Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, No. 4, pp. 929-934, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00083-6

NS-3(CG3703), a TRH analog, Ameliorates Scopolamine-Induced Memory Disruption in Rats

TAKASHI OGASAWARA, YUTAKA NAKAGAWA, YOJIRO UKAI,[1]
MASARU TAMURA AND KIYOSHI KIMURA

Research Laboratories, Nippon Shinyaku Co., Ltd., Nishiohji-Hachijo, Minamiku, Kyoto 601, Japan

Received 25 July 1994

OGASAWARA, T., Y. NAKAGAWA, Y. UKAI, M. TAMURA AND K. KIMURA. *NS-3 (CG3703), a TRH analog, ameliorates scopolamine-induced memory disruption in rats.* PHARMACOL BIOCHEM BEHAV **51**(4) 929-934, 1995.— The effects of a metabolically stable TRH analog, N-[[(3R, 6R)-6-methyl-5-oxo-3-thiomorpholinyl]carbonyl]-L-histidyl-L-prolinamide tetrahydrate (NS-3, CG3703) on the scopolamine-induced memory disruption in maze performance tests were investigated in rats. a) In the delayed nonmatching-to-sample (DNMS) task using a T-maze, NS-3 (0.3 mg/kg) produced a significant reversal of the marginal disruption of choice accuracy induced by scopolamine (0.3 mg/kg) at the short (5 s) and long (120, 480 s) interval delays. Physostigmine (0.5 mg/kg) produced a significant reversal only at a 5-s interval delay. b) In the eight-arm radial maze task, NS-3 (0.3 mg/kg) significantly reversed the deficit of choice accuracy induced by scopolamine (0.3 mg/kg), whereas neither TRH (3-30 mg/kg) nor physostigmine (0.1-1 mg/kg) had any effect. The consistent reversal of these maze-learning performances by NS-3, but not by TRH or physostigmine, may be due to its potent enhancement of cholinergic and noradrenergic neuronal activities.

Delayed nonmatching-to-sample task Radial arm maze task NS-3 (CG3703) TRH Physostigmine Scopolamine Rat

THYROTROPIN-releasing hormone (TRH) is a tripeptideamide consisting of pyroglutamyl-histidyl-prolineamide (Pyr-His-Pro NH_2), which was found to be located widely in the brain (20,33) and demonstrated to have wide varieties of neurochemical and behavioral effects independent of its hormonal action (TSH releasing action) (26,45). TRH is known to produce antiamnestic actions in rodents (41-43). However, it has some clinical disadvantages, i.e., a short duration of action due to its short biological half-life, a reflection of its rapid metabolism by endopeptidase, and poor penetration through the blood-brain barrier (3,17,24). With the aim of increasing the resistance to metabolism and CNS effects relative to its TSH-releasing activity, a variety of TRH analogs were synthesized and NS-3 (CG3703) was selected as the most appropriate candidate (4,11,12).

For determination of the short-term memory processes in animals, the delayed nonmatching-to-sample (DNMS) task and radial arm maze (RAM) task have been widely used. The DNMS task is now established as a standard test of object recognition memory, i.e., nonspatial and working memory (21,46), and consists of a forced and a choice trial. The RAM task was initially devised for studying spatial memory based on both working and reference memory in rodents (34). This task requires successive selection of a number of arms radiating from the center of the maze to obtain food as a reward. The optimal strategy is to select each arm once and avoid reentering the arm where the reward had been consumed during a previous choice (5).

The septo-hippocampal system has been shown to play an essential role in short-term or working memory. Lesions of fimbria-fornix, which contains the large majority of cholinergic inputs to the hippocampus, caused disruption of short-term and/or working memory (9,27). Centrally acting anticholinergics such as scopolamine produced disruption of the working memory in a manner similar to lesioning of the hippocampus and/or fimbria-fornix (1,9,10,38). From the above findings, cholinergic mechanisms in the septo-hippocampal system appear to be involved in the working memory process.

[1] To whom requests for reprints should be addressed.

NS-3, as well as TRH, has been shown to have a cholinomimetic property in the CNS, and NS-3 was confirmed to cause the reversal of scopolamine-induced retrograde amnesia in passive avoidance responses in rats (30).

In the present study, we investigated the effects of NS-3 on the DNMS and RAM tasks in rats. To determine the roles of cholinergic systems in the memory disruption in the DNMS and RAM tasks, the effects of NS-3 were compared with those of physostigmine, a centrally acting cholinesterase inhibitor.

METHOD

Subjects

In the DNMS task and RAM task, male Wistar rats (Japan SLC Inc., Shizuoka, Japan), initially weighing 250–320 g, were used. Throughout the experiments, they were individually housed with free access to water, but were food deprived and maintained at 80% of free-feeding body weight in an air-conditioned room maintained at 21–25°C with humidity of 45–65% and a 12 L : 12 D cycle.

DNMS TASK

Apparatus

The apparatus was a T-maze with a 20 × 20 × 30 cm start box, a 72 × 12 × 30 cm choice area, and two 50 × 12 × 30 cm goal boxes, at each end of which was a food well (1 cm deep and 6 cm in diameter). Manually operated guillotine doors separated the choice area from the start box and from each of the goal boxes.

Procedure.

Training. Training of the DNMS task was carried out according to a modification of the method of Dunnett et al. (8). Each rat received pretraining sessions. In the first pretraining session, a piece of cheese (25 to 30 mg) as a reward was placed in the food well in both goal boxes, which were not blocked by the guillotine doors. The rat was placed in the start box and allowed to run the maze to get the reward placed at either goal box. Daily sessions in this period consisted of six trials, and was continued for at least 3 days. In the first period of pretraining, the percent alternation and side bias of 120 rats were calculated according to the procedure reported by Dunnett et al. (8). Following this period, the second pretraining sessions were commenced. In this period, one of two goal boxes was baited and the guillotine door to the baited goal box was opened, while the unbaited goal box was closed. Each rat was allowed to get a reward placed at the open goal box. Animals were given six trials per day for several days.

After pretraining, each rat was given six daily sessions with approximately 2-min intersession intervals. Each session consisted of a forced and a choice trial. In the forced trial, one goal box was blocked by the guillotine door. The rat was placed in the start box, and the start door was raised to allow the animal to enter the open goal box where a piece of cheese was placed as a reward. After consumption of the reward, the animal was replaced and was kept in the start box for 5 s (a 5-s interval delay) for the choice trial. In the choice trial, both goal boxes were unblocked and the animal could choose either one freely. A reward was placed only in the goal box opposite to that baited previously during the forced trial. The sequence of forced responses on the forced run of six sessions was fully balanced over days. Training was continued until the rat reached a criterion of more than five correct choices in the six sessions for more than 3 consecutive days.

Testing. After the rat achieved this criterion, the effects of drugs on this task with 5-, 30-, 120- and 480-s interval delays were examined (the retention test). Each rat was given four interval delays for each drug test, which was repeated three times at intervals of 3 to 4 days. Each delay was presented in a random sequence. Means of correct choices of the same delay interval in the three consecutive tests were obtained. In the drug tests, scopolamine, NS-3, or physostigmine was injected intraperitoneally (IP) 10, 5, or 5 min prior to the test, respectively.

RAM TASK

Apparatus

The apparatus used consisted of an eight-arm radial maze elevated 50 cm above the floor, with a central platform surrounded by eight radial arms (60 cm long × 12 cm wide). Food wells 1 cm deep and 3 cm in diameter were placed at the distal end of each arm.

Procedure

Training. Training of the RAM task was carried out according to the method of Olton et al. (34), with slight modifications. After adapting to the experimental apparatus, the rat received one training trial per day. A piece of cheese (25 to 30 mg) as a reward was placed in each food well and the rat was allowed to choose between them freely until (a) eight rewards were taken or (b) 10 min after the start of the trial. When the rat entered the unselected arm and ate the reward, this selection was considered as a correct choice, while if the rat reentered a previously selected arm, this selection was defined as an error choice. Rats were trained for at least 10 days until they reached a criterion of seven correct choices in the first eight choices or eight correct choices in the first 10 choices for three consecutive trails.

Testing. After the rat reached this criterion, the effects of drugs on this task were examined. In the drug tests, rats were injected IP with scopolamine 30 min prior to the test, followed by NS-3, TRH or physostigmine 15, 10 and 15 min prior to the test, respectively.

Drugs. Drugs used were NS-3 (Grünenthal GmbH, Aachen, Germany), TRH (United Pharmaceutical Works, Prague, Czechoslovakia), scopolamine hydrochloride (Sigma, St. Louis, MO), and physostigmine salicylate (Tokyo Kasei, Japan). All drugs were dissolved in an appropriate volume of saline and injected IP in a volume of 1 ml/kg.

Data analysis. Statistical analysis was performed with repeated measures of variance (two-way ANOVA) for assessing group, delay, and group × delay interaction effects, and with the two-tailed Student's *t*-test for two means or with the analysis of variance followed by Dunnett's test to compare multiple means.

RESULTS

DNMS Task

Spontaneous alternation and side bias. The degrees of spontaneous alternation and side bias observed during the pretraining session were 41.8% and 70.3%, respectively. In the first training session, the average degree of correct choices and side bias were 61.3% and 83.5%, respectively. After reaching the criterion, the proportion of animals showing the degree of correct choices at 5-s interval delay was elevated to 93.3%.

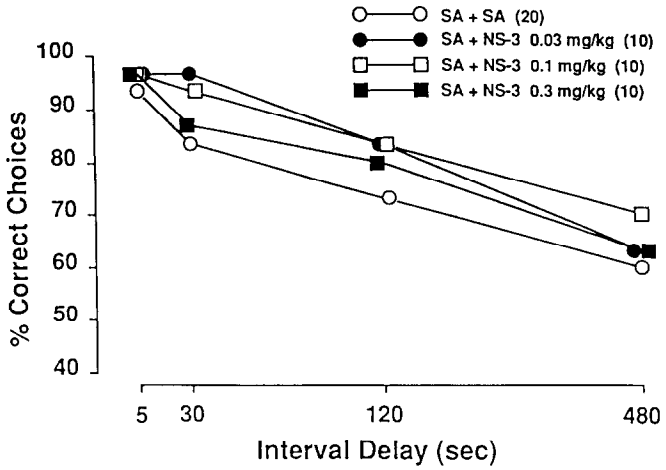

FIG. 1. Effects of NS-3 on correct choices in the DNMS task in rats. Numbers in parentheses represent number of experiments. SA; saline.

Effects of NS-3 on performance of the DNMS task. Results are shown in Fig. 1. Correct choices in the control group were decreased dependent on the interval delays. NS-3, at doses of 0.03–0.3 mg/kg, caused a slight and insignificant increase in correct choices at all interval delays studied. A two-way analysis of variance showed that group, $F(3, 46) = 3.35$, $p < 0.05$, and delay, $F(3, 138) = 37.66$, $p < 0.01$, main factor terms were significant, while the group × delay interaction, $F(9, 138) = 0.33$, $p = 0.949$, was not significant. Data concerning physostigmine (0.3–0.5 mg/kg) are not shown because this drug produced severe neurological effects on behavior such as tremors and body twitches with immobility.

Effects of scopolamine on performance of the DNMS task. Results are shown in Fig. 2. Scopolamine, at a dose of 0.1 mg/kg, significantly reduced correct choices at 30- and 120-s interval delays, but had no effect at 5- or 480-s interval delays. At a dose of 0.3 mg/kg, this drug reduced correct choices significantly at every delay time applied. A two-way analysis of variance indicated that group, $F(2, 57) = 29.55$, $p < 0.01$, and delay, $F(3, 171) = 30.32$, $p < 0.01$, were significant, while the group × delay interaction, $F(6, 171) = 1.07$, $p = 0.384$, was not significant.

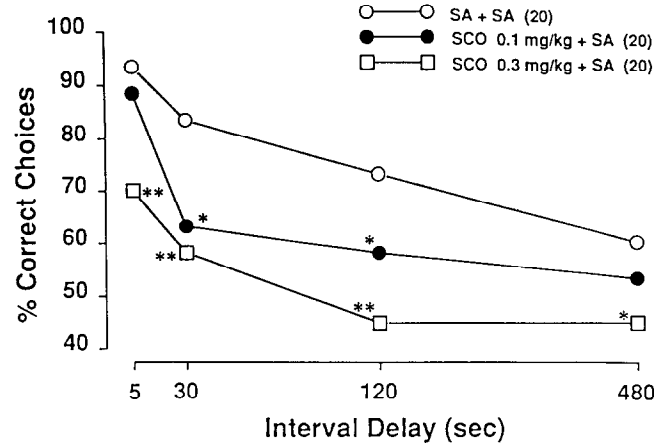

FIG. 2. Effects of scopolamine on correct choices in the DNMS task in rats. Numbers in parentheses represent number of experiments. The control data (SA + SA) is the same group data from the Fig. 1. SA; saline. SCO; scopolamine. Significantly different from control (SA + SA): $*p < 0.05$, $**p < 0.01$.

Effects of NS-3 and physostigmine on the scopolamine-induced deficit in performance of the DNMS task. Results are shown in Fig. 3. NS-3, at a dose of 0.1 mg/kg, produced a slight and insignificant reversal of the reduction in correct choices caused by scopolamine (0.3 mg/kg) at a 5-s interval delay. However, at a dose of 0.3 mg/kg, NS-3 significantly reversed this effect of scopolamine at 5-, 120- and 480-s interval delays. Physostigmine, at a dose of 0.5 mg/kg, significantly reversed the scopolamine-induced reduction in correct choices only at a 5-s interval delay. Two-way analysis of variance showed that group, $F(3, 46) = 9.38$, $p < 0.01$, and delay, $F(3, 138) = 19.94$, $p < 0.01$, were significant, while the group × delay interaction, $F(9, 138) = 0.50$, $p = 0.863$, was not significant.

RAM Task

Effects of NS-3, TRH and physostigmine on performance of the RAM task. Results are shown in Fig. 4. NS-3 and TRH showed no significant effects on the correct choices in the first eight selections at all doses employed. Physostigmine, at a dose of 0.1 mg/kg, showed no significant effect, and at doses of 0.3 and 0.5 mg/kg caused tremors and body twitches with immobility.

Effects of scopolamine on performance of the RAM task. Results are shown in Fig. 5. Scopolamine, at doses of 0.1–0.5 mg/kg, decreased correct choices in the first eight selections in a dose-dependent manner, and significant decreases were observed at doses of 0.3 and 0.5 mg/kg.

Effects of NS-3, TRH and physostigmine on the scopolamine-induced deficit in performance of the RAM task. Results are shown in Fig. 6. NS-3, at a dose of 0.3 mg/kg, significantly reversed the deficit in the RAM task caused by

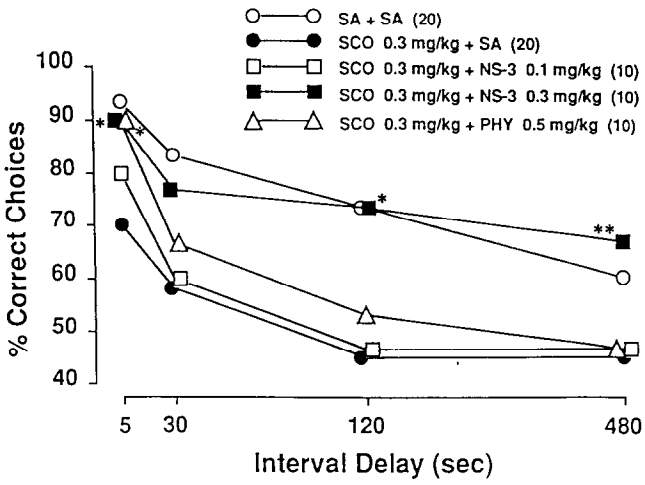

FIG. 3. Effects of NS-3 and physostigmine on the scopolamine-reduced correct choices in the DNMS task in rats. Numbers in parentheses represent number of experiments. The control (SA + SA) and the other control data (SCO 0.3 mg/kg + SA) is the same group data from the Figs. 1 and 2, respectively. SA; saline. SCO; scopolamine. PHY; physostigmine. Significantly different from control (SCO 0.3 mg/kg + SA): $*p < 0.05$, $**p < 0.01$.

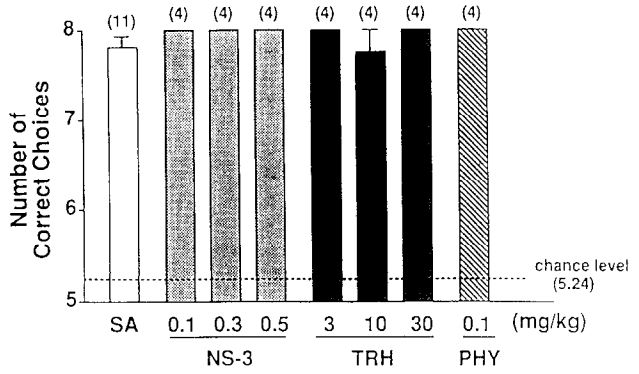

FIG. 4. Effects of NS-3, TRH and physostigmine on correct choices during the first eight selections in the RAM task in rats. Numbers in parentheses represent number of experiments. SA; saline. PHY; physostigmine.

scopolamine (0.3 mg/kg), although it had no significant effects at any other dose administered (0.03, 0.1 or 0.5 mg/kg). Neither TRH nor physostigmine reversed the scopolamine-induced deficit in the RAM task at any dose examined.

DISCUSSION

Scopolamine has been reported to impair learning and memory in healthy volunteers and in various animal species (7,28,37). In the present study, scopolamine significantly reduced correct choices at doses of 0.1–0.3 mg/kg in the DNMS task. These results confirm earlier reports that scopolamine disrupts delayed responses (9,15,16,25,35,40) in a dose-dependent manner. Scopolamine blocks muscarinic receptors at several central sites including terminal fields of cholinergic neurons in both the cerebral cortex and hippocampus. The disruptive effects of scopolamine on a delayed matching-to-sample task were reported to be attributable to a combination of disruption of the two major forebrain cholinergic systems originating in the nucleus basalis magnocellularis (NBM) and sept-diagonal band (9). It is strongly suggested that disruption of septo-hippocampal system, including cholinergic afferents via the fimbria-fornix, produces short-term or working memory impairments, whereas disruption of the cortical cholinergic system affects more stable long-term aspects or reference memory of task performance (9). Therefore, in the present study, we employed longer as well as shorter delays for the assessment of short-term and long-term memory disrupted by scopolamine.

NS-3 caused no significant effect on the DNMS task in scopolamine-untreated animals. However, at a dose of 0.3 mg/kg, NS-3 significantly reversed the scopolamine-induced reduction of correct choices at short and long delays in the DNMS task. In the same task, physostigmine, at the highest dose administered (0.5 mg/kg), reversed the scopolamine-induced reduction of correct choices only at the shortest (5-s interval) delay. These results are incompatible with those of many previous reports that physostigmine and TRH failed to ameliorate the disruption of short-term memory caused by scopolamine in DNMS tasks (2,15,44). Considering the evidence (13,22,29,31,36) that NS-3 and TRH enhanced cholinergic activity in the cerebral cortex and hippocampus, this lack of an ameliorating effect of TRH on scopolamine-induced disruption of short-term memory may be due to the short duration of action due to poor penetration through the blood–brain barrier. Despite the potent cholinomimetic activity of physostigmine, its weak and incomplete effect on DNMS and RAM tasks in comparison with NS-3 is suggestive of the involvement of mechanisms other than cholinergic mechanisms in the DNMS task.

Recently, we showed that NS-3 enhanced noradrenaline (NA) release from the cerebral cortex in rats (23). The noradrenergic system also appears to play an important role in learning and memory (30). Several experiments were conducted previously to explore the possible interactions between cholinergic and noradrenergic systems in memory tasks in rats (6,14).

Previous studies suggested that DSP-4, a neurotoxin that produces selective degeneration of noradrenergic neurons, impairs choice accuracy of rats at long delays in the T-maze paradigm (39). Therefore, we speculated that the potent enhancement of NA release from the cerebral cortex evoked by NS-3 may contribute to the observed marked reversal of scopolamine-induced reduction in correct choices at short and

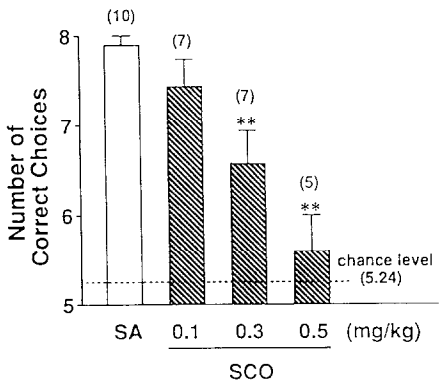

FIG. 5. Effects of scopolamine on correct choices during the first eight selections in the RAM task in rats. Numbers in parentheses represent number of experiments. SA; saline. SCO; scopolamine. Significantly different from control (SA): $^{**}p < 0.01$.

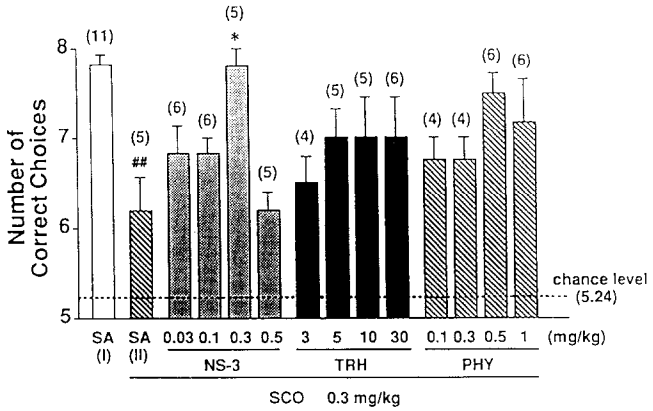

FIG. 6. Effects of NS-3, TRH, and physostigmine on the reduction in correct choices induced by scopolamine (0.3 mg/kg) during the first eight selections in rats in the RAM task. Numbers in parentheses represent number of experiments. SA; saline. SCO; scopolamine. PHY; physostigmine. Significantly different from control: $\#\#p <$ 0.01 vs. SA (I); $^{*}p < 0.05$ vs. [SA (II) + SCO 0.3 mg/kg].

long delays in the DNMS task in association with the enhancement of acetylcholine (ACh) release in the cerebral cortex and the hippocampus. The noradrenergic as well as the cholinergic system may regulate memory, especially in the consolidation process. The observed lack of effect of physostigmine with longer delays might reflect its lack of an interaction with the noradrenergic system.

The present results confirm earlier reports that scopolamine disrupts radial maze performance in a dose-dependent manner (6,18,19,32). NS-3 reversed the scopolamine-induced reduction of correct choices in the RAM task in the present study, but TRH and physostigmine did not. It was reported previously (6) that the effects of scopolamine could be enhanced by noradrenergic depletion. Functional relationships between ACh and NA systems have been suggested to contribute to memory performance in the RAM task (6,14). These previous studies indicated that the ascending noradrenergic system can regulate the activity of cholinergic neurons in the forebrain. Reversal by NS-3 of the scopolamine-induced reduction in correct choices in the RAM task may be due to activation of both cholinergic and noradrenergic systems.

In the present study, NS-3, at a dose of 0.3 mg/kg IP, significantly reversed the scopolamine-induced reduction in correct choices in both DNMS and RAM tasks in rats, while TRH and physostigmine had no effect.

In conclusion, NS-3 may improve the deficit of spatial and nonspatial memory mediated by the enhancement of ACh release in the cerebral cortex and hippocampus, and by the enhancement of NA release in the cerebral cortex. NS-3, therefore, is a promising drug for clinical use in ameliorating the cognitive impairment caused by cerebral cholinergic or adrenergic dysfunction; i.e., in patients with senile dementia of the Alzheimer's type.

ACKNOWLEDGEMENT

The authors wish to thank Ms. J. Shimizu for typing of the manuscript.

REFERENCES

1. Aggleton, J. P.; Keith, A. B.; Rawlins, J. N. P.; Hunt, P. R.; Sahgal, A. Removal of the hippocampus and transection of the fornix produce comparable deficits on delayed non-matching to position by rats. Behav. Brain Res. 52:61-71; 1992.
2. Alpern, H. P.; Marriott, J. G. Short-term memory: Facilitation and disruption with cholinergic agents. Physiol. Behav. 11:571-575; 1973.
3. Bassiri, R.; Utiger, R. D. Serum inactivation of the immunological and biological activity of thyrotropin-releasing hormone (TRH). Endocrinology 91:657-664; 1972.
4. Bauer, K. Thyroliberin analogues as competitive inhibitors of thyroliberin degradation by brain enzymes. Hoppe-Seyler's Z. Physiol. Chem. 360:1126; 1979.
5. Bernstein, D.; Olton, D. S.; Ingram, D. K.; Waller, S. B.; Reynolds, M. A.; London, E. D. Radial maze performance in young and aged mice: Neurochemical correlates. Pharmacol. Biochem. Behav. 22:301-307; 1985.
6. Decker, M. W.; Gallagher, M. Scopolamine-disruption of radial arm maze performance: Modification by noradrenergic depletion. Brain Res. 417:59-69; 1987.
7. Drachman, D. A. Memory and cognitive function in man: Does the cholinergic system have a specific role? Neurology 27:783-790; 1977.
8. Dunnett, S. B.; Low, W. C.; Iversen, S. D.; Stenevi, U.; Björklund, A. Septal transplants restore maze learning in rats with fornix-fimbria lesions. Brain Res. 251:335-348; 1982.
9. Dunnett, S. B. Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats. Psychopharmacology (Berlin) 87:357-363; 1985.
10. Eckerman, D. A.; Gordon, W. A.; Edwards, J. D.; MacPhail, R. C.; Gage, M. I. Effects of scopolamine, pentobarbital and amphetamine on radial arm maze performance in the rat. Physiol. Behav. 12:595-602; 1980.
11. Flohé, L.; Bauer, K.; Friderichs, E.; Günzler, W. A.; Hennies, H. H.; Herrling, S.; Lagler, F.; Otting, F.; Schwertner, E. Biological effects of degradation-stabilized TRH analogues. In: Griffiths, E. C.; Bennett, G. W., eds. Thyrotropin-releasing hormone. New York: Raven Press; 1983:327-340.
12. Friderichs, E.; Schwertner, E.; Herrling, S.; Günzler, W. A.; Flohé, L. Activity of thyroliberin analogs with a modified pyroglutamyl residue on the central nervous system. Hoppe-Seyler's Z. Physiol. Chem. 360:1146; 1979.
13. Giovannini, M. G.; Casamenti, F.; Nistri, A.; Paoli, F.; Pepeu, G. Effect of thyrotropin releasing hormone (TRH) on acetylcholine release from different brain areas investigated by microdialysis. Br. J. Pharmacol. 102:363-368; 1991.
14. Haroutunian, V.; Kanof, P. D.; Tsuboyama, G.; Davis, K. L. Restoration of cholinomimetic activity by clonidine in cholinergic plus noradrenergic lesioned rats. Brain Res. 507:261-266; 1990.
15. Heise, G. A.; Conner, R.; Martin, R. A. Effects of scopolamine on variable intertrial interval spatial alternation and memory in the rat. Psychopharmacology (Berlin) 49:131-137; 1976.
16. Heise, G. A.; Harabrich, B.; Lilie, N. L.; Martin, R. A. Scopolamine effects on delayed spacial alternation in the rat. Pharmacol. Biochem. Behav. 3:993-1002; 1975.
17. Hichens, M. A comparison of thyrotropin-releasing hormone with analogs: Influence of disposition upon pharmacology. Drug Metabol. Rev. 14:77-98; 1983.
18. Higashida, A.; Ogawa, N. Differences in the acquisition process and the effect of scopolamine on radial maze performance in three strains of rats. Pharmacol. Biochem. Behav. 27:483-489; 1987.
19. Hiraga, Y.; Iwasaki, T. Effects of cholinergic and monoaminergic antagonists and tranquilizers upon spatial memory in rats. Pharmacol. Biochem. Behav. 20:205-207; 1984.
20. Hökfelt, T.; Fuxe, K.; Johansson, O.; Jeffcoate, S.; White, N. Distribution of thyrotropin-releasing hormone (TRH) in the central nervous system as revealed with immunohistochemistry. Eur. J. Pharmacol. 34:389-392; 1975.
21. Hunt, P. R.; Aggleton, J. P. Medial dorsal thalamic lesions and working memory in the rat. Behav. Neural Biol. 55:227-246; 1991.
22. Itoh, Y.; Ogasawara, T.; Ukai, Y.; Yamazaki, A.; Kimura, K. Effect of NS-3, a thyrotropin-releasing hormone analog, on in vivo acetylcholine release in rat brain: Regional differences and its site of action. J. Pharmacol. Exp. Ther. 271:884-890; 1994.
23. Itoh, Y.; Ogasawara, T.; Yamazaki, A.; Ukai, Y.; Miura, A.; Kimura, K. Enhancement of noradrenaline release from rat frontal cortex by thyrotropin releasing hormone and its analog, (3R, 6R)-6-methyl-5-oxo-3-thiomorpholinylcarbonyl-L-histidyl-L-prolinamide, as studied by intracerebral microdialysis. J. Pharmacol. Exp. Ther. 268:255-261; 1994.
24. Knigge, K. M.; Schock, D. Characteristics of the plasma TRH-degrading enzyme. Neuroendocrinology 19:277-287; 1975.
25. Ksir, C. J. Scopolamine effects on two-trial delayed-response performance in the rat. Psychopharmacologia 34:127-134; 1974.
26. Metcalf, G. Regulatory peptides as a source of new drugs—The clinical prospects for analogues of TRH which are resistant to metabolic degradation. Brain Res. Rev. 4:389-408; 1982.
27. M'Harzi, M.; Jarrard, L. E. Strategy selection in a task with spatial and nonspatial components: Effects of fimbria-fornix lesions in rats. Behav. Neural Biol. 58:171-179; 1992.
28. Moss, D. E.; Rogers, J. B.; Deutsch, J. A.; Salome, R. R. Time dependent changes in anterograde scopolamine-induced amnesia in rats. Pharmacol. Biochem. Behav. 14:321-323; 1981.

29. Narumi, S.; Nagai, Y.; Miyamoto, M.; Nagawa, Y. Thyrotropin-releasing hormone (TRH) and its analog (DN-1417): Interaction with pentobarbital in choline uptake and acetylcholine synthesis of rat brain slices. Life Sci. 32:1637–1645; 1983.
30. Ogasawara, T.; Ukai, Y.; Tamura, M.; Kimura, K. NS-3 (CG3703), an analogue of thyrotropin-releasing hormone, ameliorates cognitive impairment in rats. Pharmacol. Biochem. Behav. (in press).
31. Okada, M. Effects of a new thyrotropin releasing hormone analogue, YM-14673, on the in vivo release of acetylcholine as measured by intracerebral dialysis in rats. J. Neurochem. 56:1544–1547; 1991.
32. Okaichi, H.; Oshima, Y.; Jarrard, L. E. Scopolamine impairs both working and reference memory in rats: A replication and extension. Pharmacol. Biochem. Behav. 34:599–602; 1989.
33. Oliver, C.; Eskay, R. L.; Ben-Jonathan, N.; Portar, J. C. Distribution and concentration of TRH in the rat brain. Endocrinology 95:540–546; 1974.
34. Olton, D. S.; Walker, J. A.; Gage, F. H. Hippocampal connections and spatial discrimination. Brain Res. 139:295–308; 1978.
35. Pontecorvo, M. J.; Clissold, D. B.; Conti, L. H. Age-related cognitive impairments as assessed with an automated repeated measures memory task: Implications for the possible role of acetylcholine and norepinephrine in memory dysfunction. Neurobiol. Aging 9:617–625; 1988.
36. Schmidt, D. E. Effects of thyrotropin releasing hormone (TRH) on pentobarbital-induced decrease in cholinergic neuronal activity. Psychopharmacol. Commun. 1:469–473; 1977.
37. Smith, G. Animal models of Alzheimer's disease: Experimental cholinergic denervation. Brain Res. Rev. 13:103–118; 1988.
38. Watts, J.; Stevens, R.; Robinson, C. Effects of scopolamine on radial maze performance in rats. Physiol. Behav. 26:845–851; 1981.
39. Wenk, G.; Hughey, D.; Boundy, V.; Kim, A.; Walker, L.; Olton, D. Neurotransmitters and memory: Role of cholinergic, serotonergic, and noradrenergic systems. Behav. Neurosci. 101:325–332; 1987.
40. White, S. R. Atropine, scopolamine and hippocampal lesion effects on alternation performance of rats. Pharmacol. Biochem. Behav. 2:297–307; 1974.
41. Yamamoto, M.; Shimizu, M. Effects of a new TRH analogue, YM-14673 on a passive avoidance test as a possible criterion of improvement in cognitive disturbance in rodents. Naunyn Schmiedebergs Arch. Pharmacol. 338:262–267; 1988.
42. Yamazaki, N.; Shintani, M.; Saji, Y.; Nagawa, Y. Interaction with cholinergic drugs in reversal of cycloheximide-induced amnesia by thyrotropin-releasing hormone and its analog DN-1417 in mice. Jpn. J. Psychopharmacol. 3:127–136; 1983.
43. Yamazaki, N.; Shintani, M.; Saji, Y.; Nagawa, Y. Effect of TRH and its analog DN-1417 on anoxia-induced amnesia in mice. Jpn. J. Psychopharmacol. 5:1–9; 1985.
44. Yamazaki, N.; Nagaoka, A.; Nagawa, Y. Effect of thyrotropin-releasing hormone (TRH) and its analog DN-1417 on scopolamine-induced impairment of short-term memory in rats. Jpn. J. Psychopharmacol. 6:359–366; 1986.
45. Yarbrough, G. G. On the neuropharmacology of thyrotropin releasing hormone (TRH). Prog. Neurobiol. 12:291–312; 1979.
46. Zola-Morgan, S.; Squire, L. R.; Amaral, D. G. Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkey. J. Neurosci. 9:898–913; 1989.