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Original Research

Protirelin (thyrotropin-releasing hormone) in thyroid gland: possible involvement in regulation of thyroid status

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ABSTRACT

AIM: To establish the presence of the hypothalamic hormone protirelin (thyrotropin-releasing hormone, TRH) in human thyroid and to investigate whether the concentration of this peptide in the thyroid gland is sensitive to thyroid status. **METHODS**: A procedure has been developed for the determination of TRH in the thyroid gland, distinct from TRH-like peptides which also react with TRH-antibody. **RESULTS**: Human thyroid was shown to contain both authentic TRH and TRH-like peptides, a similar pattern was seen in a range of animal thyroids. The concentrations of TRH in non-active goiter thyroids were substantial (41.6 - 248 pmol · g^{-1}); in contrast the thyroids from hyperthyroid patients contained very little TRH (0.01 - 2.52 pmol · g^{-1}). **CONCLUSION**: The physiologic role of TRH in the thyroid is not known but the large difference between the concentrations of this hormone in non-active and hyperactive thyroids suggests that thyroidal TRH may be involved in the regulation of thyroid status.

INTRODUCTION

During the course of our studies on protirelin (thyrotropin-releasing hormone, TRH) and TRH-like peptides in non-human primates[1] and on the influence of these peptides on thyroid status[2], we observed that the thyroid gland of the marmoset contained a high concentration of TRH. Since TRH originates primarily in the hypothalamus, acting via a portal system to release thyrotropin (thyroid stimulating hormone, TSH) from the pituitary[3,4], the finding of a high concentration in the thyroid gland was unexpected and led us to examine the levels of this peptide in human thyroid and in the thyroid of a number of mammalian species. In addition we have determined the levels of TRH in the thyroid glands from a series of hyperthyroid patients in order to see whether the concentrations are influenced by thyroid status.

MATERIALS AND METHODS

Thyroid glands removed at surgery were immediately frozen at - 80 ℃ and peptides were extracted from the tissues (40 - 100 mg) by homogenization at 4 ℃ in acidified acetone. After removal of solvent, the residues were dissolved in 50 % acetic acid in preparation for mini-column cation exchange chromatography[5], a procedure which separates authentic TRH from TRH-like peptides. The retention of TRH on this column was confirmed by the inclusion of ^{125}I-TRH with each tissue extract before chromatography. The TRH and TRH-like peptides present in the fractions obtained from the column were determined by RIA with a TRH-antibody[6,7]. The identity of the TRH in the thyroid with the known hypothalamic hormone pGlu-His-Pro amide was confirmed by comparison with the synthetic peptide in 3 chromatographic systems.

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RESULTS

In all mammalian thyroid glands studied, authentic TRH was present in substantial concentration (Tab 1).

Tab 1. Concentrations of protirelin (thyrotropin-releasing hormone, TRH) in thyroid glands of different mammalian species. The concentration given represents the mean values obtained by analysis of 2 – 5 animals.

Mammal	Protirelin/ pmol·g^{-1}
Rat*	28.9
Guinea pig*	37.4
Dog*	11.6
Marmoset†	276
Monkey†	15.8

* bred in the University of Murcia, † bred in the MRC Reproductive Biology Unit, Edinburgh, Scotland.

In contrast the thyroid glands from a series of hyperthyroid patients (8 with struma nodosa, 1 with Basedow), who had received thiamazole and/or propranolol for periods of 3 – 5 wk with doses related to the degree of elevation of the T_3/T_4 levels and other indications such as pulse rate, exhibited very low concentrations of TRH (Tab 2).

Tab 2. Concentrations of protirelin (thyrotropin-releasing hormone, TRH) in thyroid glands of patients with hyperthyroid and euthyroid status.

Patient	Pro/ pmol·g^{-1}	T_3/ μg·L^{-1}	T_4/ μg·L^{-1}	Thy/ mU·L^{-1}	Drug
1	0.92	1.55	88	0.20	Propranolol
2	<0.01	1.03	83	0.04	Thiamazol + propranolol
3	0.07	1.31	53	0.03	Thiamazol + propranolol
4	<0.01	1.33	74	0.45	Thiamazol
5	0.41	2.90	132	0.01	Thiamazol
6	0.28	0.90	76	0.02	Thiamazol
7	0.32	1.49	89	0.02	Thiamazol
8	0.06	1.80	86	0.01	Thiamazol
9	2.52	10.5	507	0.01	Thiamazol
10	41.6	1.32	76	3.41	–
11	206	1.43	74	2.20	–
12	215	2.80	75	1.70	–
13	248	n.d.	n.d.	n.d.	–

n.d. = not determined or data not available
*patient with Basedow hyperthyroidism
patients 1-9 were hyperthyroid and 10-13 were euthyroid (goitre).

These patients also exhibited, as expected, low or very low levels of TSH in the circulation (0.01 – 0.45 mU · L^{-1}). For comparison, normal TSH values range from 0.36 to 3.5 mU·L^{-1}. The very low levels of TRH in the hyperactive thyroids contrasted with the values in thyroid tissue from patients ($n = 4$) with non-active goiter (40 – 250 pmol · g^{-1}) who exhibited normal levels of T_3/T_4 and TSH. They were also much lower than the concentrations of TRH determined in the thyroid glands from a number of animal species. The hyperactive human thyroids alone contained negligible TRH.

The TRH-like peptides, which were not retained on the mini-column but reacted with TRH antibody, exhibited less variation. The concentrations of these peptides in the hyperactive thyroids ranged from 0.8 to 2.4 pmol·g^{-1} while the values in the euthyroid tissues were between 3.0 and 17.7 pmol · g^{-1}. TRH-like peptides are in general more widely distributed than TRH and may fulfil different roles in the thyroid and elsewhere. It is of interest, however, that while these peptides were present in low concentration in the thyroids from euthyroid patients, they accounted for the the TRH-immunoreactivity in the hyperactive thyroids. This emphasizes the need for distinguishing between authentic TRH and TRH-like peptides in studies where RIA is used for TRH determination.

A patient presenting with Basedow hyperthyroidism (Graves disease), with very low circulating TSH, contained a low but significant concentration of TRH in the thyroid. In this case it may be relevant that the hyperthyroidism was not completely suppressed, despite prolonged treatment with thiamazole (Tab 2). It may also be mentioned that a melanoma tissue was found to contain an exceptionally high concentration of both TRH (> 500 pmol · g^{-1}) and TRH-like peptides. However, the concentration of TRH in the thyroid of a patient with infiltrated carcinoma of the thyroid, without hyperactivity, was within the normal range (215 pmol·g^{-1}).

DISCUSSION

This study showed that thyroid tissue from a series of hyperthyroid patients contained little or no TRH whereas the thyroids of patients with non-active goiter contained high levels of this hormone. In the hyperthyroid patients the thyroid cells were clearly

hyperactive since they continued to produce and release the thyroid hormones T_3 and T_4 even though the levels of circulating TSH were very low. In these cases the hyperactivity could not be due to hypothalamic TRH since the action of this hormone was mediated through the release of TSH. The hyperactivity may be due to the presence of thyroid stimulating antibody; however the hyperactivity may also be related to the absence of thyroidal TRH.

The hyperthyroid tissues in this study were principally from patients with struma nodosa where the activity is confined to nodules. We observed that the levels of TRH in the thyroid of these patients were low not only in the nodules but also in the parenchyma. This indicates that the TRH deficiency was characteristic of the thyroid gland as a whole. It appears that the concentration of TRH in the thyroid gland reflects the concentrations of TRH released from the hypothalamus, since in the hyperthyroid state little TRH is released from the hypothalamus and the thyroid gland produces negligible TRH whereas in the hypothyroid state the production and release of TRH from the hypothalamus is augmented and the thyroid will contain substantial TRH. Thus a synchronization between hypothalamic and thyroidal TRH is suggested, indicating that the thyroidal TRH may be involved in the regulation of thyroid status.

One possibility is that the TRH in the thyroid acts in a paraerine manner to inhibit excessive release of thyroid hormones, consistent with the *in vitro* experiments of Delbeke *et al*[8] and Iversen and Laurberg[9] who observed that synthetic TRH had an inhibitory effect on thyroid slices *in vitro*. Alternatively the thyroidal TRH may be released into the circulation and act on the pituitary to supplement the control that is exercised by the hypothalamic hormone. In this connection it is notable that the levels of TRH in rat thyroid[10] and also in rat pancreas[11] are markedly elevated in hypothyroid rats and a common role for pancreatic and thyroidal TRH could be envisaged. Thus thyroidal TRH and possibly pancreatic TRH may fulfil a supportive role in the regulation of thyroid status.

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甲状腺中普罗瑞林可能参与甲状腺功能的调节

关键词 普罗瑞林; 甲状腺; 促甲状腺素; 甲状腺激素; 甲状腺功能亢进; 甲状腺肿

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