300 s. Drugs were administered intraperitoneally within the 2 min following each passive-avoidance test. No less than 10 mice per group were used.

Drugs

Thioperamide maleate (Tocris Cookson, Ltd, Bristol, UK) was dissolved in 1 M HCl, diluted, and adjusted to pH 7.00 using 100 mM sodium bicarbonate.

Scopolamine hydrochloride, diphenhydramine hydrochloride (Sigma–Aldrich S.r.l., Milano, Italy) and methysergide maleate (RBI–Amersham Italia S.r.1., Milano, Italy) were dissolved in 0.9% w/v saline. All drugs were injected intraperitoneally.

Statistics

One-way analysis of variance was used to evaluate the significance of the differences between the data obtained in the habituation of exploratory activity test. For individual post hoc comparison with the controls, Dunnett's test and the Student's *t*-test were used.

Following the methods used by Sasaki et al. (28) and Meguro et al. (21), the data obtained in the passive-avoidance test were expressed as the mean ± SE. The Mann–Whitney test was used to determine whether the medians of two populations differed significantly.

For all statistical tests a value of $p < 0.05$ was considered significant.

RESULTS

Effects of Thioperamide

The open-field test values were expressed as a percentage reduction in the number of squares crossed on the second day compared to the squares crossed on the first day. The results for control animals and animals given thioperamide (2 or 5 mg/kg) are shown in Fig. 1A ($n = 12$ per group).

The Analysis of variance indicated that the differences between the three experimental groups (controls and 2 and 5 mg/kg of thioperamide) were significant, $F(2, 33) = 6.15$, $p < 0.05$. The Dunnett's test for comparison with a control indicated that the increased percentage reduction in squares crossed in the second trial was only significant ($p < 0.05$) for the group given 5 mg/kg of thioperamide.

In the passive avoidance test, the Mann–Whitney test indicated that the administration of thioperamide at the end of trials performed on 4 successive days caused no modification ($n_1/n_2 = 10/10$, $U > 35$, $p > 0.05$) in mouse behavior (Fig. 2A).

Administration of Scopolamine Alone or in Combination With Thioperamide

Figure 1B shows open-field test results for control mice and mice given either 0.1 or 2 mg/kg of scopolamine, either alone or in combination with 2 and 5 mg/kg of thioperamide.

In the absence of thioperamide, analysis of variance indicated that the differences between the three experimental groups ($n = 15$ per group) were significant, $F(2, 42) = 7.25$, $p < 0.05$. The Dunnett's test showed a significant difference ($p < 0.05$) only at the dose of 2 mg/kg of scopolamine. No difference was seen, compared with controls, when scopolamine was given in combination with thioperamide (Fig. 1B). Student's *t*-test indicated a significant difference between the means obtained after administration of 5 mg/kg of thioperamide alone or in combination with 0.1 or 2 mg/kg of scopolamine ($p < 0.01$). These results indicate that both doses of scopolamine antagonized the effect seen using 5 mg/kg of thioperamide.

In the repetition of the passive-avoidance test ($n = 10$ per group) the low doses of scopolamine (0.1 mg/kg) (Figure 2B) only caused a reduction in latency (Mann–Whitney test, $n_1/n_2 = 10/10$, $U = 5$, $p < 0.05$) after the fourth repetition of the trial; this effect was lost when scopolamine was combined with thioperamide (2 or 5 mg/kg).

At the higher dose of scopolamine (2 mg/kg) (Fig. 2C) the reduction in latency was significant (Mann–Whitney test, U always less than 4.5, $p < 0.05$, $n_1/n_2 = 10/10$) in the second, third, and fourth repetition of the trial. Again, when thioperamide (2 or 5 mg/kg) was given together with this dose of scopolamine the effect was lost.

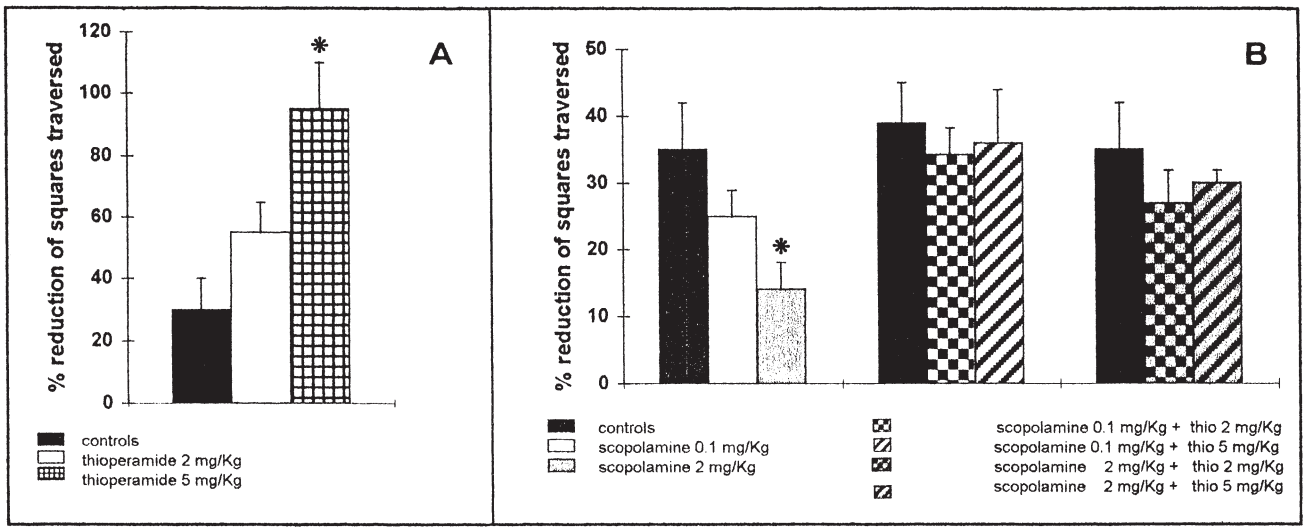

FIG. 1. Open-field repetition test. Effect of thioperamide alone (A), of scopolamine alone, or in combination (B). The results are expressed as the mean and SE of the percentage reduction in the squares crossed between the first and the second trials. *$p < 0.05$ (Dunnett's test).

Administration of Diphenhydramine (a Histamine H_1 Receptor Antagonist) Alone or in Combination With Thioperamide

In the open-field test (Fig. 3B), diphenhydramine (2 or 10 mg/kg) either alone or in combination with the same two doses of thioperamide, caused no modification of behavior ($n = 10$ per group. Dunnett's test for comparison with a control $p >$ 0.1). Student's *t*-test indicated that the differences between the means obtained using 5 mg/kg of thioperamide alone ($n =$ 12) or in combination with 2 or 10 mg/kg of diphenhydramine ($n = 10$ per group) were significant ($p < 0.05$). These results indicate that, in this test, diphenhydramine, at doses that were themselves inactive, counteracted the effect caused by 5 mg/kg of thioperamide.

In the passive-avoidance test the results obtained with diphenhydramine alone or in combination with thioperamide (Fig. 4B and C) did not differ from the control results (Mann–Whitney test, *U* always over 45, $p > 0.05$, $n_1/n_2 = 10/10$).

Administration of Methysergide Alone or in Combination With Thioperamide

The results obtained in the open-field test indicated that methysergide alone (5 and 50 mg/kg; $n = 10$ per group) caused no modification of behavior (Fig. 5B). Analysis of variance indicated that the difference between the results obtained in the controls ($n = 10$) and in the groups treated with methysergide 5 mg/kg in combination with thioperamide 2 and 5 mg/kg ($n = 10$ per group) were significant, $F(2, 27) =$ 8.45, $p < 0.05$. Dunnett's test indicated as significant ($p <$ 0.05) the difference between the results obtained in the controls and in the group treated with the combination of thio-

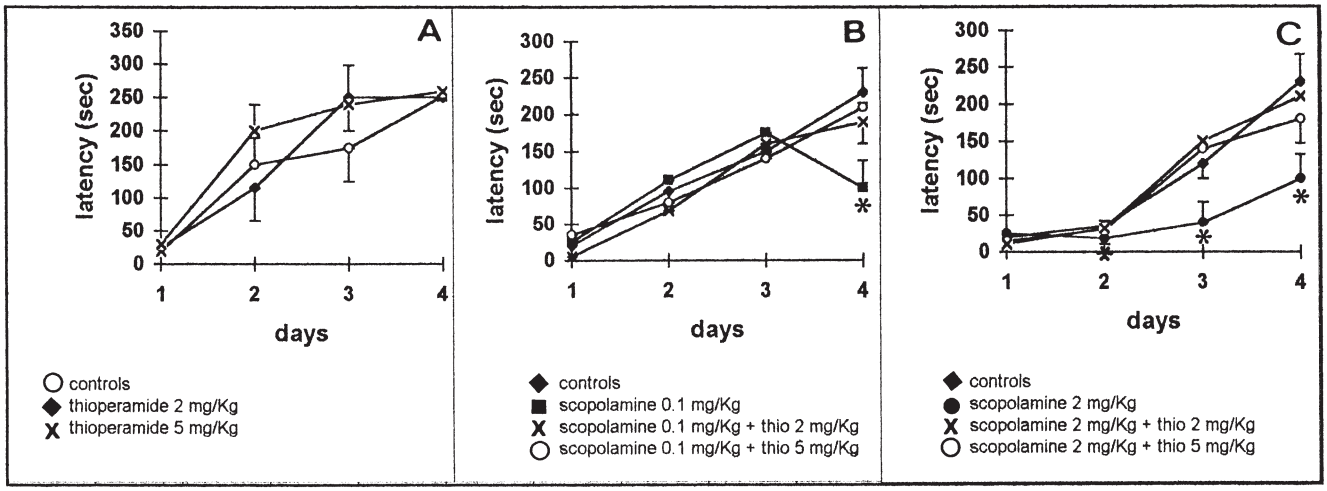

FIG. 2. Latencies in the passive avoidance repetition test after administration of thioperamide (A), scopolamine (B), and combinations (C). The results are expressed as the mean and SE of the latencies measured in four successive trials. *$p < 0.05$ (Mann–Whitney test).

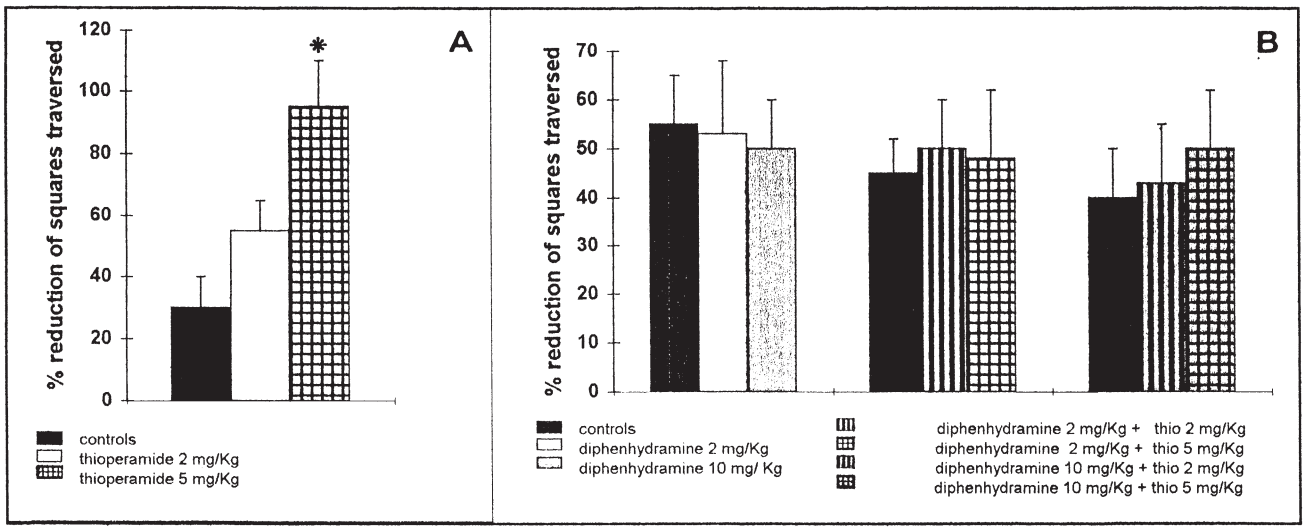

FIG. 3. Open-field repetition test. Effects of thioperamide alone (A), of diphenhydramine alone, or in combination (B). The results are expressed as the mean and SE of the percentage reduction in the squares crossed between the first and the second trials. *$p < 0.05$ (Dunnett's test).

peramide 5 mg/kg plus methysergide 5 mg/kg, but the combination of methysergide 50 mg/kg with the two doses of thioperamide caused no modification in the open-field test (Fig. 5B). These results suggest that only the dose of 50 mg/kg of methysergide was able to antagonize the effect of 5 mg/kg of thioperamide. This was confirmed by Student's *t*-test, in which no difference was found between the means when thioperamide (5 mg/kg) was used alone ($n = 12$) or in combination with 5 mg/kg of methysergide ($n = 10$), whereas there was a significant difference ($p < 0.05$) between the means for thioperamide (5 mg/kg) alone or in combination with 50 mg/kg of methysergide ($n = 10$).

The administration of methysergide (5 or 50 mg/kg) either alone or in combination with either doses of thioperamide ($n = 15$ per group) caused no significant change in latency (Mann–Whitney test, U always greater than 80, $p > 0.05$) (Fig. 6B and C).

DISCUSSION

Repetition of the open-field test makes it possible to evaluate drug effects on the habituation of exploratory activity, which provides a valid model of memory processes (16,25,26).

The results obtained show that thioperamide caused an increase in the reduction of squares crossed, suggesting that this histamine H_3 receptor antagonist caused an improvement in memory consolidation. This observation is in agreement with our previous results (11,23), and with the results of other authors (5). It should be noted that these effects on cognition function caused by thioperamide were observed when the animals were tested in a situation that did not induce painful stimulation, whereas in a test that did induce stressful stimulation, i.e., the step-through passive-avoidance test, thioperamide was ineffective. This observation is in agreement with the results obtained by Meguro et al. (21) in normally aged mice (SAM-R/1).

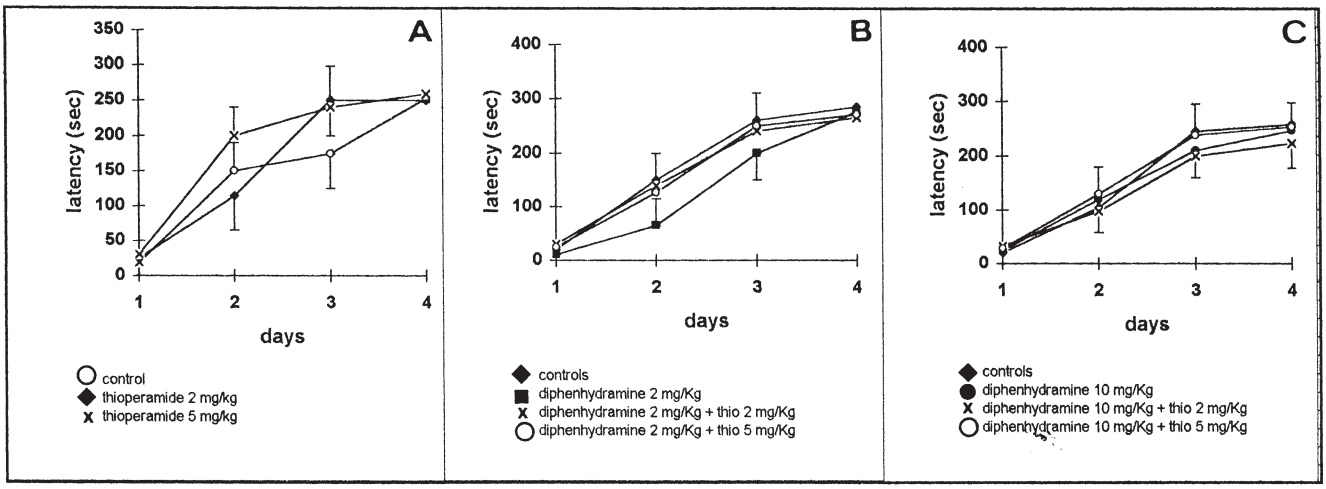

FIG. 4. Latencies in the passive avoidance repetition test after administration of thioperamide (A), diphenhydramine (B), and combinations (C). The results are expressed as the mean and SE of the latencies measured in four successive trials.

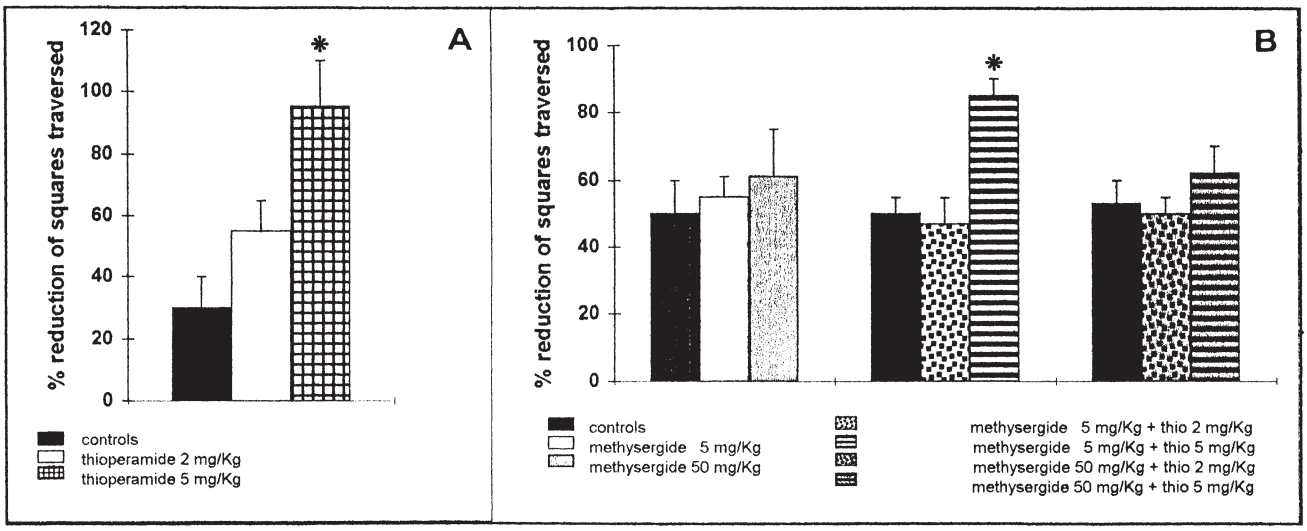

FIG. 5. Open-field repetition test. Effects of thioperamide alone (A), methysergide alone, or in combination (B). The results are expressed as the mean and SE of the percentage reduction in the squares crossed between the first and the second trials. $*p < 0.05$ (Dunnett's test).

Compared with controls, the administration of scopolamine (2 mg/kg) after the first trial in the open-field test caused an increase in the number of squares crossed in the second trial. The percentage difference between the results obtained in the two trials was lower, suggesting that scopolamine had an amnestic effect at this dosage.

In the repetition of the passive avoidance test, 2 mg/kg of scopolamine caused a shortening of the latency in the second, third, and fourth repetition, while, at a lower dose (0.1 mg/kg), this effect was only seen in the fourth trial, suggesting that the lower dose of scopolamine, given for 4 successive days, displayed some form of cumulative effect.

This deterioration in behavior caused by scopolamine in the two tests is interpreted, in agreement with published data (8,31), as the consequence of damage to memory processes. This amnestic effect of scopolamine was counteracted by thioperamide in the open-field test by doses of the histamine H_3 receptor antagonist (2 mg/kg) that were themselves ineffective. In the passive-avoidance test, the behavior of mice treated with the combination of thioperamide plus scopolamine did not differ from that of controls, indicating that thioperamide, at doses that were themselves ineffective in the test counteracted the amnestic effect of the anticholinergic scopolamine.

Considering that there is evidence that thioperamide enhances acetylcholine release in a concentration-dependent manner (6), and that the receptor agonists, imetit and R α-methyl histamine, reduce the evoked release of cortical acetylcholine (4), it may be inferred that the action of thioperamide on cognitive function and its antagonism of the effects of scopolamine are determined by its interference with cholinergic systems that appear to have a prominent role in cognitive processes (4,8,24).

It should also be noted that, in the passive-avoidance test thioperamide was ineffective, but counteracted the memory

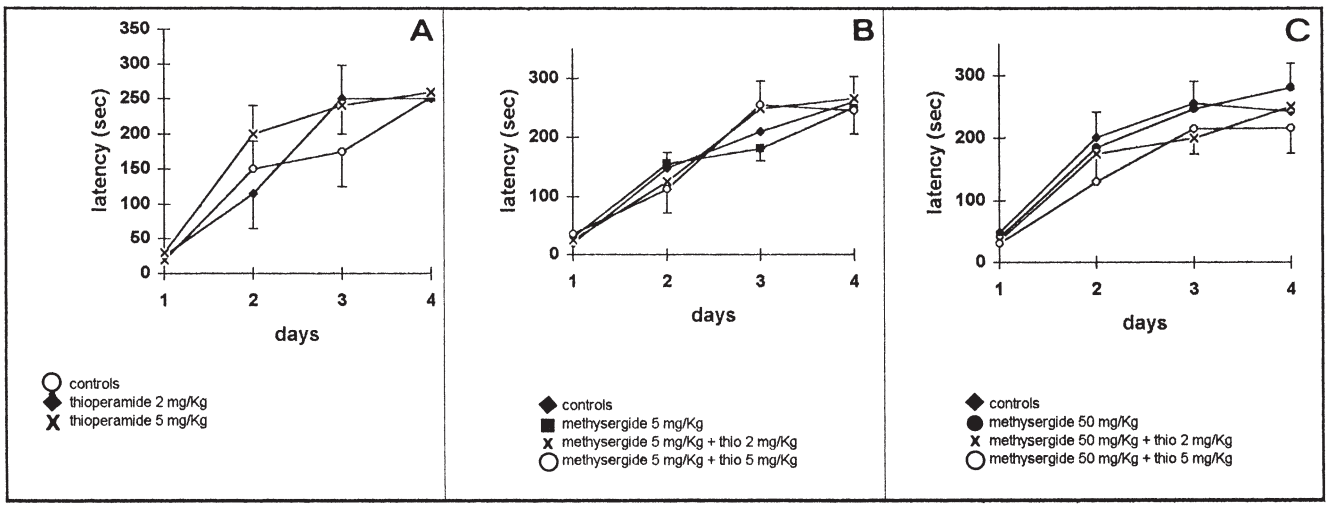

FIG. 6. Latencies in the passive avoidance repetition test after administration of thioperamide (A), of methysergide (B), and combination (C). The results are expressed as the mean and SE of the latencies measured in four successive trials.

deterioration seen after administration of scopolamine. This observation is in agreement with the report by Meguro et al. (21) that thioperamide improves the behavior of mice in the repetition of passive avoidance test only in the case of senescence-accelerated mice (SAM-P/8) that show impairment of learning and memory when compared with normal mice of the same age. These observations may suggest that, at least in certain forms of memory, thioperamide displays a favorable effect only if the cognitive process is damaged.

To assess the role played by the histaminergic system in the behavioral action of thioperamide, we studied the histamine H_1 receptor antagonist, diphenhydramine, either alone or in combination with thioperamide. In the repetition of the open-field and passive-avoidance tests, diphenhydramine was ineffective. These results appear to disagree with those of Kamei et al. (17). It must be noted, however, that in our experiments the histamine H_1 receptor antagonist was administered immediately after the training test, and the animals were tested 24 h after drug administration, whereas in the experiment of Kamei et al. (17), in which diphenhydramine had a clear behavioral effect, the histamine H_1 receptor antagonist was administered 15 min before the trials.

With the diphenhydramine/thioperamide combination, the histamine H_1 receptor antagonist abolished the improvement in memory caused by 5 mg/kg of thioperamide in the repetition of the open-field test. This observation may suggest that activation of central histaminergic systems, due to thioperamide inhibition of H_3 receptors, plays an active part in facilitation memory processes. It should be noted that De Almeida and Izquierdo (7) have shown that histamine enhances memory in a step-down inhibitory avoidance task. Using an active avoidance test, Kamei and Tasaka (18) observed that histamine reversed a retarded avoidance response induced by H_1 receptor antagonists. It should be noted that acetylcholine also reversed the histamine H_1 receptor antagonist-induced inhibition of avoidance responding. An interaction between central histaminergic and cholinergic systems has also been reported by Decker and McGaugh (8) and Miyasaki et al. (22). Thus, it may be suggested that, at least in part, the memory improvement caused by thioperamide is determined by an interaction between the histaminergic and cholinergic systems.

There are indications that drugs interfering with central serotonergic systems exert effects on memory processes. Activation of H_3 heteroreceptors by either histamine or (R)-alfa-Methyl-histamine inhibits serotonin release (9). Harder et al. (12) reported that *p*-chlorophenylalanine (pCPA), an activator of H_3 receptors, in combination with low doses of atropine or scopolamine, produces a significant deficit in acquisition in a water-maze task. In this experimental situation, pCPA causes a significant decrease in serotonin levels. These results are in agreement with the observation that the combination of a serotonin synthesis inhibitor with atropine (27) produces a marked deficit in a spatial learning task. Taken together, these results suggest that a reduction in the activity of serotonergic systems produces a deficit in memory tests, and it may be inferred that the improvement in memory processes seen with thioperamide is determined by the increased output of serotonin resulting from thioperamide action on H_3 heteroreceptors (9). Thus, it should be expected that serotonergic antagonists may produce a deficit in memory tests. This conclusion is in agreement with our results indicating that methysergide antagonized the improvement of memory caused by thioperamide in the repetition of the open-field test.

Methysergide is certainly not selective for a specific subtype of serotonergic receptor, but it is of particular interest because of its therapeutic use (12) and considering that there is evidence that methysergide significantly improves performance in a visual memory task in a group of Korsakoff amnesic (20).

These observations suggesting that a serotonergic receptor antagonist can improve memory are in agreement with several reports indicating that different serotonergic antagonists display a similar effect in experimental animals (1,15,20), but conflict with the results we obtained with the thioperamide/methysergide combination and do not support the hypothesis that the behavioral improvement caused by thioperamide in the repetition of the open-field test is determined by increased output of serotonin due to its inhibitory action on H_3 heteroreceptors (9).

The active dose of methysergide that blocked the thioperamide effect was high (50 mg/kg), and side effects may be implied. Nevertheless, it should be noted that methysergide alone produced no behavioral modification in the two experimental tests we used, making it difficult to assume that it was the side effects of methysergide that interfered with behavior. It should also be noted that Fontana et al. (10) reported that cognition enhancing properties are only seen with the (R)-enantiomer of zacopride, and concluded that its action is unrelated to serotonin receptor antagonism. Moreover, Altman et al. (2) observed different temporal effects of serotonergic antagonists on passive-avoidance retention.

The possibility cannot be excluded that all these discrepancies may be determined by a multiplicity of serotonin receptors with different physiological roles (13) although side effects of serotonergic antagonists interfering with the cognitive actions displayed by these compounds should also be considered.

ACKNOWLEDGEMENTS

This research was supported by grants from MURST (Ministero Italiano dell'Universita' e Ricerca Scientifica e Tecnologica) 40% and 60% 1996.

REFERENCES

1. Altman, H. J.; Normile, H. J.: Enhancement of the memory of previously learned aversive habit following pre-test administration of a variety of serotonergic antagonists in mice. Psychopharmacology (Berlin) 90:24–27; 1986.
2. Altman, J. H.; Normile, H. J.: Different temporal effects of serotonergic antagonists on passive avoidance retention. Pharmacol. Biochem. Behav. 28:353–359; 1987.
3. Arrang, J. M.; Garbarg, M.; Lancelot, J. C.; Lecompte, J. M.; Pollard, A.; Robba, M.; Schunack, W.; Schwartz, J. C.: Highly potent and selective ligands for histamine H_3-receptors. Nature 327:117–123; 1987.
4. Blandina, P.; Giorgetti, M.; Bartolini, L.; Cecchi, M.; Timmerman, H.; Leurs, R.; Pepeu, G.; Giovannini, M. G.: Inhibition of cortical acetylcholine release and cognitive performance by histamine H_3 receptor activation in rats. Br. J. Pharmacol. 119:1656–1664; 1996.
5. Clapham, R. P.; Dennes, G. J.; Kilpatrick, G.; Barnes, J. C.: Ability of the selective histamine H_3 receptor antagonist thioperamide to improve short-term memory and reversal learning in the rat. Br. J. Pharmacol. 110:1P–186P; 1993.
6. Clapham, J.; Kilpatrick, G. J.: Histamine H_3 receptors modulate the release of [^{3}H]-acetylcholine from slices of rat entorhinal cor-

tex: Evidence for the possible existence of H_3 receptor subtypes. Br. J. Pharmacol. 107:919–923; 1992.
7. De Almeida, M. A.; Izquierdo, I.: Memory facilitation by histamine. Arch. Int. Pharmacodyn. Ther. 283:193–198; 1986.
8. Decker, M. W.; McGaugh, J. L.: The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. Synapse 7:151–168; 1991.
9. Fink, K.; Schlinker, E.; Neise, A.; Gothert, M.: Involvement of presynaptic H_3 receptors in the inhibition effect of histamine on serotonin release in the rat brain cortex. Naunyn Schmiedebergs Arch. Pharmacol. 342:513–519; 1990.
10. Fontana, D. J.; Scott, E. D.; Eglen, R. M.; Wong, E. H. F.: Stereoselective effects of (R)- and (S)-zacopride on cognitive performance in spatial navigation task in rats. Neuropharmacology 35:321–327; 1996.
11. Ghi, P.; Di Carlo, G.; Molinengo, L.: Effects of thioperamide on locomotor activity and on memory processes. Prog. Neuropsychopharmacol. Biol. Psychiatry 22:387–395; 1998.
12. Harder, J. A.; Kelly, M. E.; Cheng, C. H. K.; Costall, B.: Combined pCPA and muscarinic antagonist treatment produces a deficit in rat water maze acquisition. Pharmacol. Biochem. Behav. 55:61–65; 1996.
13. Hardman, J. G.; Limbird, L. E., ed.: Goodman & Gilman's The pharmacological basis of therapeutics. New York: McGraw-Hill; 1996:260–261.
14. Hill, S. J.: Distribution, properties, and functional characteristics of three classes of histamine receptor. Pharmacol. Rev. 42:45–83; 1990.
15. Hodges, H.; Sowinski, P.; Turner, J. J.; Fletcher, A.: Comparison of the effects of 5-HT_3 receptor antagonists WAY-100579 and ondansetron on spatial learning in the water maze in rats with excitotoxic lesions of the forebrain cholinergic projection system. Psychopharmacology (Berlin) 125:146–161; 1996.
16. Izquierdo, I.; Pereira, M. E.; Medina, J. H.: Benzodiazepine receptor ligand influences on acquisition: Suggestion of an endogenous modulatory mechanism mediated by benzodiazepine receptors. Behav. Neurol. Biol. 54:27–41; 1990.
17. Kamei, C.; Chung, Y. H.; Tasaka, K.: Influence of certain H_1-blockers on the step-through active avoidance response in the rat. Psychopharmacology (Berlin) 102:312–318; 1990.
18. Kamei, C.; Tasaka, K.: Participation of histamine in the step-through active avoidance response and its inhibition by H_1-blockers. Jpn. J. Pharmacol. 57:473–482; 1991.
19. Kamei, C.; Okumura, Y.; Tasaka, K.: Influence of histamine depletion on learning and memory recollection in rats. Psychopharmacology (Berlin) 111:376–382; 1993.
20. McEntee, W. J.; Crook, T. H.: Serotonin, memory, and the aging brain. Psychopharmacology (Berlin) 103:143–149; 1991.
21. Meguro, K.; Yanai, K.; Sakai, N.; Sakurai, E.; Maeyamama, K.; Sasaki, H.; Watanabe, T.: Effects of thioperamide, a histamine H_3 antagonist, on step-through passive avoidance response and histidine decarboxylase activity in senescence-accelerated mice. Pharmacol. Biochem. Behav. 50:321–325; 1995.
22. Miyazaki, S.; Imaizumi, M.; Onodera, K.: Ameliorating effects of histidine on scopolamine-induced learning deficits using an elevated plus-maze test in mice. Life Sci. 56:1563–1570; 1995.
23. Molinengo, L.; Ghi, P.: Effects of thioperamide on "memory storage" in rats. Med. Sci. Res. 25:351–352; 1997.
24. Orsetti, M.; Casamenti, F.; Pepeu, G.: Enhanced acetylcholine release in hippocampus and cortex during acquisition of an operant behavior. Brain Res. 724:89–96; 1996.
25. Platel, A.; Porsolt, R. D.: Habituation of exploratory activity in mice: A screening test for memory enhancing drugs. Psychopharmacology (Berlin) 78:346–352; 1982.
26. Platel, A.; Jalfre, M.; Pawelec, C.; Roux, S.; Porsolt, R. D.: Habituation of exploratory activity in mice: Effects of combination of piracetam and choline on memory processes. Pharmacol. Biochem. Behav. 21:209–212; 1984.
27. Richter-Levin, G.; Segal, M.: Spatial performance is severely impaired in rats with combined reduction of serotonergic and cholinergic transmission. Brain Res. 477:404–407; 1989.
28. Sasaki, H.; Yanai, M.; Meguro, K.; Sekizawa, K.; Ikarashi, Y.; Maruyama, Y.; Yamamoto, M.; Matsuzaki, Y.; Takishima, T.: Nicotine improves cognitive disturbance in rodents fed with a choline-deficient diet. Pharmacol. Biochem. Behav. 38:921–925; 1991.
29. Schlicker, E.; Fink, K.; Detzer, M.; Gothert, M.: Histamine inhibits dopamine release in the mouse striatum via presynaptic H_3 receptors. J. Neural Transm. Gen. Sect. 93:1–10; 1993.
30. Schlicker, E.; Kathmann, M.; Detzer, M.; Exner, H. J.; Gothert, M. H.: H_3 receptor-mediated inhibition of noradrenaline release: An investigation into the involvement of Ca^{++} and K^+ ions and adenylate cyclase. Naunyn Schmiedebergs Arch. Pharmacol. 350:34–41; 1994.
31. Squire, L. R.; Dvis, H. P.: The pharmacology of memory: A neuro biological perspective. Annu. Rev. Pharmacol. Toxicol. 21:326–356; 1981.