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BRIEF COMMUNICATION

Effects of a New TRH Analogue, YM-14673, on Disturbance of Passive Avoidance Learning in Senescence-Accelerated Mice

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YAMAMOTO, M., A. IWAI AND Y. OZAWA. *Effects of a new TRH analogue, YM-14673, on disturbance of passive avoidance learning in senescence-accelerated mice.* PHARMACOL BIOCHEM BEHAV **35**(3) 727–729, 1990.—Effects of a new TRH analogue, YM-14673 (N^{α}-[[(S)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide dihydrate), on disturbance of passive avoidance behavior were observed in senescence-accelerated mice (SAM). Latency of step-through in SAM-P/8/Ta (SAM-P/8, senescence-prone substrain) was significantly shorter than that in SAM-R/1/Ta (SAM-R/1, senescence-resistant substrain). Successive oral administration of YM-14673 (1 and 10 mg/kg) and TRH (10 mg/kg) for 3 weeks prolonged the shortened latency of step-through. These results suggest that YM-14673 is more potent than TRH in antiamnesic activities.

YM-14673 TRH Senescence-accelerated mice Passive avoidance

THERE are a number of rodent aged and experimentally induced amnesic models, and their utility in the study of memory decline has been reported (5,6). The senescence-accelerated mouse (SAM), developed by Takeda *et al.* (10), is one of the aging models, and a number of studies for investigating the pathogenesis of SAM are now ongoing. SAM consists of the senescence-accelerated prone mouse (SAM-P), and senescence-accelerated resistant mouse (SAM-R) which shows normal aging characteristics. Acceleration of senescence evaluated by a grading score system (3), spontaneous age-related amyloidosis accompanying the presence of the amyloid protein (2), and decrease in monoamine content of the hippocampus (11) have been already observed in SAM-P/8. Furthermore, disturbance of learned behaviors such as passive avoidance, active avoidance and water-maze performance has also been demonstrated, therefore, SAM-P/8 is anticipated as the age-related amnesic model for evaluating the drug action (7,12).

It is well known that thyrotropin releasing hormone (TRH) ameliorated the disturbance of learning behavior in rodents subjected to cycloheximide, scopolamine and anoxia (16,17). Ameliorating effects of YM-14673 (N^{α}-[[(S)-4-oxo-2-azetidinyl]carbonyl]-L-histidyl-L-prolinamide dihydrate; Fig. 1), a new TRH analogue, on disturbance of passive avoidance response have already also been reported in rodents subjected to scopolamine, cycloheximide, anoxia and cerebral ischemia (15,16). In addition, YM-14673 showed analeptic actions including antagonizing effects on pentobarbital sleeping time and ameliorating effects on disturbed consciousness induced by concussive head trauma in mice (13). YM-14673 was about 10–100 times more potent than TRH in these CNS-facilitating activities (13, 14, 16). The aim of the present study was to observe effects of YM-14673 and TRH on age-related disturbance of passive avoidance response in SAM-P.

METHOD

Animals and Drugs

Disturbance of learned behavior was observed from 2-month-old SAM-P/8 in our preliminary and other's results (7,12). In addition, spontaneous survival time of SAM-P/8 is reported to be about an average of 9.7 months (10). Therefore, in the present

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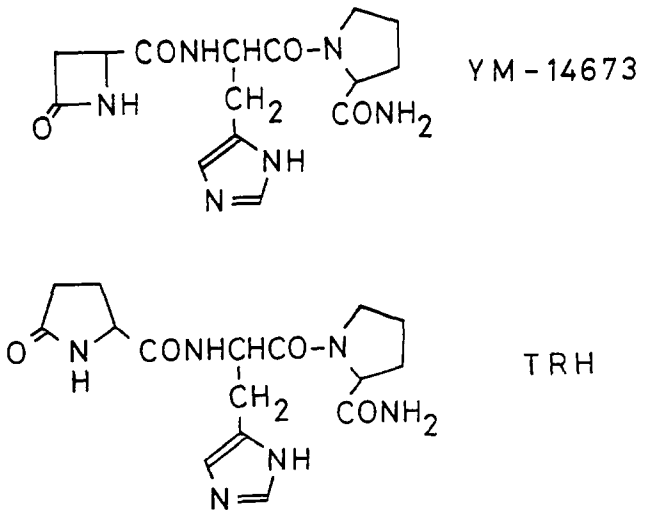

FIG. 1. Chemical structure of YM-14673 and TRH.

study, 6-month-old SAM-P/8/Ta and SAM-R/1/Ta mice were used. YM-14673 was synthesized in our laboratories and dissolved in distilled water before use. TRH (Peptide Institute) was obtained commercially and also dissolved in distilled water. Both drugs were administered orally with a volume of 0.1 ml/10 g body weight to the mouse. We used the drugs in doses which did not affect spontaneous movement and experimental pain response in normal rodents (9) (Fujihara *et al.*, personal communication). The results were analyzed with Kruskal-Wallis test and Mann-Whitney's U-test.

Passive Avoidance Learning

The training was carried out according to the one-trial step-through procedure described by Jarvik and Kopp (4). The mouse was placed in an illuminated "safe" compartment (14 × 10 × 10 cm) with a hole in the transverse wall through which the mouse could enter the dark compartment (20 × 45 × 25 cm), with a grid on the floor. Once the four paws were on the grid, a scrambled footshock (0.25 mA, 50 Hz) was delivered and the mouse could escape from the shock only by stepping back into the "safe" illuminated side. The test drugs were administered orally once a day for 20 days and thereafter administered orally 30 min before training on the 21st day after the first administration. In the test trial, 24 hr after the training, the mouse was again placed in the "safe" compartment and the response latency to enter the dark compartment was measured. The results were recorded as the average of latency of step-through for each experimental group of mice. The observation period for the behavior was maximally 300 sec in this test. The latency of mice which did not move into the dark compartment during the observation period was calculated to be 300 sec.

RESULTS

Latency of the step-through response in SAM-P/8 was significantly shorter than that in SAM-R/1 with 6-month olds (Table 1) in agreement with the report of Miyamoto *et al.* (7). Successive administration of YM-14673 (1 and 10 mg/kg PO) and TRH (10 mg/kg PO) for 3 weeks prolonged the shortened latency of step-through in the passive avoidance response (Table 1).

TABLE 1

EFFECTS OF YM-14673 AND TRH ON THE STEP-THROUGH PASSIVE AVOIDANCE RESPONSE IN SAM

SAM	Treatment	Dose (mg/kg PO)	N	Latency of Step-Through (sec)
R/1	Solvent	—	9	266 ± 13
P/8	Solvent	—	10	110 ± 24*
	YM-14673	0.1	8	190 ± 39
		1	8	218 ± 36†
		10	8	238 ± 33†
	TRH	1	8	134 ± 39
		10	8	221 ± 34†

Each value represents the mean ± SE. The solvent and drugs were administered orally once a day for 20 days and thereafter administered 30 min before training on 21st day after first administration. Significantly different from the value for SAM-R/1: *$p<0.01$ (Mann-Whitney U-test). Significantly different from the value for solvent group in SAM-P/8: †$p<0.05$, statistically significant at $p=0.012$ by Kruskal-Wallis H-test. Each comparison was done by Mann-Whitney U-test.

DISCUSSION

In the present study, the shortened latency of step-through was observed in SAM-P/8 in agreement with other's results (7,12). It suggests that SAM-P/8 exhibits learning impairments that parallel those seen with aging. YM-14673, as well as TRH, prolonged the shortened latency of step-through in SAM-P/8. Since spontaneous movement and experimental pain response in rodents were not affected by administration of both drugs in doses showing the ameliorating effects on disturbance of learned behavior (9) (Fujihara, personal communication), the ameliorating actions of TRH and the TRH analogue may be ascribable to the facilitation of cognitive function itself. Furthermore, since the drugs were administered before training, the pharmacological actions of YM-14673 and TRH may be due to their effects on acquisition and consolidation phase of learned behavior.

A number of biochemical studies in SAM have been now ongoing. Recently, Tanaka *et al.* (11) reported that a decrease in norepinephrine contents of the hippocampus was observed in SAM-P/8. Therefore, the disturbance of learned behavior in SAM-P/8 may be ascribable to the decrease in norepinephrine contents. YM-14673, as well as TRH, antagonized hypothermia and PGO (ponto-genicullo-occipital) wave in reserpinized animals (14), and increased monoamine metabolites in rat's brain (Terai, personal communication, 1988). Involvement of central noradrenergic and serotonergic systems has been proposed in inducing hypothermia and PGO wave of reserpinized animals, respectively (1,8). These results suggest that the YM-14673 and TRH possess facilitatory effects on central monoaminergic systems. Therefore, ameliorating effects of both YM-14673 and TRH on disturbance of learned behavior may be ascribable to their facilitatory effects on central monoaminergic systems.

It has been already reported that YM-14673 ameliorated the disturbance of learned behavior in rodents subjected to scopolamine, cycloheximide, anoxia and cerebral ischemia (15,16). These results were evaluated by measuring the latency 24 hr after the training (acute effect). In the present study, the drugs were administered for 3 weeks (chronic effect), but we did not study the acute effect. From previous acute and present chronic studies, there do not seem to be differences between acute and chronic effects. In addition, the previous and present results strongly support that YM-14673 possesses facilitatory effects on cerebral function. Therefore, clinical efficacy of YM-14673 is anticipated for treatment of psychiatric symptoms in patients with organic brain syndrome such as cerebral vascular disease, head injury and senile dementia.

In conclusion, both YM-14673 and TRH ameliorated the age-related disturbance of learned behavior suggesting that YM-14673 possesses the facilitatory effects on cerebral functions.

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