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TRH: Pathophysiologic and Clinical Implications

C. R. Pickardt[1] and **P. C. Scriba**[2]

[1] Medizinische Klinik Innenstadt der Universität München, Federal Republic of Germany
[2] Klinik für Innere Medizin der Medizinischen Hochschule Lübeck, Federal Republic of Germany

Summary

Thyrotropin releasing hormone is thought to be a tonic stimulator of the pituitary TSH secretion regulating the setpoint of the thyrotrophs to the suppressive effect of thyroid hormones. The peptide stimulates the release of normal and elevated prolactin. ACTH and GH may increase in response to exogenous TRH in pituitary ACTH and GH hypersecretion syndromes and in some extrapituitary diseases.

The pathophysiological implications of extrahypothalamic TRH in humans are essentially unknown.

The TSH response to TRH is nowadays widely used as a diganostic amplifier in thyroid diseases being suppressed in borderline and overt hyperthyroid states and increased in primary thyroid failure. In hypothyroid states of hypothalamic origin, TSH increases in response to exogenous TRH often with a delayed and/or exaggerated time course.

But in patients with pituitary tumors and suprasellar extension TSH may also respond to TRH despite secondary hypothyroidism. This TSH increase may indicate a suprasellar cause for the secondary hypothyroidism, probably due to portal vessel occlusion. The TSH released in these cases is shown to be biologically inactive.

Keywords: TRH; diagnostic significance; hypothalamic diseases; pituitary failure.

TRH, initially detected and synthesized as the hypothalamic hormone that controls the thyrotrophic activity was found to stimulate the prolactin release in vivo and in vitro[43, 45, 63, 72, 77]. Moreover, TRH has been shown to be widely distributed over the central nervous system[36, 37, 44, 71], where it is believed to have neurotransmitter functions besides the hypophysiotropic effects.

TRH has been detected in the upper gastrointestinal tract[14], where its endogenous functions are unknown. Exogenous TRH inhibits the pentagastrin stimulated gastric secretion[12] and by some degree the glucagon and pancreatic polypeptide release after insulin induced hypoglycemia[13].

TRH and Thyrotropic Activity

Experimental and pathological disruption of the hypothalamic supply of the pituitary with TRH results in decreased thyroid function[47], called secondary hypothyroidism. TRH antibodies induce impairment of thyroid function with some effects on the prolactin secretion as well[28, 32, 39, 76]. But until now, there are no consistent data on the physiological hypothalamo-pituitary relationship in humans. This is due to the fact that serum and urinary TRH is mainly derived from extrahypothalamic sources[46]. In experimental hypo- and hyperthyroidism the hypothalamic content of TRH does not change[52] arguing against a feedback inhibition between TRH and TSH. There are few studies reporting a decrease of TRH in hyper- and an increase in hypothyroidism with marked differences in the reported normal levels[29, 50]. Most authors postulate today that TRH is a tonic stimulator of the TSH secretion, modulating the set point of the thyrotrophs to the suppressive effect of thyroid hormones[47].

TSH responses to TRH are modulated by estrogens in females and in males[20]. This modulation is due to increasing binding sites of pituitary cells under estrogen influence which can be partly antagonized by thyroid hormones[42].

Repetitive intravenous and chronical oral TRH administration in euthyroid and hypothyroid individuals results in a decrease of serum TSH[1, 4, 34, 38, 62, 75] and in euthyroids in an increase of thyroid hormones within the upper normal range[3, 34, 62]. The TSH decrease following TRH administration was also observed in athyroid patients[75]. The latter finding may be suggestive for down regulation of the TRH receptor of the thyrotrophs which is transient[62], or for a predominant stimulation of TSH release and a slower de novo synthesis of pituitary TSH[38]. The simultaneous de-

crease of PRL under these conditions was more pronounced [51].

The thyrotropic activity is under an inhibitory control of somatostatin [78] and dopamine [5, 11, 27, 48, 63, 66], which is more evident in euthyroids, mild and treated hypothyroidism than in severe hypothyroidism [8, 25]. Dopamine modulates the diurnal variations of TSH [67, 74]. In states with increased hypothalamic dopamine turnover the tonic inhibition of TSH is thought to be enhanced [68]. This seems to have no clinical implications since oral treatment with dopamine agonists [40] and antagonists [81] does not influence TSH levels and TSH response to TRH.

TRH and Other Pituitary Hormones

In normal adults TRH does not influence the release of GH and ACTH [53]. In states with borderline or overt functional disturbances of the GH producing cells, such as active acromegaly [82, 83], children with constitutional tall stature and elevated somatomedin levels [17] and in type I diabetes, predominantly in females [7] and in newborns, when TRH was administered to the mother shortly before delivery [64], TRH may stimulate GH release. In addition, TRH reduces the somatostatin induced inhibition of GH release in vitro [16].

TRH stimulates prolactin release in normal, hyper- and hypothyroid individuals [43, 45, 63]. Elevated prolactin levels have been observed in patients with primary hypothyroidism and can be lowered by thyroid hormones. In hyperthyroidism mean prolactin levels are lower as compared to normals and increase during antithyroid treatment [72]. Recently, specific inhibition of prolactin synthesis (decrease of PRL m RNA) by T 3 in vitro was shown [49].

In normals prolactin is mainly under the inhibitory hypothalamic control and the observed modulation of prolactin secretion by TRH gain clinical significance only in severe hypothyroidism.

In prolactinomas the TRH induced prolactin increase is low with high basal levels of prolactin and vice versa [26].

In patients with Cushing's disease [61] TRH may induce a paradoxical rise of ACTH.

Thus, TRH like GnRH may be recognized as a stimulator by non thyrotropic pituitary cells under pathological conditions.

Modulation of the TSH Response to TRH by Non-thyroidal Endocrine and Non-Endocrine Diseases

The TSH response to TRH is nowadays widely used as a diagnostic tool in thyroidology. Therefore, it was necessary to evaluate factors and hormones which modulate the TSH response in non-thyroidal endocrine and non-endocrine diseases.

In Cushing's syndrome irrespective of the pathogenesis and during glucocorticosteroid pharmacotherapy basal TSH and TSH response may be blunted or suppressed [21, 41, 54, 73, 84], and return to normal after successful treatment of hypercortisolism. In Addison's disease moderately elevated basal TSH levels have been observed [3].

In patients with active acromegaly blunted TSH response to TRH has been reported [10, 82] and TSH response may be elevated in GH deficiency [10].

Recently, diminished TSH stimulation has been reported in chronic hypercalcemia and a pronounced increase in hypoparathyroid individuals [33], variations which return to normal after correction of serum calcium levels.

There is an increasing number of data on decreased TSH response to TRH in patients with severe non-thyroidal illness and during total fasting [35, 70]. The pathogenesis of these disturbances in the TSH responsiveness of the pituitary is not yet well understood. Patients do not exhibit clinical signs of hypothyroidism despite the concomittant development of considerable alterations in the peripheral thyroid hormone metabolism. These phenomena were recently reviewed [80].

These modulations of the TSH response to TRH in endocrine and non-endocrine diseases have to be kept in mind when using the TRH-test for clinical purposes.

TRH Test in Diagnosis of Hypothalamic and Pituitary Diseases

When TRH became available for clinical investigations, the TRH-test was expected to differentiate between hypothalamic and pituitary origin of central hypothyroidism. Patients with hypothyroidism of obvious hypothalamic origin were shown to have the expected response of TSH to TRH [31, 56, 58, 69], which is often delayed and or exaggerated [19, 22, 23].

But patients with pituitary tumors, suprasellar extension and visual field impairment exhibited an unexpected TSH response to TRH [19, 56] which is often delayed and exaggerated as well. The net increment of TSH may not differ from normals or from euthyroid patients with pituitary tumors (Fig. 1).

In none of our patients the TSH-response to TRH was completely absent before pituitary surgery and only in some of them postoperatively [56, 57].

Similar data were reported from other groups [19, 31, 55]. Thus, the failure of TRH test to differentiate

between hypothalamic and pituitary insufficiency was documented.

These findings allow at least two hypothetical explanations. From our data in patients with large pituitary tumors we suggested, that the increase of TSH levels after TRH indicates a suprasellar cause of

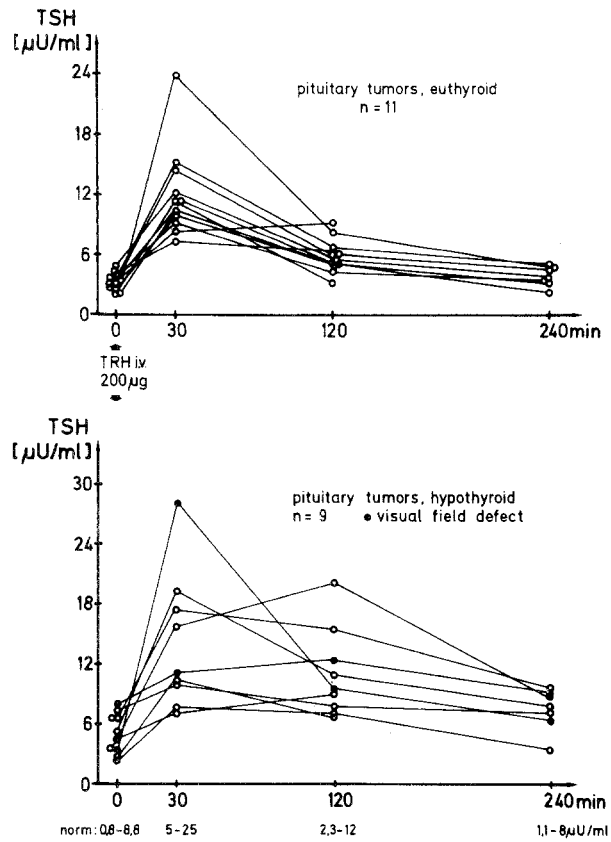

Fig. 1. TSH-response to TRH in patients with pituitary tumors. The upper panel depicts the TSH-response to TRH in 11 euthyroid patients, in the lower panel the TSH-response in 9 hypothyroid patients is demonstrated

secondary hypothyroidism, probably due to a partial occlusion of the portal vessel system, thus preventing the endogenous TRH from reaching the remaining pituitary thyrotrophs [56, 57, 58, 69]. This explanation was picked up very recently for the recovery of partial pituitary insufficiency after treatment of large inactive pituitary tumors [2] and for a moderate increase in PRL levels after irradiation of the pituitary in acromegaly [9].

Faglia and coworkers initially postulated the secretion of a biologically inactive TSH [19]. In further investigations they documented an impaired T3 increase after TRH induced elevation of the TSH levels [22] and diminished biological activity of the TSH in a cytochemical bioassay despite immunoidentity to standard TSH [23]. More recently, the group published the observation of an elevated ratio of β TSH to α TSH subunit in idiopathic central hypothyroidism [24]. Oral treatment with TRH in one patient resulted in a decrease of the β/α ratio and his thyroid became responsive to the endogenous TRH-stimulated TSH. The authors conclude that TRH may be imperative in the secretion of TSH with full biological potency.

TRH Test as a Thyroid Function Test

In euthyroid men basal TSH levels as measured by radioimmunoassay are undetectable in about 30%. Thus, by means of basal TSH one can not distinguish suppressed TSH secretion from normal. Therefore, TRH-unresponsiveness of TSH offers more information. The test is nowadays used as an amplifyer in cases of borderline hyperthyroidism in "euthyroid" Graves' disease before and after treatment, in cases with autonomous functioning solitary and multiple adenomas and in nodular goiters [30]. Using the TRH test for routine purposes it became obvious that in our hospital population in 446 patients observed over a period of 12 months TSH suppression was due to preclinical hyperthyroidism in 88 (20)%. Out of these about 44% were iodine contaminated. In our area with nutritional iodine deficiency, endemic goiter and an increased prevalence of autonomous adenomas, patients at risk for hyperthyroidism are more easily detected by TRH-test as compared to investigations of the peripheral thyroid hormone levels alone. In this context it may be of interest that in the course of longterm treatment with the antiarhythmic drug Amiodarone about 30% of bavarian patients developed preclinical hyperthyroidism [60].

By the combination of TRH stimulation test and the scinti-scans autonomous adenoma [59] can be classified into different groups depending on the extent of TSH suppression. For economical reasons some European investigators use the test as a first step diagnostic tool.

In primary thyroid failure exaggerated TSH-response may indicate earlier thyroid insufficiency, undetectable by clinical signs, lowered thyroid hormones or elevated basal TSH, a situation found in about 20% of patients with endemic goiter in this area.

Therapeutical Aspects

Experimental investigations of cardiovascular function and survival rates in endotoxic shock gave rise to the conclusion that TRH administered intravenously in high dosages improves the outcome in experimental animal models. In addition, Faden and coworkers observed a significantly better neurological recovery after spine injury in cats [18]. They explain these effects by

a partial opiate antagonism of TRH because similar effects occur during treatment with naloxone.

In humans, TRH was found to improve ataxia in patients with spinocerebellar degeneration. Recently, Engel and coworkers[15] reported marked improvement of weakness and spasticity in amyotrophic lateral sclerosis after TRH i. v. The justification for treatment was derived from the observation in animals, where TRH has been detected in nerve endings in the ventral horn of lower motor neurons and in nerve endings in motor nuclear V, VII, XII. In a preliminary study the authors found reduced TRH levels in CSF of patients with amyotrophic lateral sclerosis and other spastic diseases.

Because amyotrophic lateral sclerosis is a progressive disease, these observations prompted us to initiate a pilot study with oral TRH in one patient who is presently under investigation.

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Author's address: Dr. C. R. Pickardt, Medizinische Klinik Innenstadt der Universität München, Ziemssenstrasse 1, D-8000 München, Federal Republic of Germany.