THE ROLE OF THYROID HORMONE RESISTANCE IN ENDOCRINE AND METABOLIC DISORDERS

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doi:https://doi.org/10.5281/zenodo.22768995

Abstract: Thyroid hormone resistance is a rare endocrine condition characterized by reduced tissue responsiveness to circulating thyroid hormones. The disorder is most commonly associated with pathogenic variants in the thyroid hormone receptor beta gene and may produce a paradoxical biochemical profile with elevated free thyroxine and triiodothyronine concentrations despite non-suppressed thyroid-stimulating hormone levels. The aim of this study was to analyze the pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic principles of thyroid hormone resistance. A literature-based analytical approach was used to review thyroid hormone synthesis, receptor signaling, hypothalamic-pituitary-thyroid axis regulation, genetic mechanisms, and differential diagnosis. The analysis shows that clinical manifestations vary significantly because different tissues may exhibit different degrees of hormone sensitivity. Some patients show features of thyrotoxicosis, while others have hypothyroid-like manifestations or remain clinically euthyroid. Accurate diagnosis requires careful interpretation of thyroid function tests, exclusion of assay interference and thyroid-stimulating pituitary adenoma, and, when appropriate, molecular genetic testing. Thyroid hormone resistance demonstrates the importance of receptor-level mechanisms in endocrine disease and illustrates why serum hormone concentrations alone do not always reflect biological hormone action.
Keywords: thyroid hormone resistance, thyroid hormone receptor, THRB, TSH, thyroxine, triiodothyronine, endocrine resistance, thyroid dysfunction.

Introduction

Thyroid hormones play a central role in the regulation of basal metabolic rate, thermogenesis, cardiovascular function, growth, neurodevelopment, lipid metabolism, and carbohydrate homeostasis. Thyroxine, or T4, is produced primarily by the thyroid gland, while triiodothyronine, or T3, represents the more biologically active hormone at the nuclear receptor level. Their actions depend not only on hormone production and circulating concentration but also on cellular transport, intracellular conversion, receptor binding, and transcriptional regulation.

Under normal physiological conditions, circulating free T4 and T3 suppress thyroid-stimulating hormone secretion through negative feedback at the hypothalamic and pituitary levels. In most forms of primary hyperthyroidism, elevated thyroid hormone concentrations are therefore associated with suppressed TSH. Thyroid hormone resistance represents an important exception to this rule.

In patients with thyroid hormone resistance, target tissues respond inadequately to thyroid hormones despite normal or elevated circulating concentrations. As a result, the hypothalamic-pituitary system may perceive thyroid hormone action as insufficient and maintain TSH secretion. This can produce a characteristic biochemical pattern of elevated free T4 and T3 with normal or elevated TSH.

The condition is particularly important because it can be misdiagnosed as conventional hyperthyroidism. Inappropriate treatment aimed at reducing thyroid hormone production may worsen symptoms in tissues that are already relatively resistant.

The aim of this study was to analyze the molecular basis and clinical significance of thyroid hormone resistance and to review the main principles of diagnosis and management.

Materials and Methods

This study was prepared as a qualitative literature-based analytical review. Scientific publications and standard endocrinology references concerning thyroid hormone physiology, nuclear thyroid hormone receptors, resistance to thyroid hormone, pituitary-thyroid feedback, molecular genetics, and differential diagnosis were analyzed.

The review focused on receptor-level mechanisms, particularly abnormalities involving the thyroid hormone receptor beta gene, and on the consequences of reduced hormonal sensitivity in different tissues.

Particular attention was given to biochemical patterns, clinical variability, differential diagnosis with TSH-secreting pituitary adenoma and laboratory assay interference, and the rationale for individualized treatment.

No original patient data were used. The Results section summarizes established physiological and clinical evidence from the endocrine literature.

Results

Thyroid hormone action begins when circulating thyroid hormones enter target cells through specific membrane transporters. Within the cell, T4 may be converted to T3 by deiodinase enzymes. T3 then binds to nuclear thyroid hormone receptors, which interact with thyroid hormone response elements in DNA and regulate transcription of target genes.

The main thyroid hormone receptor isoforms are encoded by the THRA and THRB genes. Receptor alpha is expressed prominently in tissues such as the heart, skeletal muscle, bone, and central nervous system, whereas receptor beta has major roles in the liver, hypothalamus, pituitary gland, and other tissues.

Resistance to thyroid hormone beta is most commonly associated with pathogenic variants in the THRB gene.

Many of these variants produce receptors that have reduced affinity for T3 or impaired transcriptional activity. Mutant receptors may also interfere with normal receptor function through dominant-negative effects.

The hypothalamic-pituitary-thyroid axis is strongly dependent on thyroid hormone receptor beta activity. When pituitary tissues become relatively resistant to T3, normal feedback suppression of TSH is impaired.

Consequently, TSH secretion may remain normal or elevated despite increased circulating thyroid hormone concentrations.

Persistent TSH stimulation can lead to thyroid enlargement and may cause goiter.

The biochemical profile typically includes elevated free T4, elevated free or total T3, and non-suppressed TSH.

However, the clinical presentation is highly variable.

Some tissues may retain relatively normal thyroid hormone responsiveness while others are resistant. This tissue-specific variation can produce apparently contradictory manifestations.

For example, a patient may have tachycardia because cardiac tissue remains sensitive to thyroid hormone while simultaneously having elevated TSH because pituitary tissues are resistant.

Other patients may show features resembling hypothyroidism, including fatigue, poor concentration, or delayed growth.

Some individuals remain almost asymptomatic and are identified only because of abnormal laboratory findings.

Goiter is a common finding because the thyroid gland remains exposed to continued TSH stimulation.
Children may present with growth abnormalities, attention difficulties, hyperactivity, or developmental problems in some cases.
Adults may demonstrate palpitations, anxiety, tremor, heat intolerance, or no significant symptoms.
The main differential diagnosis includes TSH-secreting pituitary adenoma.
Both conditions can produce elevated thyroid hormones with inappropriately normal or high TSH.
Clinical assessment, family history, pituitary imaging, measurement of other pituitary hormones, sex hormone-binding globulin, alpha-subunit evaluation where available, dynamic testing, and genetic analysis may help distinguish the two disorders.
Laboratory assay interference is another important cause of discordant thyroid function tests.
Heterophile antibodies, abnormal binding proteins, or assay-specific artifacts may produce falsely elevated free hormone measurements.
For this reason, unexpected laboratory patterns should be confirmed using alternative methods when appropriate.
Familial occurrence is common in hereditary thyroid hormone resistance.
Identification of a similar thyroid function pattern in relatives can support the diagnosis.
Molecular testing for THRB variants provides strong diagnostic confirmation in many patients.

Discussion

The findings demonstrate that thyroid hormone resistance is fundamentally different from disorders caused by excessive thyroid hormone production.
In conventional hyperthyroidism, the main problem is excess hormone synthesis or release. In thyroid hormone resistance, the central problem is impaired biological response at the receptor or post-receptor level.
This distinction is clinically critical.
If a patient with thyroid hormone resistance is mistakenly treated with antithyroid drugs or radioactive iodine solely because of elevated free T4 and T3, circulating hormone concentrations may decrease without correcting the underlying receptor defect.
This can result in tissue hypothyroidism in organs that were already relatively resistant.
Interpretation of thyroid function tests therefore requires consideration of feedback physiology.
A non-suppressed TSH concentration in the presence of elevated free thyroid hormones should prompt evaluation for thyroid hormone resistance, TSH-secreting pituitary adenoma, assay interference, medication effects, and rare binding-protein abnormalities rather than immediate classification as primary hyperthyroidism.
The variable clinical phenotype can be explained by tissue-specific expression of thyroid hormone receptor isoforms.
Because receptor alpha and receptor beta are distributed differently throughout the body, the effects of receptor dysfunction are not uniform.
This helps explain why some patients simultaneously display features associated with both thyroid hormone excess and deficiency.
The cardiovascular system provides a clear example. If the heart remains relatively sensitive while pituitary feedback is resistant, elevated circulating T3 may produce tachycardia despite persistent TSH secretion.
In contrast, some neurological or developmental tissues may respond differently depending on the receptor defect and age of the patient.

Diagnosis should therefore integrate biochemical findings with clinical evaluation rather than relying on hormone concentrations alone.
Family history is particularly valuable because many forms are inherited in an autosomal dominant pattern.
Genetic testing can confirm the diagnosis and prevent unnecessary treatment.
Therapeutic management must be individualized.
Asymptomatic patients may require observation rather than active treatment.
Beta-blockers can be used in selected patients with troublesome tachycardia or palpitations.
In some circumstances, treatment may be directed toward reducing TSH stimulation or improving tissue hormone action, but specialist endocrinological supervision is necessary.
The disorder also illustrates an important general principle of endocrinology: endocrine disease can result not only from abnormal hormone production but also from altered receptor sensitivity.

Similar concepts are seen in insulin resistance, androgen insensitivity, glucocorticoid resistance, and other receptor-related disorders.
Thus, receptor biology is essential for understanding endocrine pathophysiology.

Conclusion

Thyroid hormone resistance is an uncommon but clinically important endocrine disorder characterized by reduced tissue responsiveness to thyroid hormones.
The most frequent form is associated with pathogenic variants in the THRB gene and produces impaired thyroid hormone feedback at the pituitary level.
The typical biochemical pattern consists of elevated free T4 and T3 with non-suppressed TSH.
Clinical manifestations vary widely because different tissues may have different degrees of hormone sensitivity.
Patients may show hyperthyroid-like symptoms, hypothyroid-like symptoms, goiter, developmental abnormalities, or minimal clinical findings.
Accurate diagnosis requires exclusion of assay interference and TSH-secreting pituitary adenoma and may be confirmed through molecular genetic testing.
Treatment should be individualized and should not be based solely on elevated thyroid hormone concentrations.
Thyroid hormone resistance clearly demonstrates that effective endocrine signaling depends on both hormone concentration and tissue receptor responsiveness.

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