

THYROID TODAY

Editor: J. H. Oppenheimer, M.D.
Volume 3, Number 2
April/May, 1980

PITUITARY THYROTROPIN SECRETION IN THYROID DISORDERS



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Thyrotropin (TSH) is synthesized and secreted by the pituitary thyrotroph, which is a distinctive cell type of the anterior pituitary gland both by special stains and by electron microscopy. TSH binds to a specific receptor site on the thyroid cell membrane, activating cyclic adenosine monophosphate (cAMP), and stimulates every step in the biosynthesis of the thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃). Increased secretion of T₄ and/or T₃ decreases TSH synthesis and secretion. Because of the sensitive negative feedback relationship between the levels of thyroid hormones and pituitary TSH, measurement of serum TSH has been found to be important clinically in the diagnosis of both thyroid and pituitary disorders.

Chemistry of TSH and Assay Methods

TSH is a glycoprotein hormone with a molecular weight of approximately 28,000. It is structurally similar to the two other pituitary glycoprotein hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as to the placental glycopeptide, chorionic gonadotropin (CG). Each of these hormones is composed of two dissimilar, non-covalently bound subunits, alpha and beta. The alpha subunits of the four hormones are virtually identical; the beta subunits are distinct for each hormone and confer biologic and immunologic specificity.^{1,2} Individual alpha and beta subunits are biologically inert as shown by lack of binding to target organ cell membrane receptors and lack of activation of cAMP.³ The alpha and beta subunits of TSH are independently synthesized in precursor forms,

which are subsequently glycosylated, and then combined to form TSH prior to secretion from the thyrotroph.^{4,5}

The earliest attempts to measure human TSH utilized urinary bioassays; unfortunately, these assays were both insensitive and non-specific. Once human pituitary TSH had been purified,⁶ the development of antibodies to human TSH in laboratory animals provided the basic ingredients for a specific radioimmunoassay to measure serum concentrations of TSH.⁷ Such a TSH radioimmunoassay was capable of distinguishing abnormally elevated serum TSH levels from normal ones. However, distinction between normal and low concentrations of TSH was not possible until several modifications were made in the immunoassay.⁸ Some crossreactivity of the structurally related LH and CG molecules does occur in the TSH radioimmunoassay, but sufficient specificity can be achieved to demonstrate that postmenopausal women (↑ LH levels) and pregnant women (↑ CG levels) have normal serum concentrations of TSH.

Normal TSH Secretion

Serum TSH concentrations are relatively constant throughout the day. Therefore, useful clinical information can be obtained from a single blood sample drawn at any time. There is only a small diurnal variation in TSH levels, with a brief increase in the early morning hours. TSH levels are not affected by glucose, amino acids, stress, exercise, and most drugs. Certain drugs, such as lithium carbonate⁹ and iodides,¹⁰ can cause elevations of serum TSH, presumably due to small depressions in the serum thyroid hormone concentrations. Furthermore, dopamine agonists such as L-dopa and bromergocryptine have been shown to reduce elevated TSH levels found in hypothyroid patients.¹¹ Cold exposure significantly increases serum TSH levels only in the human neonate, not in the adult.¹²

In addition to the extremely sensitive negative feedback control of thyroid hormone levels on pituitary TSH secretion, thyrotropin releasing hormone (TRH), carried to the pituitary in the hypophysial portal venous system, stimulates TSH release into the circulation (Figure 1). The isolation and purification of this hypothalamic tripeptide, followed by its synthesis, has provided a simple means of

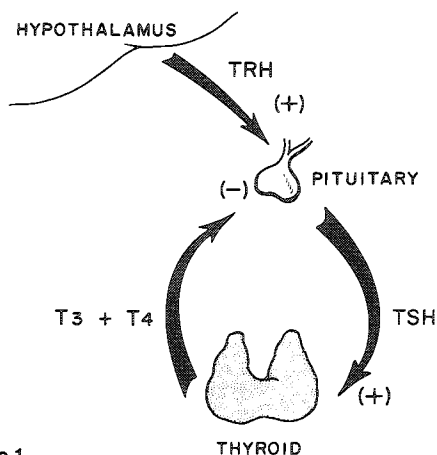


Figure 1

testing pituitary TSH reserve.¹³ Synthetic TRH elevates serum TSH levels in normal individuals after either oral or parenteral administration. Although TRH was originally isolated from the hypothalamus, it has since been found widely distributed throughout the central nervous system and recently also in the gastrointestinal tract, the pancreas, and the placenta.¹⁴ Such a distribution suggests that TRH has important neurotransmitter functions in addition to its role in stimulating TSH secretion. It has not yet been clearly established whether thyroid hormone levels affect hypothalamic TRH secretion because of the rapid degradation of TRH in both tissue extracts and serum.

Although other hormones can influence TSH secretion, their effects are relatively minor compared to those of TRH and thyroid hormones. Pharmacologic doses of glucocorticoids markedly decrease basal and TRH-stimulated TSH secretion; physiologic fluctuations in cortisol levels may also influence TSH levels.¹⁵ Elevated growth hormone levels, whether due to acromegaly or to the therapeutic administration of growth hormone, can also decrease TRH-stimulated TSH secretion.¹⁶ Somatostatin, a recently isolated growth hormone inhibitory factor, decreases TSH secretion, as well as the secretion of glucagon, insulin, and other peptide hormones.¹⁷ Finally, women demonstrate slightly greater TSH release after TRH administration than do men, implying that estrogen may increase TSH secretion.

In normal individuals, the administration of TRH (200 μ g intravenously as a bolus) causes a rapid increase in the serum TSH level from a mean value of 1.6 μ U/ml (range 0.5-3.2 μ U/ml) to a mean peak value of 12 μ U/ml (range 5-22 μ U/ml) thirty minutes after injection (Table 1). The total TSH response to TRH can be quantitated by measuring the area under the TSH curve after TRH administration and has been called the pituitary TSH reserve.⁸ The TSH response to TRH is dose-related up to about 200 μ g intravenously; the peak TSH response then plateaus. The response is slightly greater in women and inversely related to age in men.¹⁸

Since exogenous thyroid hormone is frequently administered to shrink a goiter in a euthyroid patient, serum TSH suppression is a clinically useful parameter for determining the adequacy of the thyroid hormone dosage. Levo-thyroxine (L-T₄) 0.2 to 0.3 mg daily will usually suppress serum TSH and TRH-stimulated TSH secretion even though endogenous serum T₄ and T₃ values may remain within the high-normal range. Thus, pituitary TSH secretion appears to be a more sensitive indicator of the tissue effects of thyroid hormones than are the circulating T₄ and T₃ levels. After discontinuing thyroid hormone administration, particularly L-T₄, at least four weeks and probably eight weeks should elapse before measuring serum TSH or TRH-stimulated TSH secretion since tissue effects of T₄ and T₃ require longer times to return to baseline than do the circulating T₄ and T₃ levels.¹⁹ Recovery of the pituitary-thyroid axis almost always occurs within eight weeks, in contrast to the much longer period of time required for normalization of the pituitary-adrenal axis after the administration of glucocorticoids.

Primary Thyroid Gland Failure

Primary hypothyroidism, accompanied by decreased serum levels of T₄ and T₃, results in markedly increased pituitary TSH secretion. The increased serum TSH levels are widely variable (10-1000 μ U/ml) and are due to both increased pituitary production and a decreased metabolic clearance rate of TSH.⁸ If some functional residual thyroid tissue remains, the elevated serum TSH levels may cause preferential T₃ secretion from the failing thyroid gland. Thus, in patients with primary hypothyroidism, T₄ levels are always low, but T₃ levels may be either normal or low.²⁰ The most common etiologies of primary hypothyroidism are chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) or prior treatment of hyperthyroidism (particularly Graves' disease) with radioactive iodine, subtotal thyroidectomy, or even thionamide antithyroid drugs alone. Although the TSH response to TRH is also markedly enhanced in primary hypothyroidism, the elevated basal TSH levels suffice to make a diagnosis of primary thyroid gland failure (Table 1). Patients with primary hypothyroidism also have measurable circulating levels of the individual alpha and beta subunits of TSH.²¹ Secretion of both subunits is also increased after the administration of TRH. The subunits of TSH are directly secreted from the pituitary rather than arising from peripheral dissociation of the secreted TSH. Nevertheless, levels of free subunits represent only a small percentage of the circulating TSH.

a. Asymptomatic Thyroid Dysfunction

The sensitivity of the TSH radioimmunoassay has allowed the detection of more subtle forms of thyroid impairment.²⁰ Patients with Hashimoto's thyroiditis or treated Graves' disease, in particular, may have persistently elevated TSH levels with low-normal T₄ and T₃ levels. These patients do have decreased thyroid reserve since their

Table 1:
TSH Secretion in Thyroid and Pituitary Disorders

	TSH	TSH response to TRH	T4	T3
Normal	0.5-3.2 μ U/ml	peak 5-22 μ U/ml at 30 min	4-11 μ g/dl	70-170 ng/dl
Primary hypothyroidism	$\uparrow \uparrow$	$\uparrow \uparrow$	\downarrow	usually \downarrow
Decreased thyroid reserve	\uparrow	\uparrow	low normal	low normal
Conventional hyperthyroidism (Graves', nodular goiter)	\downarrow	\downarrow	\uparrow	\uparrow
"Euthyroid" hyperfunctioning thyroid nodule	\downarrow	\downarrow	high normal	high normal
Pituitary hypothyroidism	\downarrow or normal	\downarrow	\downarrow	usually \downarrow
Hypothalamic hypothyroidism	\downarrow or normal	delayed, but normal peak (60-180 min)	\downarrow	usually \downarrow
Pituitary hyperthyroidism with a pituitary tumor	\uparrow	no response	\uparrow	\uparrow
without a pituitary tumor	\uparrow	\uparrow	\uparrow	\uparrow
Non-thyroidal acute or chronic illnesses	normal	normal	slight \downarrow	\downarrow

thyroid glands cannot secrete sufficient amounts of T4 and/or T3 to decrease the elevated pituitary TSH secretion to normal. Serum TSH levels of such patients are usually between those of euthyroid individuals and patients with primary hypothyroidism; the peak serum TSH response to TRH is also intermediate (Table 1). Many of these patients also have a deficient response to the administration of bovine TSH intramuscularly. They fail to increase normally their radioactive iodide uptake and serum T4 and T3 levels. Since increases in endogenous TSH secretion occur earlier than decreased responsiveness to exogenous bovine TSH, a sensitive TSH radioimmunoassay essentially obviates the need for a bovine TSH test to diagnose decreased thyroid reserve. Although it is not known whether all such patients will eventually develop overt hypothyroidism, that is, whether they are truly prehypothyroid, any patient with symptoms should be treated with thyroid hormone. All asymptomatic patients should be carefully followed for the possible development of overt hypothyroidism. Certain patients with decreased thyroid reserve have been followed for longer than 4 years without any further increase in serum TSH or decrease in thyroid hormone levels. Serum TSH levels should also be determined in any patient with diabetes mellitus, primary adrenal insufficiency, or pernicious anemia, since such patients have an increased incidence of Hashimoto's thyroiditis.²²

b. Thyroid Hormone Replacement Therapy

Measurement of serum TSH is the most reliable method available for validating the adequacy of thyroid hormone replacement in hypothyroid patients. Exogenous L-T4, in a daily dose of 150-200 μ g daily, usually normalizes serum TSH levels and TRH-induced TSH secretion four to eight weeks after initiating therapy.⁹ Complete suppression of basal serum TSH levels and the TSH response to TRH

probably indicates excessive administration of L-T4, particularly if serum thyroid hormone levels are also slightly elevated. Elevated basal serum TSH levels with increased TSH secretion after TRH administration would suggest inadequate replacement therapy.

c. Hypersecretion of Prolactin in Primary Hypothyroidism

Increased prolactin secretion, particularly after the administration of TRH, may also occur in patients with primary hypothyroidism. Galactorrhea usually occurs only in the most severely hypothyroid, premenopausal women, probably because adequate estrogen levels are necessary for lactation. Patients with severe primary hypothyroidism may even have increased pituitary size, as shown by increased volume of the sella turcica on polytomography.²⁰ Pituitary enlargement is presumably due to hyperplasia and hypertrophy of the TSH-secreting and prolactin-secreting cells of the anterior pituitary gland. There have been reports of pituitary tumors occurring in patients with primary hypothyroidism, but usually these tumors have not been proved to be TSH-secreting. The precedent for an increased incidence of TSH-secreting pituitary tumors occurring in the presence of thyroid gland failure has been well established in lower mammals. Certain strains of thyroidectomized mice almost universally develop TSH-secreting pituitary tumors.²³

TSH Secretion in Hyperthyroidism

In conventional hyperthyroidism, with elevated serum concentrations of T3 and usually T4, including Graves' disease, toxic nodular goiter, and hyperthyroidism due to the ingestion of excess thyroid hormone, serum TSH levels are undetectable ($<0.5 \mu$ U/ml).^{6,21} Furthermore, in the hyperthyroid phase of subacute thyroiditis²⁴ or in the rarer in-

stances of hyperthyroidism due to struma ovarii or functioning metastatic thyroid cancer, TSH secretion is likewise suppressed.

Patients with Graves' disease or a hyperfunctioning thyroid nodule with high-normal circulating thyroid hormone levels have traditionally been considered to be "euthyroid"; yet they may also have undetectable serum TSH levels basally and after TRH administration (Table 1). Since decreased pituitary TSH secretion is the most sensitive indicator of excessive tissue thyroid hormone levels, these patients are probably mildly hyperthyroid rather than euthyroid.

Many of the currently available TSH radioimmunoassays do not have sufficient sensitivity to distinguish normal from suppressed TSH values; thus, a TRH test demonstrating a lack of increase in serum TSH is valuable in the diagnosis of hyperthyroidism. The absence of a serum TSH response after TRH implies thyroid hyperfunction, whereas lack of thyroid gland suppressibility using a classical T3 suppression test (75 or 100 µg daily for ten days) suggests thyroid gland autonomy from TSH control, but not necessarily hyperthyroidism. A normal T3 suppression test rules out hyperthyroidism, but an abnormal T3 suppression test may occur in a euthyroid patient due to another thyroid stimulator such as the thyroid-stimulating immunoglobulins.²⁵

a. Trophoblastic Tumors

TSH secretion is also suppressed in the hyperthyroidism sometimes found in patients with tumors of trophoblastic origin, such as hydatidiform moles or choriocarcinoma. These patients are apparently hyperthyroid because of the small intrinsic thyroid-stimulating activity of the huge amounts of human chorionic gonadotropin secreted by these tumors.²⁶

Pituitary and Hypothalamic Hypothyroidism

Hypothyroidism can also occur because of pituitary deficiency of TSH. The most common cause of pituitary hypothyroidism is a pituitary tumor destroying the pituitary TSH-secreting cells. Serum T4 and T3 levels are decreased; basal serum TSH levels are low or normal; no TSH is released after the administration of TRH (Table 1). Hypothyroidism can also be caused by a hypothalamic deficiency of TRH, for example, due to a hypothalamic tumor such as a craniopharyngioma or metastatic cancer. Such patients also have decreased serum T4 and T3 levels, low or normal basal TSH levels, but a delayed peak TSH response occurring 60 to 180 minutes after the administration of TRH (Table 1).

Basal serum TSH levels easily distinguish primary thyroid gland failure from hypothyroidism on a pituitary or hypothalamic basis; however, a TRH test of pituitary TSH reserve is essential to differentiate pituitary TSH deficiency from hypothalamic TRH deficiency. Central hypothyroidism may present with a mixed pituitary and hypothalamic picture. A patient may have a pituitary tumor extending into

the suprasellar region, causing a deficiency of TRH but not destroying all of the pituitary thyrotrophs.⁸ These patients may be hypothyroid although they have apparently normal serum TSH levels. Since TSH is measured by immunoassay, these immunoactive TSH molecules may have subtle abnormalities rendering them biologically inactive, or less than normally active.

Pituitary or TSH-Induced Hyperthyroidism

In a fashion analogous to TSH deficiency causing hypothyroidism, increased pituitary TSH secretion may cause hyperthyroidism. However, TSH-induced hyperthyroidism was not recognized until sufficiently sensitive and specific TSH radioimmunoassays were developed, allowing the demonstration of inappropriately increased serum TSH concentrations in the presence of elevated serum T3 and/or T4 levels. The first patients described with TSH-induced hyperthyroidism had TSH-secreting pituitary tumors; however, patients have now also been identified without any apparent pituitary tumor.²⁷⁻²⁹ Measurements of the individual alpha and beta subunits of TSH have been useful in differentiating those patients with TSH-induced hyperthyroidism who have a pituitary tumor from those without a tumor.²⁸ The patients with a pituitary tumor have had markedly elevated serum alpha subunit levels relative to their elevated TSH levels (Table 2), but undetectable beta subunits of TSH. The non-tumor patients have had modestly increased serum concentrations of both alpha and beta subunits of TSH, but predominantly increased TSH secretion. In addition, the pituitary tumor patients demonstrated no significant increase in the concentration of TSH or its subunits after TRH administration, while the patients without a pituitary tumor showed both increased TSH and subunit secretion (Table 1). Patients with a pituitary tumor appear to have autonomous TSH and subunit secretion, whereas non-tumor patients have a disordered set point for TSH and subunit secretion. The patients without a pituitary tumor do not seem to have TRH-induced hyperthyroidism, since their elevated thyroid hormone levels would normally inhibit TSH secretion totally after even large doses of exogenous TRH. Reliable measurements of endogenous TRH will be needed before the inappropriate TSH secretion in the non-tumor patients can be more fully understood.

Table 2:
TSH and Alpha Subunit Concentrations in Patients with TSH-Induced Hyperthyroidism

	TSH* (µU/ml)	Alpha† (ng/ml)
Pituitary tumor (7 patients)	1.7-88	12.5-105
No pituitary tumor (6 patients)	9.3-160	0.5-5.2

*Patients with conventional hyperthyroidism normally have serum TSH concentrations <0.5 µU/ml.

†Normal men and premenopausal women have serum alpha concentrations between <0.5 and 2.5 ng/ml; postmenopausal women have serum alpha concentrations between 1.0 and 7.0 ng/ml.

Treatment of the TSH-secreting pituitary tumors by hypophysectomy and radiotherapy has usually cured the hyperthyroidism and decreased the elevated serum TSH and alpha subunit levels.²⁸ Appropriate therapy for the non-tumor patients is less apparent since increasing the serum thyroid hormone concentrations would decrease the TSH secretion, but aggravate the hyperthyroidism; directly treating the thyroid gland would increase the TSH secretion further, with the theoretical risk of causing a TSH-secreting pituitary tumor. Although serum TSH levels have not routinely been measured in all hyperthyroid patients in the past, such measurements should increase the future recognition of TSH-induced hyperthyroidism.

Non-Thyroidal Acute or Chronic Illnesses

The measurement of serum TSH is helpful in differentiating patients with a wide variety of non-thyroidal acute or chronic illnesses from patients with thyroid gland failure. These sick patients show decreases in serum T4 and especially T3 due to changes in the binding of thyroid hormones to serum proteins or decreased peripheral conversion of T4 to T3, but they do not have increased serum TSH concentrations.

Recent Studies on TSH Biosynthesis

The alpha and beta subunits are independently synthesized in precursor forms by the translation of separate messenger RNA molecules.³⁰ These subunits are then processed to glycosylated forms, followed by combination of the subunits to form the biologically active TSH molecule prior to secretion from the thyrotropic pituitary cell.^{4,5} Recombinant DNA methodology has now been utilized to clone DNA molecules complementary to alpha and beta TSH messenger RNA.³¹ These TSH DNA molecules can be used to investigate the hormonal regulation of TSH gene expression.

Summary

An evaluation of the dynamics of TSH secretion is valuable clinically in the diagnosis of disorders of the hypothalamic-pituitary-thyroid axis. Although a single serum TSH level is sufficient in most circumstances to diagnose primary thyroid failure, a TRH test of pituitary TSH reserve is important to differentiate pituitary from hypothalamic hypothyroidism and to diagnose hyperthyroidism, including the relatively rare syndromes of TSH-induced hyperthyroidism.

To prescribe any drug mentioned in this article, the readers should consult full prescribing information.

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