Pergamon

Pharmacology Biochemistry and Behavior, Vol. 50, No. 4, pp. 499–503, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00312-2

NS-3 (CG3703), an Analog of Thyrotropin-Releasing Hormone, Ameliorates Cognitive Impairment in Rats

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

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

Received 1 February 1994

OGASAWARA, T., Y. UKAI, M. TAMURA AND K. KIMURA. *NS-3 (CG3703), an analog of thyrotropin-releasing hormone, ameliorates cognitive impairment in rats.* PHARMACOL BIOCHEM BEHAV **50**(4) 499–503, 1995. – The effects of thyrotropin-releasing hormone (TRH) and its analog, N-[[(3R, 6R)-6-methyl-5-oxo-thiomorpholinyl] carbonyl]-L-histidyl-L-prolinamide tetrahydrate (NS-3, CG3703) on disturbance of memory of a passive avoidance response (PAR) and an escape response in rats were investigated. NS-3 improved amnesia caused by scopolamine, electroconvulsive shock (ECS), and cycloheximide (CXM), but TRH improved only the ECS-induced amnesia. NS-3 reversed learning deficits caused by hypercapnia, but TRH had no effect. These differences in the effect between NS-3 and TRH may be due to their biological half-life in rat plasma. These results suggest that NS-3 possesses more potent antiamnestic effects than TRH in rats.

NS-3 (CG3703) Amnesia Scopolamine ECS Cycloheximide Hypercapnia Rats

THYROTROPIN-RELEASING hormone (TRH) was first isolated from porcine hypothalamus (38) and chemically identified as a tripeptideamide consisting of pyroglutamyl-histidyl-prolinamide (Pyr-His-Pro NH_2) (3). Soon after, it was found to be located widely in extrahypothalamic brain areas (17,33) and demonstrated to have a wide variety of neurochemical and behavioral effects that were independent of hormonal action (TSH releasing action) (26,47).

TRH is known to produce antiamnestic actions in rodents (43–45). It is, however, known to be easily inactivated by TRH-degrading enzymes in plasma, brain, and other tissues, and to penetrate poorly through the blood-brain barrier (2,16,21). NS-3 is a TRH analog synthesized to increase its resistance to enzymatic degradation and to increase its CNS, but not endocrine effects, and was investigated for possible therapeutic potential in CNS disturbances (11). In our previous study (31), NS-3 showed various CNS effects more markedly than TRH.

In the present study, we compared the effects of NS-3 and TRH on cognitive impairment caused by scopolamine, electroconvulsive shock, cycloheximide, and hypercapnia in rats according to the methods of Cumin et al. (7).

METHOD

Subjects

Male Wistar rats (Japan SLC Inc., Shizuoka, Japan), 6–7 weeks of age, were housed with free access to food (Clea Japan Inc., Tokyo, Japan) and water in an air-conditioned room maintained at 21–25°C, with a relative humidity of 45–65% and a 12 L : 12 D cycle.

Procedures for a Passive Avoidance Task

Rats were first trained to remain on a rubber platform (15 × 15 × 0.5 cm) placed at a corner of the Skinner box (25 × 30 × 33 cm) that had been equipped with an electrifiable grid floor. When the rats moved away from the safety zone, they were exposed to continuous electroshocks (0.8 mA) from the grid floor.

The training session of PAR was composed of five consecutive trials. Each trial was carried out every 1 min. All animals learned not to step down the grid floor by the final trial of training session.

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

Prevention of Scopolamine-Induced Disruption of a PAR

Immediately after the training session, scopolamine (0.5 mg/kg) was administered IP and followed by NS-3 or TRH. Fifteen minutes later, the latent periods of step-down onto the grid floor were measured up to 60 s.

Prevention of Electroconvulsive Shock (ECS)-Induced Disruption of a PAR

Immediately after the training session, the rats received ECS (45 mA, 2 s) through the ears and were subsequently injected IP with NS-3 or TRH. Fifteen minutes later, their PAR was tested.

Reversal of Cycloheximide (CXM)-Induced Disruption of Retrieval of a PAR

Immediately after the training session, CXM (3 mg/kg) were administered SC and animals were returned to their cages. Forty-eight hours later, they were subjected to the PAR test. Test drugs were administered IP 15 min before the test session.

Reversal of Hypercapnia-Induced Deficit of Learning

After the test drugs were injected IP 15 min before CO_2 exposure for 12 s, rats were placed into the shuttle box (Ugo Basil, Italy) and then acquisition sessions were started with the following schedule: a 10-s silence, a 5-s buzzer presentation, a 15-s buzzer presentation plus foot shocks. The shock intensity was 40–80 V. The grid floor was connected to a shocker (Ugo Basil) that was set to deliver scrambled foot shock. One acquisition session consisted of six consecutive trials. A shuttle response, i.e., moving to the other compartment during the presentation of both buzzer and buzzer plus foot shocks was considered as a discrete escape response. The results were expressed as the number of animals that performed the discrete escape response at the sixth trial.

Drugs

NS-3 was synthesized at the laboratories of Grünenthal GmbH (Germany). The following drugs were commercially obtained. Scopolamine HCl (Sigma), Cycloheximide (Nacalai tesque, Japan), TRH (United Pharmaceutical Works, Czechoslovakia). NS-3, TRH and scopolamine were dissolved in saline and injected IP in a volume of 1 ml/kg. Cycloheximide was dissolved in a saline and injected SC in a volume of 1 ml/kg. Regarding to the pretreatment time and injection route, we employed the 15-min and IP injection according to our previous study (31).

Statistical Analysis

Statistical analyses for the latent periods were made by Dunnett's test and for the yes/no response data were made by Fisher's Exact Probability test.

RESULTS

Acquisition of a Passive Avoidance Task

In the training session, the normal reaction of naive animals was to jump back onto the platform at first and/or second trial. All rats never stepped down onto the grid floor after the third trial.

More than 80% of rats given vehicle instead of amnestic agents, retained a PAR when tested 15 min to 48 h after the training session.

Prevention of Scopolamine-Induced Disruption of a PAR

NS-3, at doses from 0.03–1 mg/kg, produced no changes in the PAR in naive rats (data not shown). Figure 1 shows the effects of NS-3 and TRH on the scopolamine-induced disruption of a PAR in rats. As shown in the figure, scopolamine, at a dose of 0.5 mg/kg, produced a marked reduction in the number of animals showing retention of the acquired task (disruption of a PAR).

NS-3 prevented the scopolamine-induced disruption of PAR significantly at the dose range of 0.05–0.3 mg/kg. The dose–response results showed a bell-shaped curve, with doses higher than 0.5 mg/kg showing no significant increase in the latent period, as compared to the scopolamine + saline (control) group.

TRH also showed a bell-shaped dose–response curve, but no significant effect was observed at the doses used, i.e., 5–30 mg/kg.

Prevention of ECS-Induced Disruption of a PAR

NS-3, at doses from 0.1 to 3 mg/kg, produced no changes in the PAR in naive rats (data not shown). As shown in Fig. 2, ECS produced complete disruption of PAR. When NS-3 was injected IP immediately after convulsive seizures at the dose range of 0.1–3 mg/kg, a bell-shaped dose–response curve was obtained against the disrupted PAR, with significant effects being observed at doses of 0.3–1 mg/kg.

TRH also showed a bell-shaped dose–response curve at the dose range of 3–30 mg/kg, and significant effects were observed only at 10 mg/kg.

Reversal of CXM-Induced Disruption of Retrieval of a PAR

NS-3, at doses from 0.01–0.3 mg/kg, produced no changes in the PAR in naive rats (data not shown). Figure 3 shows the effects of NS-3 and TRH on the CXM-induced disruption of a PAR in rats. As shown in the figure, NS-3 or TRH was

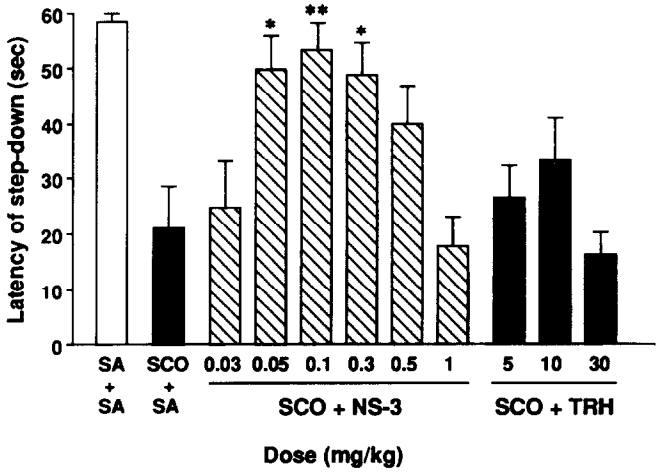

FIG. 1. Effects of NS-3 and TRH on the scopolamine-induced disruption of a PAR in rats. Each value represents the mean ± SE of latency of step-down onto the grid floor in a group of 10 animals. Significantly different from SCO + SA; $*p < 0.05$, $**p < 0.01$ (Dunnett's test). SA: saline, SCO: scopolamine.

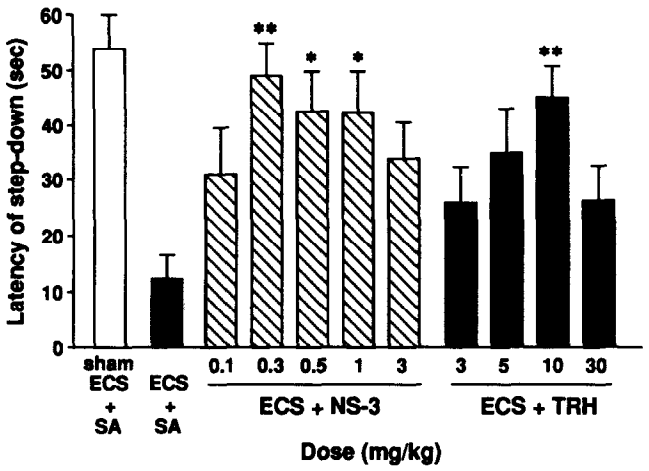

FIG. 2. Effects of NS-3 and TRH on the ECS-induced disruption of a PAR in rats. Each value represents the mean ± SE of latency of step-down onto the grid floor in a group of 10 animals. Significantly different from ECS + SA; $*p < 0.05$, $**p < 0.01$ (Dunnett's test). SA: saline.

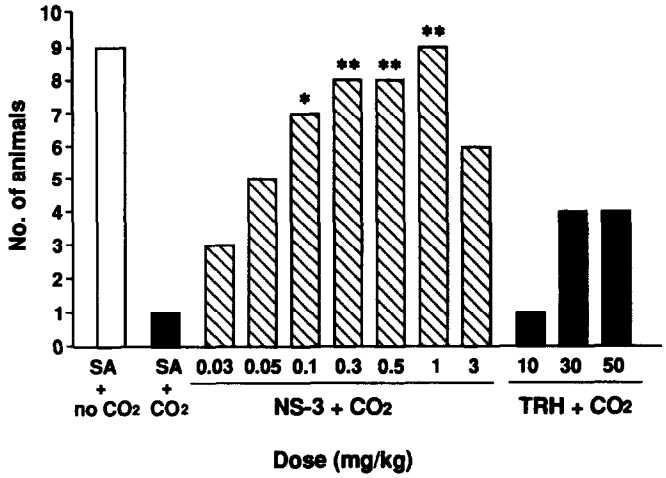

FIG. 4. Effects of NS-3 and TRH on the deficit of learning acquisition caused by hypercapnia in rats. Each value represents the number of animals that performed the discrete escape response at the sixth trial. Ten animals were used for each group. Significantly different from CO_2 + SA; $*p < 0.05$, $**p < 0.01$ (Fisher's exact probability test). SA: saline.

injected IP 15 min before the test sessions, which were conducted 48 h after CXM injection.

NS-3, at the dose range of 0.01–0.3 mg/kg, showed a bell-shaped dose-response curve against CXM-induced disruption of retrieval of the memory, and a significant reversal was observed at a dose of 0.05 mg/kg.

TRH showed no significant effect in this test at all doses employed, i.e., 1–30 mg/kg.

Reversal of Hypercapnia-Induced Deficit of Learning

Results are shown in Fig. 4. Number of naive animals that showed the discrete escape response at each trial was increased gradually during the five training trials, and at the sixth trial, 9 out of 10 animals performed the escape response. NS-3, at the doses from 0.03–3 mg/kg, produced no changes in the escape response in naive rats (data not shown). In contrast, control animals that were exposed to CO_2 showed deficits of learning of escape responses. NS-3, at doses of 0.1–1 mg/kg, significantly reversed the deficit of learning, but TRH at doses of 10–50 mg/kg had no effect. NS-3 and TRH showed no increase of locomotor activity in rats exposed to hypercapnia.

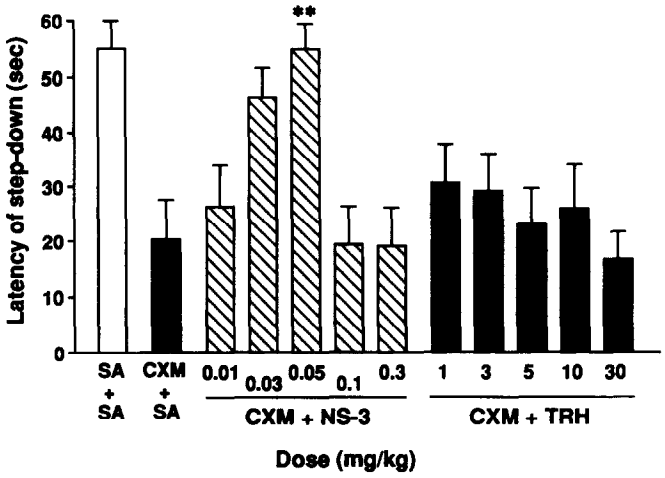

FIG. 3. Effects of NS-3 and TRH on the CXM-induced disruption of the retrieval of a PAR in rats. Each value represents the mean ± SE of latency of step-down onto the grid floor in a group of 10 animals. Significantly different from CXM + SA; $**p < 0.01$ (Dunnett's test). SA: saline, CXM: cycloheximide.

DISCUSSION

NS-3 was selected as a compound having the most potent resistance to enzymatic degradation and having CNS activities with a wide potency ratio between CNS and TSH-releasing activities (11,31). NS-3 has been shown to have potent CNS stimulant activities including an increase of locomotor activity, antagonism of barbiturate-narcosis, and reserpine-induced hypothermia (11,15,31). These activities of NS-3 were at least 20 times more potent than those of TRH.

In this study, ameliorating effects on amnesia were compared with those of TRH in rats with experimentally impaired learning and memory. We first investigated the effect of NS-3 on scopolamine-induced retrograde amnesia, because there is much evidence showing the linkage of neuropharmacological and pathologic changes and cholinergic deficits in dementia of the Alzheimer's type. Scopolamine has been found to impair the function of learning and memory in healthy volunteers as well as Alzheimer's patients, and in various animal species (6,29,41).

In our present study using rats, NS-3 prevented scopolamine-induced amnesia effectively at very low doses. TRH and its analogs have been shown to ameliorate the cognitive impairment caused by scopolamine in rats (42,46) and humans (28). Several investigators (12,30,32,39) suggested that the ameliorating effect of TRH on scopolamine-induced impairment of cognition may be due to the enhancement of cholinergic activity in the frontal cortex and hippocampus, which are well known to play an essential role in the learning and memory.

NS-3 was effective in ameliorating amnesia caused by ECS. Scopolamine (1,7,13) and ECS (24,25,34) have been widely employed to cause retrograde amnesia by interfering with memory consolidation, if applied immediately, or shortly after learning or training sessions. Therefore, these results indicate that NS-3 reverses the deficit of consolidation of the memory process (7). One of the mechanisms involved in the ECS-induced retrograde amnesia is considered to be a deficit in cholinergic functions in CNS because ECS decreases cholinergic activity in CNS (8,14,22). The authors (19,20) reported that TRH and NS-3 improved the performance in a T-maze and water maze task of rats subjected to ECS and suggested that ameliorating effects of NS-3 and TRH on ECS-induced retrograde amnesia may be due to the enhancement of cholinergic neuronal activity in CNS.

Inhibition of cerebral protein synthesis has been reported to impair the formation of long-term memory, especially the memory retrieval (7,35). NS-3 prevented the impairment of memory retrieval induced by CXM. The protein synthesis inhibitors are commonly known to cause the disruption of central adrenergic systems and induce amnesia (4,35,37,40). Therefore, in addition to the cholinergic mechanisms, enhancement of noradrenergic activity in the CNS may be contributing to the antiamnestic effects of NS-3 in rats treated with protein synthesis inhibitors. Such an idea is supported by the report (18) that NS-3 enhances the noradrenaline (NA) release from the rat cerebral cortex.

NS-3 restored hypercapnia-induced deficit of learning in rats. Conditions that reduce the energy supply to the brain have been reported to cause cognitive impairment or learning deficits (23). It remains to be determined whether NS-3 protects against the CNS cytotoxic effect caused by hypercapnia or whether it improves directly the processes involved in learning and memory. The authors (27) have reported that behavioral disturbances induced by hypoxia are considered to be due to the failure of synaptic transmission rather than to an insufficiency of energy supply in the brain. They suggest that the turnover rate of NA under hypoxia is decreased only in the cerebral cortex and hippocampus. The authors (9,10) have also shown that hypoxia decreases synthesis and metabolism of monoamines in rat brain. Therefore, ameliorating effect of NS-3 on hypercapnia-induced learning deficit is considered to be due to the facilitation of NA release.

A bell-shaped dose-response curve has been repeatedly reported in studies with other drugs that are thought to improve cognitive functions (7,43). The mechanism responsible for this dose-effect function is not clarified, but we assume that at higher doses, NS-3 produced neuronal and/or behavioral disadvantages that may counteract the ameliorating effect of the disruption of the memory.

TRH has been reported to produce consistent antiamnestic actions in mice (44,45); however, in our present study using rats, TRH produced no significant antiamnestic effect except for the prevention of ECS-induced retrograde amnesia. This species difference may be partly due to the difference of its biological half-life of TRH in plasma. The plasma half-life of TRH in rats is short, being about one-tenth of that in mice (5). The fact that the greater resistance of NS-3 to enzymatic degradation was responsible for the antiamnestic effect in various types of amnestic models suggests that substantially TRH could also have similar effects in rats if plasma concentrations could be maintained at higher levels.

In conclusion, NS-3 will be a promising drug in ameliorating the cognitive impairment caused by cerebral cholinergic or adrenergic dysfunction, i.e., patients with senile dementia of the Alzheimer's type.

ACKNOWLEDGEMENT

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

REFERENCES

1. Alpern, H. P.; Marriott, J. G. Short-term memory: Facilitation and disruption with cholinergic agents. Physiol. Behav. 11:571–575; 1973.
2. Bassiri, R.; Utiger, R. D. Serum inactivation of the immunological and biological activity of thyrotropin-releasing hormone (TRH). Endocrinology 91:657–664; 1972.
3. Bøler, J.; Enzmann, F.; Folkers, K.; Bowers, C. Y.; Schally, A. V. The identity of chemical and hormonal properties of the thyrotropin releasing hormone and pyroglutamyl-histidyl-prolineamide. Biochem. Biophys. Res. Commun. 37:705–710; 1969.
4. Botwinick, C. Y.; Quartermain, D. Recovery from amnesia induced by pretest injections of monoamine oxidase inhibitors. Pharmacol. Biochem. Behav. 2:375–379; 1974.
5. Brewster, D. Species variations in TRH inactivation: Advantages of stable analogues. In: Griffiths, E. C.; Bennett, G. W., eds. Thyrotropin-releasing hormone. New York: Raven Press; 1983: 109–118.
6. Collerton, D. Cholinergic function and intellectual decline in Alzheimer's disease. Neuroscience 19:1–28; 1986.
7. Cumin, R.; Bandle, E. F.; Gamzu, E.; Haefely, W. E. Effects of the novel compound antiracetam (Ro 13-5057) upon impaired learning and memory in rodents. Psychopharmacology (Berlin) 78:104–111; 1982.
8. Dasheiff, R. M.; Savage, D. D.; McNamara, J. O. Seizures downregulate muscarinic cholinergic receptors in hippocampal formation. Brain Res. 235:327–334; 1982.
9. Davis, J. N.; Carlsson, A. Effect of hypoxia on tyrosine and tryptophan hydroxylation in unanaesthetized rat brain. J. Neurochem. 20:913–915; 1973.
10. Davis, J. N.; Carlsson, A. The effect of hypoxia on monoamine synthesis, levels and metabolism in rat brain. J. Neurochem. 21: 783–790; 1973.
11. Flohè, L.; Bauer, K.; Friderichs, E.; Gunzler, 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. 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.
13. Glick, S. D.; Zimmerberg, B. Amnesic effects of scopolamine. Behav. Biol. 7:245–254; 1972.
14. Gulati, A.; Nath, C.; Dhawan, K. N.; Bhargava, K. P.; Agarwal, A. K.; Seth, P. K. Effect of electroconvulsive shock on central cholinergic (muscarinic) receptors. Brain Res. 240:357–358; 1982.
15. Heal, D. J.; Stoodley, N.; Elliott, J. M.; Marsder, C. A.; Bennett, G. W.; Youdim, M. B. H. Behavioural and biochemical evidence for the release of noradrenaline in mouse brain by TRH and some of its biologically stable analogues. Neuropharmacology 26:313–322; 1987.
16. Hichens, M. A comparison of thyrotropin-releasing hormone with analogs: Influence of disposition upon pharmacology. Drug Metab. Rev. 14:77–98; 1983.
17. 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.

18. 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 studies by intracerebral microdialysis. J. Pharmacol. Exp. Ther. 268:255–261; 1994.
19. Khan, A.; Shim, H.; Mirolo, M. H.; Horita, A.; Douglas, R.; Tucker, G. J. TRH effects on arousal, locomotor activity and spontaneous alternation in ECS post-ictal state. Psychopharmacology (Berlin) 106:570–571; 1992.
20. Khan, A.; Lai, H.; Ukai, Y.; Mirolo, M. H. NS-3, a TRH-analog, reverses repeated ECS-induced deficits in water-maze performance in the rat. Pharmacol. Biochem. Behav. 47:477–481; 1994.
21. Knigge, K. M.; Schock, D. Characteristics of the plasma TRH-degrading enzyme. Neuroendocrinology 19:277–287; 1975.
22. Lerer, B.; Stanley, M.; Demetriou, S.; Gershon, S. Effect of electroconvulsive shock on muscarinic cholinergic receptors in rat cerebral cortex and hippocampus. J. Neurochem. 41:1680–1683; 1983.
23. Lewis, D. J. Sources of experimental amnesia. Psychol. Rev. 76: 461–472; 1969.
24. Marlin, N. A.; Berk, A. M.; Miller, R. R. Vulnerability of memory to electroconvulsive shock in relation to onset and offset of reinforcement. Physiol. Behav. 22:217–221; 1979.
25. McGaugh, J. L.; Alpern, H. P. Effects of electroshock on memory: Amnesia without convulsions. Science 152:665–666; 1966.
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. Miwa, S.; Fujiwara, M.; Inoue, M.; Fujiwara, M. Effects of hypoxia on the activities of noradrenergic and dopaminergic neurons in the rat brain. J. Neurochem. 47:63–69; 1986.
28. Molchan, S. E.; Mellow, A. M.; Lawlor, B. A.; Weingartner, H. J.; Cohen, R. M.; Cohen, M. R.; Sunderland, T. TRH attenuates scopolamine-induced memory impairment in humans. Psychopharmacology (Berlin) 100:84–89; 1990.
29. 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.
30. Narumi, S.; Nagai, Y.; Miyamoto, M.; Nagawa, Y. Thyrotropin-releasing hormone (TRH) and its analog (DN1417): Interaction with pentobarbital in choline uptake and acetylcholine synthesis of rat brain slices. Life Sci. 32:1637–1645; 1983.
31. Ogasawara, T.; Ukai, Y.; Tamura, M.; Taniguchi, N.; Kimura, K.; Sato, A. Effects of NS-3, an analogue of thyrotropin-releasing hormone, on the central nervous system. Biomed. Res. 14:317–328; 1993.
32. 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.
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. Pfeifer, W. D.; Bookin, H. B. Vasopressin antagonizes retrograde amnesia in rats following electroconvulsive shock. Pharmacol. Biochem. Behav. 9:261–263; 1978.
35. Quartermain, D.; Altman, H. J. Facilitation of retrieval by *d*-amphetamine following anisomycin-induced amnesia. Physiol. Psychol. 10:283–292; 1982.
36. Quartermain, D.; Botwinick, C. Y. Role of biogenic amines in the reversal of cycloheximide-induced amnesia. J. Comp. Physiol. Psychol. 88:386–401; 1975.
37. Roberts, R. B.; Flexner, J. B.; Flexner, L. B. Some evidence for the involvement of adrenergic sites in the memory trace. Proc. Natl. Acad. Sci. USA 66:310–313; 1970.
38. Schally, A. V.; Bowers, C. Y.; Redding, T. W.; Barrett, J. F. Isolation of thyrotropin releasing factor (TRF) from porcine hypothalamus. Biochem. Biophys. Res. Commun. 25:165–169; 1966.
39. Schmidt, D. E. Effects of thyrotropin releasing hormone (TRH) on pentobarbital-induced decrease in cholinergic neuronal activity. Commun. Psychopharmacol. 1:469–473; 1977.
40. Serota, R. G.; Roberts, R. B.; Flexner, L. B. Acetoxycycloheximide-induced transient amnesia: Protective effects of adrenergic stimulants. Proc. Natl. Acad. Sci. USA 69:340–342; 1972.
41. Smith, G. Animal models of Alzheimer's disease: Experimental cholinergic denervation. Brain Res. Rev. 13:103–118; 1988.
42. Yamamoto, M.; Ozawa, Y.; Takeuchi, H. Effects of YM-14673, a new thyrotropin-releasing hormone analogue, on impaired learning of passive avoidance in mice. Arch. Int. Pharmacodyn. 321:5–13; 1993.
43. 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.
44. 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.
45. 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.
46. 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.
47. Yarbrough, G. G. On the neuropharmacology of thyrotropin releasing hormone (TRH). Prog. Neurobiol. 12:291–312; 1979.