HYPERTHERMIA INDUCED BY THYROTROPIN-RELEASING HORMONE (TRH, PROTIRELIN) IN THE RAT

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The effect of the thyrotropin-releasing hormone (TRH, protirelin), one of the hypothalamic releasing hormones, on body temperature was investigated in the rat. TRH tartrate dissolved in saline, in doses of 1, 5, 10 and 20 mg/kg, was injected intraperitoneally to male Wistar rats weighing 200-250 g. The rectal temperature was measured with the electronic thermometer inserted into 5 cm inner from the anus. TRH tartrate caused a temporary rise in body temperature dose-dependently. The degree of the rise in body temperature ranged from 0.5°C to 1.5°C as a mean and the hyperthermia appeared early and lasted for 80 min after the peptide administration. The thyroidectomized rats injected 20 mg/kg of TRH which induced a significant hyperthermia in the sham-operated animals, failed to show a rise in body temperature. The present results suggest that a release of thyroid hormone might participate in the hyperthermic action of TRH.

INTRODUCTION

Recently, many literatures on neurohormones have been published. Among the peptides in the brain, thyrotropin-releasing hormone (TRH, protirelin) has been studied not only because of its usefulness for diagnostic and/or therapeutic aspects of neuroendocrinological disorders but also because of its efficacies on some psychiatric disorders.

Prange and Wilson (1972a) and Prange et al. (1972b) reported TRH was effective in depressed patients and the results were supported by other authors. However, Takahashi et al. (1973) described this peptide was not useful for the treatment of these patients. Inanaga et al. (1975a, 1975b) reported TRH given with a combination of neuroleptics improved symptoms in some type

of schizophrenics and these results have been confirmed by the double-blinded controlled study of TRH in schizophrenic patients (Inanaga et al. 1978).

In addition to these clinical values of TRH, it has also been reported that TRH not only antagonized the hypothermia induced by chlorpromazine in mice, rats and rabbits (Kruse 1975) and by pentobarbital in rodents (Prange et al. 1974) and ethanol narcosis in mice (Breese et al. 1974) but also potentiated the action of L-DOPA (Plotnikoff et al. 1974a, 1974b). According to their reports, the action of TRH on body temperature has been considered to be independent of thyroid hormone releasing action. In the present study, the authors, however, describe the possibility

that a release of thyroid hormone might have a close relation to the hyperthermia induced by TRH in the rat.

METHODS

Ninety male Wistar rats weighing 200-250 g were subjected to the study. In the first experiment, 50 rats were divided into five groups randomly. Four doses of TRH tartrate dissolved in physiological saline, i. e., 1 mg/kg, 5mg/kg, 10 mg/kg and 20 mg/kg, were administered intraperitoneally to the four groups and saline to the remaining control group. Rectal temperature was measured at the place 5 cm inner from the anus with the electronic thermister (Nihon Kohden) before and after treatment with TRH or saline.

In the second experiment, 40 rats were thyroidectomized or sham-operated

under the anesthesia by thiopental sodium. Ten days after the operation, 20 mg/kg of TRH or saline was administered to the thyroidectomized and sham-operated animals by i. p. and rectal temperature was measured using the same method as used in the first experiment.

These two experiments were undertaken from 1 p. m. to 4 p. m. and the room temperature was kept at $24 \pm 1^\circ\text{C}$ through the experiments including the breeding period.

For a statistical analysis, Student's t test (two-tailed) was adopted.

RESULTS

The Effect of TRH on Rectal Temperature in the Rat

The changes in the rectal temperature after treatment with TRH and saline are shown in Table 1. The rectal

TABLE 1
Effect of TRH on rectal temperature in the rat

Treatment (i. p.)	Rectal temperatures ($^\circ\text{C}$) at various time after TRH							
	0	20	40	60	80	100	120	180 min
Saline	37.9	38.4	38.3	38.2	38.1	38.1	37.9	38.0
	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.13	0.09	0.09	0.08	0.03	0.06	0.08	0.10
TRH 1 mg/kg	37.9	38.5	38.2	38.2	38.1	38.1	37.9	37.9
	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.04	0.08	0.10	0.04	0.08	0.06	0.08	0.07
TRH 5 mg/kg	37.9	38.6	38.3	38.4	38.2	38.1	38.1	38.0
	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.08	0.07	0.07	0.08	0.05	0.08	0.08	0.06
TRH 10mg/kg	37.9	38.9**	38.9***	38.5	38.3*	38.4	38.3	38.0
	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.05	0.11	0.12	0.11	0.10	0.06	0.09	0.09
TRH 20mg/kg	37.9	39.2***	39.3***	38.9***	38.5***	38.3	38.2	38.0
	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	0.05	0.08	0.07	0.07	0.06	0.08	0.09	0.08

Each group consists of 10 rats. All groups treated with TRH were compared with the saline-treated group. Each value is shown as a mean $\pm$ S.E.M.. Statistical significances are indicated as follows: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

temperature of the rat injected 20 mg/kg of TRH rose markedly 20 min after injection, reached to the peak at 40 min, then gradually decreased and recovered to the range of saline injected rats approximately 100 min after. The increase in body temperature in the group treated with 20 mg/kg was statistically significant as compared with that in the saline group at 20, 40, 60 and 80 min after injection. Also, TRH 10 mg/kg group showed a similar tendency; the rectal temperature increased significantly at 20, 40 and 80 min and the maximum rise was obtained at 40 min. In the rats injected 1 or 5 mg/kg of TRH, no significant rise in rectal temperature was observed. This temporary hyperthermia induced by TRH occurred dose-dependently.

The Effect of Thyroidectomy on Hyperthermia induced by TRH

As shown in Fig. 1, TRH induced the marked rise in rectal temperature at 20-80 min, when given to the sham-operated rats, and these rises significantly differed from those in the saline injected, sham-operated rats at 20, 40, 60 and 80 min after injection ($P < 0.001$). However, the thyroidectomized rats injected 20 mg/kg of TRH did not show any significant rise in rectal temperature as compared with those injected saline (Fig. 2).

DISCUSSION

In the present study, it was observed that TRH caused the rise in rectal temperature in the rat and that the hyperthermia occurred in a dose-dependent manner. The degree of the rises in body temperature ranged from 0.5°C to 1.5°C as a mean. The hyperthermia appeared early after injection and the duration was not so long. Metcalf (1974)

reported hypothermia occurred by intraventricular injection of TRH in the cat and suggested the action of the peptide was similar to that of Ca^{++} or noradrenaline. A dose-related increase in body temperature after intraventricular administration of TRH in the rabbit was found by Horita et al. (1975). As for the rat, Kruse (1975) reported TRH antagonized chlorpromazine-induced hypothermia, however, did not significantly raise body temperature. Wei et al. (1975) described intracranial injection of TRH in the rat induced shaking which was considered to be much related to heat gain mechanisms. As far as the effects of this peptide on body temperature are concerned, the results reported previously are conflicting. The same phenomenon is seen in the studies concerned with thermoregulation and brain monoamines. Cooper et al. (1965) pointed out there existed a great species difference as for thermoregulation, especially with its relationship to monoamines. Moreover, experimental condition should be strictly controlled since body temperature is easy to be influenced by such factors as environmental temperature. The present study exhibited that the systemic administration of TRH induced hyperthermia in the rat. The mechanism of the hyperthermia induced by the peptide was uncertain. It appears likely that the action of TRH on body temperature occurred mainly via the thyroid gland since thyroidectomized animals failed to show hyperthermia even after injection of a high dose of TRH 20 mg/kg which caused the marked rise in body temperature in the sham-operated animals from 20 min to 80 min after injection.

According to other evidences obtained in animals, it has been suggested that TRH can possess actions independent of pituitary-thyroid system and

Fig. 1. Time course change in rectal temperature in the sham-operated rats after an i. p. injection of TRH 20 mg/kg or saline. The experiment was undertaken 10 days after the operation. Each group consists of 10 rats.

Fig. 2. Time course change in rectal temperature in the thyroidectomized rats after injection of TRH 20 mg/kg or saline. The experiment was undertaken 10 days after the operation. Each group consists of 10 rats.

many reports have been published on a relationship between TRH and the brain monoamine metabolism. Constantinidis et al. (1974) suggested the turnover of noradrenaline was enhanced by TRH in the cerebral cortex and hypothalamus of the rat using a fluorescence microscopic method. Keller et al. (1974) investigated about the accumulation of 3-methoxy-4-hydroxy phenylethylene-glycol (MOPEG, isolated as the sulphate ester), the major metabolite of noradrenaline in the rat brain after an i. p. injection of TRH and described that TRH probably caused an activation of noradrenergic neuron in the rat brain. Horst and Spirt (1975) reported using H^3 -labelled noradrenaline that TRH caused an increase in the release and turnover of noradrenaline in rat brain tissue. Also, Plotnikoff et al. (1974 a, 1974 b) reported TRH potentiated the behavioral effects of L-DOPA in the rat. Clinically, Inanaga et al. (1975) reported a relatively small amount of TRH and L-DOPA showed a similar improvement in a certain type of the schizophrenics if administered with a combination of neuroleptics. However, Reigle et al. (1974) described that with the possible exception of a slight enhancement of release, acute or chronic administration of TRH had little effect on the disposition and metabolism of H^3 -noradrenaline in the rat brain. Plotnikoff (1975) and Miyamoto and Nagawa (1977) suggested the possibility that TRH acted via the dopamine system in the rat brain. As described above, the data in the previous reports on a relationship between TRH and the brain monoamine metabolism are conflicting similarly as those in many literatures on the role of these monoamines on thermoregulation. However, most reports suggested the turnover of noradrenaline in rat brain was enhanced by TRH treatment. These data being

taken into consideration, the enhanced noradrenaline turnover in the brain might be involved in the hyperthermia induced by TRH independent of the mechanism via the thyroid system. However, such possibility seems unlikely and the finding in the study subjected to the thyroidectomized rats, suggests a release of thyroid hormone might mainly participate in the hyperthermic action of the peptide.

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