NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.

Physiology, Thyroid

Authors

Yasaman Pirahanchi[1]; Muhammad Ali Tariq[2]; Ishwarlal Jialal[3].

Affiliations

[1] California Northstate College Medicine
[2] Tower Health
[3] VA MEDICAL CENTER, MATHER , CA

Last Update: February 13, 2023.

Introduction

The thyroid gland comprises thyroid follicles that synthesize and store thyroid hormone. The epithelial cells, referred to as follicular cells or thyrocytes, surround the colloid in the lumen. The ultimo-branchial cells or neural cells accompanying them are the origins of the C-cells in the thyroid gland, which secrete the hormone calcitonin.[1] The hypothalamus releases thyroid-releasing hormone (TRH), which stimulates thyrotrophs of the anterior pituitary to secrete thyroid-stimulating hormone (TSH). The anterior pituitary releases TSH and stimulates the thyroid follicular cells to release thyroxine, T4 (80%), triiodothyronine, or T3 (20%). The synthesis of thyroid hormones depends on the availability of iodide, TSH stimulation, and tyrosine residues on thyroglobulin. When T4 is released into circulation, it can convert to T3 through deiodination. T4 and T3 can then exert negative feedback on TSH levels, with high levels of T3/T4 decreasing TSH and low levels of T3/T4 increasing TSH levels from the anterior pituitary. This topic reviews the physiology, biochemistry, and clinical relevance of thyroid hormones.[2]

Issues of Concern

The thyroid follicular cells within the thyroid gland respond to the TSH released from the thyrotrophs of the anterior pituitary. TSH release from the anterior pituitary is modulated by the release of thyroid-releasing hormone (TRH) from the hypothalamus. In primary disease, the disease originates in the thyroid gland. If the thyroid gland is secreting high levels of T3/T4, this provides negative feedback on the anterior pituitary and, thus, decreases the secretion of TSH. If the thyroid gland is secreting low levels of T3/T4, the absence of negative feedback on the anterior pituitary increases TSH secretion from the anterior pituitary.

The disease originates in the anterior pituitary for secondary disease or central hyperthyroid or hypothyroid disease. If a tumor in the anterior pituitary is secreting excessively high TSH, this stimulates the thyroid follicular cells to secrete high levels of T3/T4. If the anterior pituitary is secreting low TSH levels, such as in pan-hypopituitarism, this lack of stimulation of thyroid follicular cells causes them to secrete low levels of T4.[3] One must assay the TSH in conjunction with T3/T4 levels to assess whether thyroid disease is primary or secondary. If TSH and T3/T4 increase or decrease together, this indicates either secondary (central) hypothyroidism or secondary hyperthyroidism. However, if the TSH and T3/T4 change in opposite directions, this indicates primary thyroid disease.

Cellular Level

The thyroid gland comprises thyroid follicles that synthesize and store thyroid hormone. These follicles have lost all luminal connections with other parts of the body. They are the primary units of the organ that are responsible for the secretion of the thyroid hormone. The epithelium of the normal gland is cuboidal. Blood vessels surround follicular

epithelial cells, and the colloid is within the follicular lumen, where the thyroid hormone is synthesized. The acinar surface of thyroid parenchymal cells is smooth and is covered with tiny villi and some pseudopods. Each cell has a cilium in the follicular lumen. The colloid is eosinophilic in hyperactive follicles resorption vacuoles scallop the margin of the colloid.

The thyroid epithelial cells organize into thyroid follicles. The follicle lumen consists of a single layer of polarized cells that forms the envelope of a spherical structure with an internal compartment in the follicle lumen. The cell polarity of the gland allows for targeting the membrane protein on the external side of the follicle facing the blood capillaries or on the internal side at the cell-lumen boundary. The cell polarity and the tightness of the follicle lumen allow for gathering substrates and storing thyroid hormones, modulating thyroid hormone synthesis.[4] The expression of thyroid hormone receptor subtypes appears in different tissues. The thyroid hormone receptor alpha (TRa) is predominantly expressed in the brain, heart, and bone. The thyroid hormone receptor beta (TRb1) is expressed in the liver, kidney, and thyroid. TRb2 is primarily found in the retina, cochlea, and pituitary. Mutations in TRa or TRb can result in disease, which is beyond the scope of this review.[5]

Development

The thyroid gland is embryonically the earliest endocrine structure to appear in human development and appears at embryonic day 22 in humans. The thyroid gland originates from the endoderm. Specifically, it derives from a median endodermal down-growth from the tongue. After embryogenesis, the physiology of the thyroid is controlled by the requirement for thyroid hormones and the supply of iodide. Hypothalamic supraoptic nuclei and thyrotrophs of the anterior pituitary monitor thyroid hormone plasma levels and action. The expression of transcription factors NK2 homeobox and paired box (PAX 8) are crucial for the proper expression of proteins creating the thyroid gland.[4]

Organ Systems Involved

The thyroid gland affects almost every organ system of the body. It affects the cardiovascular system by regulating the cardiac output, stroke volume, heart rate, and contractility. The defects in the thyroid mechanism can affect the nervous system, presenting as numbness, tingling, pain, or burning in the affected parts of the body. Hypothyroidism can also cause depression in patients. It is also involved with gastrointestinal motility. Thyroid gland disorders affect the reproduction system, with women suffering from irregularities in their menstrual cycles and problems when trying to conceive.[6]

Function

TSH from the anterior pituitary modulates the release of T3/T4 from thyroid follicular cells. T4 is deiodinated to T3, which is a more potent thyroid hormone. While about 20% of T3 originates from the thyroid gland, 80% of T3 is produced by peripheral conversion via a deiodinase, especially type 2. More than 99% of thyroid hormone is protein-bound to thyroid-binding globulin, pre-albumin, and albumin. T3 then binds to its receptor in the nucleus; this promotes the translation of mRNA and the synthesis of new proteins involved in the gland's functioning.[7]

The thyroid influences many organ systems, such as promoting bone growth and maturation, and the central nervous system's maturation. The basal metabolic rate is increased, with an increase in the synthesis of sodium (Na+)-potassium (K+)-ATPase, oxygen consumption, and heat production. Metabolism becomes activated with increased glucose absorption, glycogenolysis, gluconeogenesis, lipolysis, protein synthesis, and degradation (net catabolic). The hormones influence the cardiovascular system by increasing cardiac output, stroke volume, heart rate, and heart contractility by increasing the number of beta-1 receptors on the myocardium, such that the myocardium is more sensitive to stimulation by the sympathetic nervous system, thereby increasing contractility.[8]

Mechanism

TSH binds and activates the thyroid gland. The TSH binds to the membrane receptor on the epithelial cell surface, activating the adenylate cyclase located in the plasma membrane, which increases the cyclic adenosine monophosphate (cAMP) levels. This leads to the stimulation of additional intracellular signaling events, resulting in the formation of thyroid hormones.[9] Iodide from the plasma is concentrated and absorbed by thyroid cells through the sodium/iodide symporter (NIS) on the basolateral membrane of thyrocytes (follicular cells). This process depends on sodium and active transport, meaning it couples inward translocation down its electrochemical gradient with inward translocation of iodide against its electrochemical gradient. The iodide has to be delivered to the thyroglobulin-enriched colloid at the apical surface; this appears to be a function of another protein, pendrin, which is a chloride/iodide exchanger that promotes iodide efflux in the colloid-rich lumen. Within the thyroid follicle, thyroid peroxidase oxidizes, organifies, and couples iodine to tyrosine residues on thyroglobulin. Defects in any of these steps can result in dyshormonogenetic goiter and congenital hypothyroidism. Thyroglobulin is a glycoprotein with a molecular mass of 660 kDa enriched in tyrosine residues and secreted and stored in the colloid. Initially, thyroid peroxidase forms iodine by oxidation of the iodide ion. When TSH stimulates the thyroid follicle, thyroid peroxidase organifies or covalently bonds the tyrosine of the thyroglobulin molecule to colloid to iodine. If 1 iodine covalently bonds to tyrosine on the thyroglobulin, this forms monoiodotyrosine (MIT). If 2 iodine covalently bonds thyroglobulin, this forms diiodotyrosine (DIT). Thyroid peroxidase then couples an MIT with a DIT to form triiodothyronine (T3) or couples a molecule of DIT with another DIT to form thyroxine (T4). After the coupling, thyroglobulin is taken up by the thyrocyte for lysosomal degradation, releasing T4 and T3. DIT and MIT that are uncoupled are deiodinated by a dehalogenase to recycle and conserve any iodide. The thyroid gland secretes thyroxine (T4), which can convert to T3 in the periphery or reverse T3 (rT3). Triiodothyronine (T3) is active, whereas rT3 is inactive.[10]

The hypothalamic-pituitary axis regulates TSH release. The hypothalamus secretes the thyroid-releasing hormone (TRH), which stimulates thyrotrophs in the anterior pituitary to secrete TSH. The anterior pituitary releases TSH and stimulates the thyroid follicular cells to release thyroxine, T4 (80%), triiodothyronine, or T3 (20%). When T4 is released into circulation, it can convert to T3 through deiodination. T4 and T3 can then exert negative feedback on TSH levels, with high levels of T3/T4 decreasing TSH and low levels of T3/T4 increasing TSH levels from the anterior pituitary. T3 is the predominant inhibitor of TSH secretion. Because TSH secretion is so sensitive to minor changes in serum-free T4 through this negative feedback loop, abnormal TSH levels are detected earlier than free T4 in hypothyroidism and hyperthyroidism. There is a log-linear relationship between T3/T4 and TSH, with minor changes in TH resulting in major changes in TSH.[11]

Related Testing

Thyroid function monitoring is predominantly via TSH analysis, as it is the best first-line test in evaluating hypothyroidism and hyperthyroidism since the test is more reliable than plasma T3/T4, which fluctuates.[12] Testing for TSH is a first-line screening test for both hypothyroidism and hyperthyroidism.[13] If values are outside the reference range of 0.4 to 4.5 milliunits/ml, measure T4 if TSH is elevated or measure T4 and T3 if TSH is decreased.[14] In hypothyroidism, if the cause is primary (originating in the thyroid gland), high TSH would be detected, which is the best first-line test.[15] This finding would be accompanied by low total T4, low free T4, hypercholesterolemia (decreased LDL receptor synthesis), plus elevated creatinine kinase levels and thyroid antibodies in Hashimoto disease.[16]

Pathophysiology

Graves' disease can cause hyperthyroidism in that there is an increased thyroid-stimulating immunoglobulin, thyroid neoplasm (for example, toxic adenoma), excess TSH secretion, or exogenous T3 or T4. Treatment for this should

include propylthiouracil (which inhibits peroxidase enzyme and thyroid hormone synthesis), thyroidectomy, radioiodine therapy, which destroys the thyroid, and beta-adrenergic blocking agents (adjunct therapy).[17] The Jod-Basedow Effect occurs when excessive iodine loads induce hyperthyroidism. It is an observation in hyperthyroidism caused by Graves disease, toxic multinodular goiter, and toxic adenoma. The large iodine doses from dietary changes, contrast administration, and iodine-containing medication such as amiodarone can cause symptomatic thyrotoxicosis in these patients.[18]

Hypothyroidism has symptoms that include decreased basal metabolic rate, weight gain and nitrogen balance, reduced heat production, cold sensitivity, decreased cardiac output, hypoventilation, lethargy and mental slowness, drooping eyelids, myxedema, growth retardation, mental retardation in perinatal patients, and goiter. When a patient exhibits these symptoms, an increased TSH would indicate negative feedback if the primary defect is in the thyroid gland. At the same time, a decreased TSH would indicate a defect in the hypothalamus or anterior pituitary. Hypothyroidism can result from thyroiditis (autoimmune or Hashimoto thyroiditis), surgery for hyperthyroidism, iodine deficiency, congenital (cretinism), or decreased TRH or TSH. Treatment for this should include thyroid hormone replacement. [19]

The Wolff-Chaikoff effect occurs in patients with autoimmune thyroiditis when increasing doses of iodine increase thyroid hormone synthesis. The thyroid hormone synthesis ceases when iodine concentration increases further due to negative feedback. In patients with functional thyroid tissue, the thyroid can counter this decrease in iodine through the release and leakage of iodine. However, in patients with decreased functional thyroid tissue due to autoimmune thyroiditis, the thyroid cannot adapt and compensate for the decrease in thyroid hormone synthesis as iodine increases further does not occur, causing the patient to become hypothyroid.[18]

Clinical Significance

Dyshormonogenesis can result in goitrous congenital hypothyroidism. All of the disorders are generally autosomal recessive. A defect in iodide uptake due to a mutation in the sodium/iodide symporter (NIS) gene can result in hypothyroidism, goiter, and mental impairment. Classically, tracer uptake is reduced, and thyroglobulin increases with low T4 and high TSH in the diagnostic workup.[20] Thyroid peroxidase mutations can result in congenital hypothyroidism with goiter, given the crucial role of this enzyme in TH biosynthesis.[21] TPO antibodies are present in Hashimoto thyroiditis, which is an autoimmune disorder leading to hypothyroidism. Pendred syndrome results from mutations in the Pendrin gene, resulting in sensorineural deafness, goiter, and thyroid dysfunction in the second decade of life. Mutations in the thyroglobulin gene can result in congenital hypothyroidism with low levels of thyroglobulin. DUOX2 is crucial for the generation of hydrogen peroxide and can result in congenital hypothyroidism.[20]

Iodotyrosine deiodinase controls the reuse of iodide for thyroid hormone synthesis, and mutations in the *DEHALI* gene lead to a deficiency in this enzyme. Patients have normal thyroid hormone levels at birth but develop congenital hypothyroidism.[22] The *MCT8* gene is highly expressed in the brain and is responsible for expressing the iodine transporter in the cell membrane that brings iodine into the cell. *MCT8*-specific thyroid hormone cell-membrane transporter deficiency is X-linked recessive; thus, it mainly occurs in males and is diagnosed by high serum 3,3’,5-triiodothyronine (T3) concentration and low serum 3,3’,5’ triiodothyronine (reverse T3 or rT3) concentration. Its characteristic presentation shows a severe cognitive deficiency, infantile hypotonia, diminished muscle mass, generalized muscle weakness, spastic quadriplegia that increases in severity, joint contractures, dystonic or athetoid movement with paroxysms, or kinesigenic dyskinesias, and seizures.[23] A mutation in the BRAF V600E gene is known to be a cause of papillary thyroid cancer. The BRAF gene codes for the protein that is involved in the signaling pathway and cell growth.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

References

1. Nussey S, Whitehead S. Endocrinology: An Integrated Approach. BIOS Scientific Publishers; Oxford: 2001. [PubMed: 20821847]
2. Mariotti S, Beck-Peccoz P. Physiology of the Hypothalamic-Pituitary-Thyroid Axis. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hamilton E, Hofland J, Jan de Beur S, Kalra S, Kaltsas G, Kapoor N, Kim M, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Muzumdar R, Purnell J, Rey R, Sahay R, Shah AS, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. MDText.com, Inc.; South Dartmouth (MA): Apr 20, 2021. [PubMed: 25905193]
3. Gupta V, Lee M. Central hypothyroidism. Indian J Endocrinol Metab. 2011 Jul;15(Suppl 2):S99-S106. [PMC free article: PMC3169862] [PubMed: 21966662]
4. Maenhaut C, Christophe D, Vassart G, Dumont J, Roger PP, Opitz R. Ontogeny, Anatomy, Metabolism and Physiology of the Thyroid. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hamilton E, Hofland J, Jan de Beur S, Kalra S, Kaltsas G, Kapoor N, Kim M, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Muzumdar R, Purnell J, Rey R, Sahay R, Shah AS, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. MDText.com, Inc.; South Dartmouth (MA): Jul 15, 2015. [PubMed: 25905409]
5. Medici M, Visser TJ, Peeters RP. Genetics of thyroid function. Best Pract Res Clin Endocrinol Metab. 2017 Mar;31(2):129-142. [PubMed: 28648503]
6. Chattergoon NN. Thyroid hormone signaling and consequences for cardiac development. J Endocrinol. 2019 Jul 01;242(1):T145-T160. [PMC free article: PMC6613780] [PubMed: 31117055]
7. Grasberger H, Refetoff S. Resistance to thyrotropin. Best Pract Res Clin Endocrinol Metab. 2017 Mar;31(2):183-194. [PMC free article: PMC5569899] [PubMed: 28648507]
8. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012 Sep;122(9):3035-43. [PMC free article: PMC3433956] [PubMed: 22945636]
9. Endres D, Leypoldt F, Bechter K, Hasan A, Steiner J, Domschke K, Wandinger KP, Falkai P, Arolt V, Stich O, Rauer S, Prüss H, van Elst LT. Autoimmune encephalitis as a differential diagnosis of schizophreniform psychosis: clinical symptomatology, pathophysiology, diagnostic approach, and therapeutic considerations. Eur Arch Psychiatry Clin Neurosci. 2020 Oct;270(7):803-818. [PMC free article: PMC7474714] [PubMed: 32166503]
10. Rousset B, Dupuy C, Miot F, Dumont J. Chapter 2 Thyroid Hormone Synthesis And Secretion. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hamilton E, Hofland J, Jan de Beur S, Kalra S, Kaltsas G, Kapoor N, Kim M, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Muzumdar R, Purnell J, Rey R, Sahay R, Shah AS, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. MDText.com, Inc.; South Dartmouth (MA): Sep 2, 2015. [PubMed: 25905405]
11. Stathatos N. Thyroid physiology. Med Clin North Am. 2012 Mar;96(2):165-73. [PubMed: 22443969]
12. Esfandiari NH, Papaleontiou M. Biochemical Testing in Thyroid Disorders. Endocrinol Metab Clin North Am. 2017 Sep;46(3):631-648. [PMC free article: PMC5957513] [PubMed: 28760230]
13. Sheehan MT. Biochemical Testing of the Thyroid: TSH is the Best and, Oftentimes, Only Test Needed - A Review for Primary Care. Clin Med Res. 2016 Jun;14(2):83-92. [PMC free article: PMC5321289] [PubMed: 27231117]
14.

Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab. 2013 Dec;27(6):745-62. [PMC free article: PMC3857600] [PubMed: 24275187]

15. Feldt-Rasmussen U, Klose M. Clinical Strategies in the Testing of Thyroid Function. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hamilton E, Hofland J, Jan de Beur S, Kalra S, Kaltsas G, Kapoor N, Kim M, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Muzumdar R, Purnell J, Rey R, Sahay R, Shah AS, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. MDText.com, Inc.; South Dartmouth (MA): Nov 20, 2020. [PubMed: 25905413]
16. Kaur J, Jialal I. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Feb 6, 2026. Hashimoto Thyroiditis. [PubMed: 29083758]
17. Blick C, Nguyen M, Jialal I. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jan 18, 2025. Thyrotoxicosis. [PubMed: 29489233]
18. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014 Mar;10(3):136-42. [PMC free article: PMC3976240] [PubMed: 24342882]
19. Chakera AJ, Pearce SH, Vaidya B. Treatment for primary hypothyroidism: current approaches and future possibilities. Drug Des Devel Ther. 2012;6:1-11. [PMC free article: PMC3267517] [PubMed: 22291465]
20. Hannoush ZC, Weiss RE. Defects of Thyroid Hormone Synthesis and Action. Endocrinol Metab Clin North Am. 2017 Jun;46(2):375-388. [PMC free article: PMC5424610] [PubMed: 28476227]
21. Stoupa A, Chaabane R, Guériouz M, Raynaud-Ravni C, Nitschke P, Bole-Feysot C, Mnif M, Ammar Keskes L, Hachicha M, Belguith N, Polak M, Carré A. Thyroid Hypoplasia in Congenital Hypothyroidism Associated with Thyroid Peroxidase Mutations. Thyroid. 2018 Jul;28(7):941-944. [PubMed: 29790453]
22. Moreno JC, Klootwijk W, van Toor H, Pinto G, D'Alessandro M, Lèger A, Goudie D, Polak M, Grüters A, Visser TJ. Mutations in the iodotyrosine deiodinase gene and hypothyroidism. N Engl J Med. 2008 Apr 24;358(17):1811-8. [PubMed: 18434651]
23. Sarret C, Oliver Petit I, Tonduti D. Allan-Herndon-Dudley Syndrome. In: Adam MP, Bick S, Mirzaa GM, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. University of Washington, Seattle; Seattle (WA): Mar 9, 2010. [PMC free article: PMC26373] [PubMed: 20301789]

Disclosure: Yasaman Pirahanchi declares no relevant financial relationships with ineligible companies.

Disclosure: Muhammad Ali Tariq declares no relevant financial relationships with ineligible companies.

Disclosure: Ishwarlal Jialal declares no relevant financial relationships with ineligible companies.

Copyright © 2023, StatPearls Publishing LLC.

This book is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits others to distribute the work, provided that the article is not altered or used commercially. You are not required to obtain permission to distribute this article, provided that you credit the author and journal.

Bookshelf ID: NBK519566 PMID: 30137850