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BIOCHEMICAL ASPECTS AND INTERPRETATION OF THYROID STIMULATING HORMONE IN THYROID DYSFUNCTIONS

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ABSTRACT

The thyroid gland is responsible for the formation and secretion of thyroid hormones as well as iodine homeostasis within human body. It is responsible for adjusting metabolic rate of the body. The thyroid produces approximately 90% inactive thyroid hormone or thyroxine (T4) and 10% active thyroid hormone or triiodothyronine (T3). Thyroid Stimulating Hormone (TSH) is a hormone released by pituitary gland which triggers thyroid to produce and release its own hormones T4 and T3. It aids in identifying subjects who suffer from thyroid malfunction. Thyrotropin Releasing Hormone (TRH) is secreted from the hypothalamus and reaches the anterior pituitary via the hypophyseal portal circulation. Activation of receptors stimulates the release of TSH which activates its own receptors on the follicular cells of the thyroid gland. TSH is the primary biomarker for the diagnosis of thyroid dysfunction and for guiding treatment of thyroid diseases. This paper focuses on the functions, diagnostic importance, diurnal and circannual variations in TSH levels.

KEYWORDS: TSH, T3, T4, TRH, Thyroid Dysfunction, Thyroid Function Tests.

INTRODUCTION

The thyroid is an endocrine gland. Its location is in the inferior, anterior neck and it is responsible for the formation and secretion of thyroid hormones as well as iodine homeostasis within human body. The thyroid gland is responsible for adjusting metabolic rate of body.[1] The thyroid produces approximately 90% inactive thyroid hormone, or thyroxine (T4), and 10% active thyroid hormone, or triiodothyronine (T3). Inactive thyroid hormone is converted peripherally to either activated thyroid hormone or an alternative inactive thyroid hormone. The development of fetus and fetal central nervous system depends on thyroid hormones.[2,3] The thyroid-stimulating hormone (TSH) adjusts the amount of hormone production by the thyroid.[4] TSH is a glycoprotein hormone produced by the anterior pituitary. It is the primary stimulus for thyroid hormone production by the thyroid gland. It also exerts growth effects on thyroid follicular cells leading to enlargement of thyroid. The hypothalamic-pituitary axis regulates TSH release. Specifically, neurons in the hypothalamus release thyrotropin releasing hormone (TRH) or thyroid-releasing hormone, which stimulates thyrotrophs of the anterior pituitary to secrete TSH. The thyroid hormones inhibit the secretion of TSH by pituitary thyrotrophs.[5] This inhibition acts directly on thyrotrophs and also via the inhibition of hypothalamic secretion of TRH.[6]

Functions of TSH

TSH is a hormone released by the pituitary gland, which triggers thyroid to produce and release its own hormones T4 and T3. It aids in identifying subjects who suffer from thyroid malfunction. Subclinical hypothyroidism and hyperthyroidism are defined as increased and decreased TSH, respectively, with normal thyroid gland hormones.[7] The increased awareness of thyroid ailments and health check-ups is causing increased incidences of subclinical hypothyroidism and hyperthyroidism.[8]

It binds to and activates the TSH receptor (TSHR), which is a G-protein coupled receptor (GPCR) on the basolateral surface of thyroid follicular cells. TSHR is coupled to both Gs and Gq G-proteins, activating both the cAMP pathway (via Gsa) and the phosphoinositol/calcium (IP/Ca2+; via Gq) second messenger signalling cascades. The Gs pathway activates iodide uptake, thyroid hormone secretion and gland growth and differentiation. The Gq pathway is rate-limiting for hormone synthesis by stimulating iodide organification. A gain in function mutation of the TSH receptor results in hyperthyroidism, while a loss in function mutation results in hypothyroidism. TSH stimulates thyroid hormone secretion through enhancing iodide uptake, thyroglobulin synthesis and thyroperoxidase activity. TSH also increases blood flow to the thyroid gland and stimulates hypertrophy and

hyperplasia of thyroid follicular cells to exert growth effects on the thyroid gland.[9]

Pathophysiology

The primary thyroid disease refers to problems arising from the thyroid gland itself. The secondary thyroid disease refers to central problems arising from the anterior pituitary that indirectly affects thyroid function. A thyroid problem can exist in the form of hyperthyroidism or hypothyroidism. Hyperthyroidism occurs when there is excessive thyroid hormone synthesis or release. Hypothyroidism, on the other hand happens due to inadequate thyroid hormone production.

In primary hyperthyroidism, the thyroid produces large amounts of T3 and T4, which, through negative feedback inhibition, suppress TSH secretion from the anterior pituitary. In primary hypothyroidism, the thyroid produces insufficient amounts of T3 and T4, which leads to loss of negative feedback inhibition and increased production of TSH from the anterior pituitary. In secondary hyperthyroidism, the anterior pituitary produces large amounts of TSH, which, in turn, stimulate the thyroid follicular cells to secrete thyroid hormones in excessive amounts. On the other hand, if the anterior pituitary were to produce low levels of TSH, lack of stimulation of thyroid follicular cells causes T3 and T4 levels to go down, thus secondary hypothyroidism.

Hyperthyroidism

Hyperthyroidism is a condition characterized by excessive secretion of thyroid hormones. There are various medical conditions lead to hyperthyroidism, including Grave's disease, thyroid neoplasm, thyroid adenomas, excess TSH secretion or exogenous T3 or T4 administration. Symptoms of hyperthyroidism include increased basal metabolic rate, weight loss, increased appetite, sweating, tremors, heat sensitivity, irritability, diarrhea, and insomnia. In primary hyperthyroidism, as in the case of a thyroid adenoma, TSH levels tend to decrease due to negative feedback inhibition exerted on the anterior pituitary by T3 and T4. In secondary hyperthyroidism, as in the case of a TSH or Thyrotropin-releasing hormone (TRH) secreting tumor, both TSH and T3/T4 levels increase.[10,11]

Hypothyroidism

Hypothyroidism occurs when the thyroid gland fails to produce thyroid hormone in sufficient amounts. The most common cause of hypothyroidism is Hashimoto thyroiditis, which is a condition caused by autoantibodies that attack thyroid follicular cells leading to decreased thyroid hormone synthesis. The common causes of hypothyroidism include radiation therapy, thyroid surgery, overtreatment with anti-thyroid medications, congenital hypothyroidism, iodine deficiency or pituitary tumors. The symptoms of hypothyroidism are decreased basal metabolic rate, weight gain despite the decreased appetite, cold sensitivity, decreased cardiac output, hypoventilation, lethargy and mental slowness, drooping eyelids, myxedema, growth retardation, mental retardation in perinatal patients and goiter. In primary hypothyroidism, as in the case of Hashimoto thyroiditis, TSH levels increase due to loss of negative feedback inhibition. In secondary hypothyroidism, as in the case of a benign pituitary gland tumor, TSH levels go down. Treatment for hypothyroidism includes thyroid hormone replacement therapy.[12,13,14]

TSH and Thyroid Hormones

TRH is secreted from the hypothalamus and reaches the anterior pituitary via the hypophyseal portal circulation. Activation of TRH receptors stimulates the release of TSH, which activates its own receptors on the follicular cells of the thyroid gland. It causes increased cellular uptake of iodine from the blood, increased synthesis of thyroglobulin and secretion into the blood stream of T3 and T4 via activation of the enzyme thyroid peroxidase (TPO). Feedback circuits result in an inverse relationship between serum levels of thyroid hormones and TSH, i.e., low T4 (as observed in hypothyroidism) and high T4 (as seen in hyperthyroidism) levels are associated with elevated and low TSH, respectively. The relationship between TSH and T4 varies amongst individuals and is affected, amongst other factors, by age, smoking, levothyroxine treatment and the presence of antibodies.[15–19] These large alterations in TSH are more amenable to identification by routine measurements in clinical laboratories than small variations in T4 and this explains the use of TSH measurements as the gold standard for the diagnosis of thyroid disorders in current guidelines for the management of hypothyroidism.[20,21]

Thyroid Function Tests

Thyroid function assessments are commonly used in the clinical chemistry. These tests are vital for disease management of the patients. TSH is an important indicator of thyroid function, and it is imperative to consider all factors affecting its determination of reference ranges. The reference ranges may be device, laboratory and population-specific, normal or abnormal results may be diagnosed using reference ranges from populations local to the laboratory.[22] The normal reference range for TSH in adults is 0.4–4.0 mIU/mL.[21] Subclinical hypothyroidism is defined as TSH above the reference and when thyroid hormone levels are normal and the subclinical hyperthyroidism is characterised by T4 and T3 within the normal range and low TSH. In most laboratories, measurement of FT4 only occurs when TSH is out of range. An Australian study showed that restricting FT4 measurements to patients whose serum TSH was clearly outside its reference range had little or no impact on the diagnostic utility of the TSH test.[23]

As the reference intervals are influenced by age, gender, race, and iodine intake, the Clinical and Laboratory Standards Institute (CLSI) and the International Federation of Clinical Chemistry (IFCC) have

encouraged laboratories to set their own so that patients with thyroid-related diseases in different countries can receive appropriate testing and diagnosis.[24]

TSH is the first-line screening test for the majority of patients with a suspected thyroid problem. Together, with T3 and T4, it helps to assess whether thyroid disease is primary or secondary. Thyroid function tests measure the levels of T3, T4 and TSH in the blood. They are critical not only for diagnosing thyroid problems but also in differentiating between a primary and secondary cause of thyroid disease. A change in TSH that parallels T3 and T4 changes indicates a secondary problem originating in the anterior pituitary. In contrast, a TSH change that follows the opposite direction of T3 and T4 suggests a problem in the thyroid gland itself.[25]

Diurnal and Circannual Variations in TSH Levels

A diurnal variation exists for TSH levels in euthyroid and hypothyroid patients, with lower values in the daytime. The magnitude of the circadian rhythm in TSH is greater for older people due to a larger increase in nocturnal TSH production and the circadian rhythms for TSH have been observed to differ according to ethnicity. The nadir in TSH levels occurs around the middle of the day so that the daytime sampling of blood for TSH measurements should minimise interference with the test from this source. A circannual variation for TSH has been reported with lower values recorded in the summer and another study reported no change in the TSH reference range at different times of the year.[26.27]

CONCLUSION

TSH is the primary biomarker for the diagnosis of thyroid dysfunction and for guiding treatment of thyroid disease. It adjusts the amount of hormone production by the thyroid. The functional thyroid condition is assessed by the TSH secreted by pituitary gland, which is the most delicate marker. It aids in identifying subjects who suffer from thyroid malfunction. Subclinical hypothyroidism and hyperthyroidism are defined as increased and decreased TSH, respectively, with normal thyroid gland hormones.

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