

# Thyrotrophin-releasing hormone in clinical practice

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Thyrotrophin-releasing hormone (TRH), a tripeptide with the formula pyroglutamyl histidylprolinamide, was first isolated by Schally and his coworkers in 1969 and now has an established role in clinical endocrine practice. When given to animals in pharmacological doses it has a variety of neurotropic actions. These include arousal; increased respiration, muscle tone, and body temperature; and emotional behaviour. It also increases the LD<sub>50</sub> of barbiturates. Side effects in man are minor and transient with the 200- $\mu$ g intravenous dose used in the standard TRH test. They include nausea, a desire to micturate, flushing, dizziness, an unusual taste, and an increase in the pulse rate. No adverse effects on the liver, kidney, or bone marrow have been reported.

The widespread distribution of TRH in the cerebral cortex, hypothalamus, and spinal cord have led to the suggestion that it may act as a neurotransmitter, but in man there is no good evidence to support this view. It has no effect on the contingent negative variation, a sensitive indicator of the brain activity which results from other agents such as diazepam and nicotine (Ashton *et al.*, 1976).

## Factors affecting TRH test in normal subjects

The peak TSH response to an intravenous 200- $\mu$ g bolus of TRH occurs between 20 and 30 minutes, and 20 minutes has usually been chosen as the peak for the standard TRH test. TSH levels return towards basal after 60 minutes, but it is unnecessary to take a 60-minute specimen when investigating a patient with thyroid disease. The TSH released by TRH acts on the normal thyroid to release tri-iodothyronine (T<sub>3</sub>), with a peak level at about 3 hours after injection, and thyroxine (T<sub>4</sub>), with a peak level at 4-6 hours after injection. Measurements of T<sub>3</sub> and T<sub>4</sub> at these intervals can be used to monitor the response of the thyroid. Women, especially in the premenstrual phase of the cycle, show a greater response than men. The TSH response to TRH has been reported to fall with age. The response is greater at night, which would be expected because of the nocturnal rise of TSH levels.

A variety of drugs affect the TSH response to

TRH. It is enhanced by theophylline (a phosphodiesterase inhibitor), by over-treatment with antithyroid drugs, and by oestrogens—both in women taking an oral contraceptive and in men being treated with oestrogens. The response is reduced by corticosteroids, thyroid hormones, levodopa, dopamine, and propranolol.

## Definition of normal TSH response to TRH

Interpretation of the results of a TRH test varies in different centres according to the TSH assay used. Definition of an absent TSH response to TRH depends on the precision of the TSH assay, but in centres experienced in TSH measurements an increment of <1 mU/l would usually be regarded as an absent response. A normal response to TRH can be properly defined only in terms of the experience in a given centre and, as stated above, depends on the age and sex of the individual. A rise of >2 mU/l with a peak value above the normal basal TSH level for the centre would be accepted as a simple qualitative criterion of a normal response, though ideally each centre should establish its own normal range.

## TRH test in thyroid disease

### HYPOTHYROIDISM

In patients with primary hypothyroidism the TSH response to TRH is often exaggerated, but the raised basal TSH level usually suffices for diagnosis. Occasionally in very early subclinical hypothyroidism the basal TSH is normal but the response to TRH is exaggerated. Treatment with thyroid hormone in such cases is rarely warranted. The response to TRH of most patients with hypothyroidism due to pituitary-hypothalamic disease is impaired or absent, but a few respond (see below). Recent studies have shown that TRH also releases  $\alpha$ - and  $\beta$ -subunits of TSH from the pituitary in hypothyroid people.

### NON-TOXIC GOITRE

In most patients with diffuse non-toxic goitre both basal TSH and the response to TRH are normal. However, about 15% of such patients in some large

series fail to respond to TRH despite normal levels of T3 and T4. Of those who fail to respond to TRH about two-thirds show normal suppression of the thyroidal  $^{99m}\text{Tc}$  or  $^{131}\text{I}$  uptake by T3. The reason for this discrepancy is uncertain. Measurements with the highly sensitive cytochemical bioassay have confirmed that there is no release of biologically active TSH in such patients.

#### HYPERTHYROIDISM

Hyperthyroidism is much more common than previously realised. An epidemiological study in the north-east of England showed that 2.3% of women had had hyperthyroidism. Minor degrees of thyroid overactivity are easily overlooked and probably often remit spontaneously. In hyperthyroid patients there is no TSH response to TRH because of the suppressive action of T3 and T4 on the pituitary. The TRH test is useful in screening for mild hyperthyroidism, along with measurements of the serum T3. In overt hyperthyroidism the serum T4 measurement suffices except in T3 toxicosis, where total and free T4 levels are normal, but the TRH test is always abnormal.

#### CAUSES OF ABSENT RESPONSE TO TRH IN A CLINICALLY EUTHYROID PATIENT

A normal TSH response to TRH excludes hyperthyroidism, in which the response is absent. There are many other causes of an absent response, among them ophthalmic Graves's disease, hyperthyroidism for up to 6 months after the patient has become clinically and biochemically euthyroid, multinodular goitre, subclinical toxic adenoma, diffuse non-toxic goitre, thyroid hormone treatment (usually thyroxine exceeding 0.15 mg/day), Cushing's syndrome (spontaneous or iatrogenic), hypopituitarism due to pituitary tumours or other causes, acromegaly, depression, chronic renal failure, and starvation (for 36 hours).

Responses are not invariably absent or impaired in these conditions. In several the mechanism is not understood. In some—for example, some cases of multinodular goitre and subclinical toxic adenoma—T3 or T4 levels, or both, may be at or just above the upper limit of normal and the patients may be regarded as having subclinical hyperthyroidism.

An absent or impaired TRH test usually correlates with absent or impaired T3 suppression of the thyroid, but some as yet unexplained discrepancies have been described. In routine clinical practice the TRH test has replaced the T3 suppression test since it is more rapid, safer, does not depend on patient co-operation, does not require the administration of an isotope, and also recognises thyroid failure.

#### OPHTHALMIC GRAVES'S DISEASE

Such patients have the eye signs of Graves's disease yet are not hyperthyroid and give no past history of hyperthyroidism. In some the pattern of the eye signs is diagnostic of Graves's disease, but in others, especially those with unilateral proptosis, an orbital tumour must be excluded. In those cases the finding of an abnormal TRH test indicating a minor thyroid abnormality is helpful in diagnosis. Any pattern of TSH response to TRH can be observed in ophthalmic Graves's disease from exaggerated to normal or impaired to absent, depending on the level of thyroid function ranging from overt hypothyroidism to subclinical hyperthyroidism.

#### TRH test in hypothalamic-pituitary disease

Patients with hypothalamic-pituitary disease can be investigated with the TRH test. A normal TRH test usually correlates with normal circulating thyroid hormone levels, but occasional patients with hypothyroidism due to hypothalamic-pituitary disease also have a normal or exaggerated response. Some of them fail to show any T3 or T4 response to TRH despite a release of TSH detected by radioimmunoassay. But by cytochemical bioassay the results are different and only small amounts of biologically active TSH are detected.

Patients with acromegaly often fail to respond to TRH, even when they are clinically and biochemically euthyroid. Suppression of the TRH test by an autonomous nodular goitre is often responsible for this finding. Patients with hypothalamic disease may show a normal peak response to TRH even when hypothyroid but the response is characteristically a delayed one, the level at 60 minutes being greater than at 20 minutes.

#### Neuroregulation of TSH secretion

This is poorly understood, although the finding that the TSH response to TRH is reduced after administration of certain neuroactive agents has thrown some light on the matter. Thus both continuous administration of levodopa and acute dopamine infusion inhibit the TSH response to TRH, suggesting an overall inhibitory dopaminergic control of TSH secretion.

Growth hormone release-inhibiting hormone (GHR-IH) (somatostatin) also suppresses TRH-induced TSH release. A physiological role for GHR-IH in TSH regulation in man has been inferred from the rise in basal TSH levels that occurs after administration of an antiserum to somatostatin in animals.

### **Therapeutic applications of TRH**

As yet no firm therapeutic applications have been found for TRH. It has no place in the treatment of depression. An absence of response to TRH after a course of antithyroid drugs may forecast relapse before a rise in serum T3 or T4, but in general an absent response to TRH at the end of a course of antithyroid drugs has not been found to be a good predictor of which patients are liable to relapse. The TRH test is of no value in assessing thyroid function during antithyroid treatment. TRH may be used to enhance release of endogenous TSH in patients with thyroid cancer instead of giving bovine TSH, after the withdrawal of thyroid medication, to reduce the duration of hypothyroidism and possibly enhance

radioiodine uptake by tumour tissue. TRH can be used to treat hypothalamic hypothyroidism, but thyroxine is cheaper and more convenient. Prolactin levels can be raised post-partum by oral TRH, but there is no enhancement of milk production.

### **References**

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