Thyroid Physiology

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KEYWORDS

• Thyroid physiology • Thyroxine • Triiodothyronine • Deiodinase
• Nuclear receptors

The thyroid gland is a butterfly-shaped organ located anteriorly to the trachea at the level of the second and third tracheal rings. It was so named by Thomas Wharton in 1656, not because of its shape (*thyreos* in Greek means "shield"), but because of its similarity in shape to the nearby thyroid cartilage of the larynx.[1]

Three major components play a role in regulating the production of thyroid hormones: First is the thyroid gland itself with its functional unit, the thyroid follicle; this is the location of synthesis and release into the circulation of thyroid hormone. The other 2 components are the hypothalamus and the pituitary gland.

THYROID EMBRYOLOGY

Embryologically, the thyroid gland is the earliest endocrine structure to appear during human development.[2] It originates from the embryonic endoderm. The earliest morphologic evidence for the thyroid gland is the thyroid enlage (or thyroid placode), a thickening of the endodermal layer in an area overarching the aortic arch.[3] The appearance is evident at about embryonic day 22 in humans. With the development of modern techniques in molecular biology, there is now evidence that the development of the thyroid enlage is not the first step in the development of the primitive thyroid follicular cells. The expression of transcription factors (such as the NK2 homeobox [Nkx2]-1 and paired box [Pax]-8) that are critical for the development of the thyroid gland has been documented 12 to 24 hours before thickening occurs. It is obvious that a complex, but recently more clearly elucidated sequence of embryonic events needs to take place for the normal development of the thyroid gland.[3] A defect in any of these events can lead to number of developmental thyroid anomalies that range from complete or partial agenesis of the thyroid gland[4] resulting in congenital hypothyroidism, to syndromes of reduced sensitivity to thyroid hormone.[5]

The primitive thyroid gland continues to expand ventrally while remaining attached to the pharyngeal floor by a stalk, called thyroglossal duct. As the gland expands laterally to form the 2 lobes, the lumen of the thyroglossal duct disappears, and in most cases the duct itself is no longer present at the end of this process. Occasionally,

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however, a significant remnant is not only detectable after birth or during adult life,[6] but significant abnormality can originate there, including thyroid malignancies.[7] Remnants of thyroid tissue or, occasionally, the only thyroid tissue in the body can be detected as distantly from the normal adult anatomic position of the thyroid gland as the base of the tongue, the embryonic origin of the gland.[8]

Thyroid hormone is first detected in the human fetal circulation at about 11 to 13 weeks of gestation. The responsiveness of the different developing tissues to thyroid hormones seems to be tightly regulated, as evidenced by a sufficient amount of thyroid hormone being critical for the proper development of specific cellular functions in embryonic neural cells[9] as well as the expression of different deiodinases at different time points, usually before specific developmental points. There is evidence, for example, that the development of specific parts of the brain is preceded by the increased expression of deiodinases in those regions that allows conversion of thyroxine (T_4) to the more active triiodothyronine (T_3). This step seems to be a critical and necessary one for the proper development of these regions of the brain. A large body of literature is now available, including guidelines from the major medical organizations (eg, the American Thyroid Association and the Endocrine Society), indicating the importance of proper management of thyroid dysfunction during pregnancy.[10]

A developmentally separate part of the thyroid gland is a group of cells that are present in between the thyroid follicles, called parafollicular cells (also called C-cells). Parafollicular cells are the main source of the hormone calcitonin, but their embryologic origin is different. These cells originate in the embryonic ectoderm and migrate into the thyroid gland during the development of the gland itself.

HYPOTHALAMIC-PITUITARY-THYROID AXIS

One of the most important regulators of thyroid function is the thyroid-stimulating hormone (TSH). TSH is a peptide hormone produced in the anterior pituitary gland, itself under the influence of both thyrotropin-releasing hormone (TRH), produced in the hypothalamus, and thyroid hormone (negative feedback, **Fig. 1**). TSH is very sensitive to small changes in levels of serum thyroid hormone (**Fig. 2**). This feedback system requires the regulatory action of the hypothalamus with the production of TRH. Thyroid hormone has a direct inhibitory effect on TRH production. By contrast, low levels of thyroid hormone lead to increased TRH synthesis in the hypothalamus, which is released into the portal circulation of the hypothalamic-pituitary system. TRH in turn stimulates TSH production in the pituitary gland, resulting in an improved level of serum thyroid hormone (through TSH stimulation of the thyroid gland) and restoration of the axis. TSH measurement in serum is now thought to be the most sensitive test available to clinicians for the diagnosis of most states of thyroid dysfunction, such as hypothyroidism or hyperthyroidism (exemptions include pituitary or hypothalamic disorders).[11]

Damage to the pituitary gland or the hypothalamus can lead to what is known as secondary hypothyroidism, which represents rare but challenging forms of hypothyroidism.[12] On rare occasions pituitary tumors can secrete TSH in excess, leading to secondary hyperthyroidism.[13]

PHYSIOLOGY OF THE THYROCYTE

The functional unit of the thyroid gland is the thyroid follicle (**Fig. 3**). This follicle is a cystic structure the wall, made up of a single layer of specialized epithelial cells often referred to as thyrocytes or follicular cells. The content of the follicle is termed colloid.

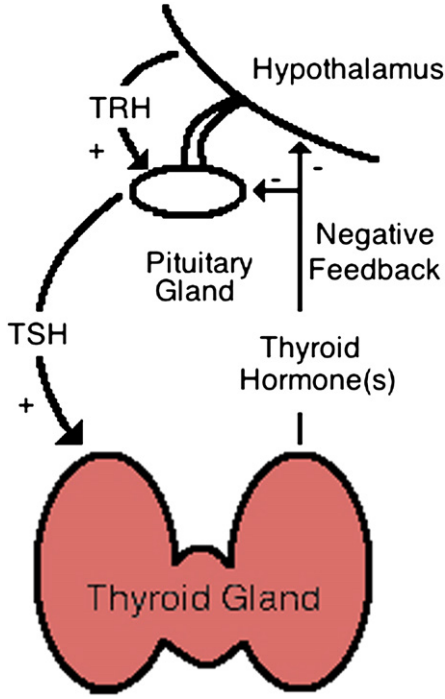

Fig. 1. Regulation of the hypothalamic-pituitary-thyroid axis.

It is largely made up of thyroglobulin (Tg), a large glycoprotein (~660 kDa) that serves as the main storage form of thyroid hormone.

TSH exerts its effects on thyrocytes through its specific receptor known as the TSH receptor (TSHR),[14] located on the basolateral thyrocyte membrane. TSHR is a 7-transmembrane G-coupled receptor protein. Its structure and role in thyroid pathology has been extensively studied. Antibodies against this receptor are central in the development of Graves disease, the most common form of hyperthyroidism.[15] The intracellular effects of activation of this receptor are mainly mediated by the stimulation of adenylyl

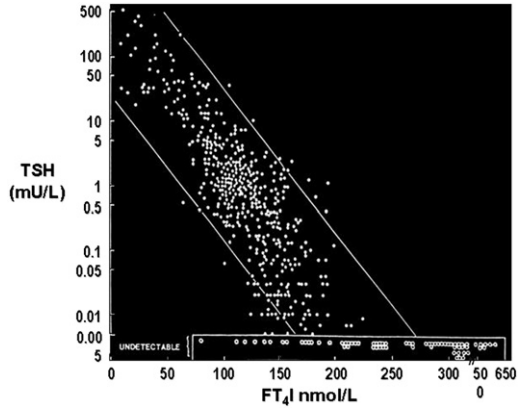

Fig. 2. Log-linear relationship between serum TSH and free T_4.

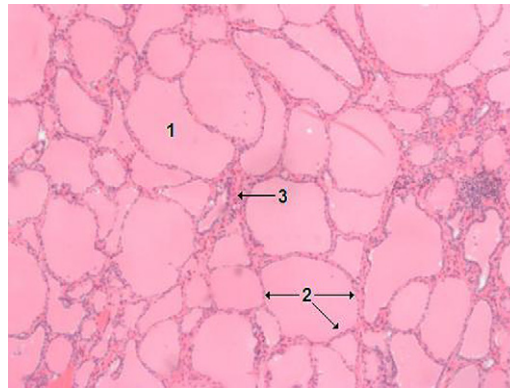

Fig. 3. Thyroid histology. (1) Thyroid follicle. (2) Follicular cells. (3) Parafollicular (C-) cells.

cyclase and the resulting increase in concentrations of intracellular cyclic adenosine monophosphate (cAMP).[16] TSH has a stimulatory effect on thyrocytes that results in increased iodine uptake and increased production of thyroid hormone. It also has a trophic effect on the thyroid gland. These actions have very important physiologic, pathophysiologic, diagnostic, and therapeutic implications. In cases of prolonged hypothyroidism, chronic exposure of the thyroid gland to increased levels of TSH results in the formation of an enlarged gland, also known as a goiter. Stimulating thyroid cells with TSH (endogenous or synthetic) is a critical and necessary step for both the diagnostic and therapeutic use of radioactive iodine in cases of thyroid cancer.

There are 2 main types of thyroid hormone: thyroxine (also called T_4 because it carries 4 iodine atoms) and triiodothyronine (also called T_3 because it carries 3 iodine atoms) (**Fig. 4**). Under normal circumstances, about 90% of the thyroid output is in the form of T_4 and about 10% is T_3. As evidenced by the amount of iodine in each molecule of thyroid hormone, this element is central and critical for the function of the thyroid gland. Thyrocytes concentrate iodine against a concentration gradient to be able to synthesize thyroid hormone. A complex molecular mechanism is in place for this synthesis (see **Fig. 4**) involving an active, energy-consuming process, with the sodium/iodide symporter (NIS) playing a key role.[17] The NIS is a transporter protein located at the basolateral membrane (**Fig. 5**). It has the ability to concentrate iodine in the thyrocytes some 20- to 40-fold above its serum concentration. This transporter has been studied intensively because it is a critical factor in many pathologic states,

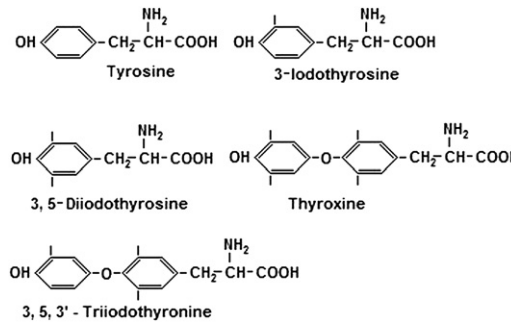

Fig. 4. Iodotyrosine compounds including T_3 and T_4.

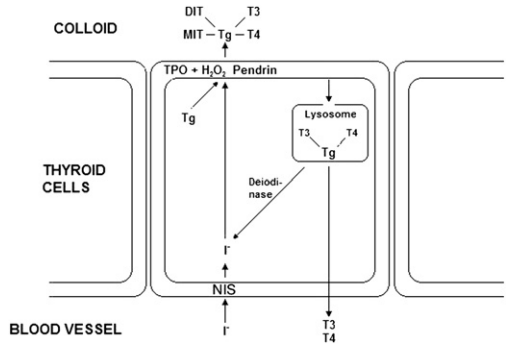

Fig. 5. Organification of iodine. DIT, diiodothyronine; MIT, monoiodothyronine; NIS, sodium/iodide symporter; Tg, thyroglobulin; TPO, thyroid peroxidase.

including thyroid cancer. Loss of expression in thyroid cancer cells leads to decreased iodine uptake in malignant thyrocytes, resulting in a reduced efficacy of radioactive iodine as both a diagnostic and therapeutic tool. Medications that may induce redifferentiation and reexpression of NIS have been investigated (lithium, rosiglitazone[18]) or are currently under investigation (eg, BRAF inhibitors).

Once in the thyrocytes, iodine is organified into tyrosine residues present in Tg. This process takes place at the apical membrane of these cells facing the colloid (see **Fig. 5**). The thyroid peroxidase (TPO) enzyme is a key player in this process, together with hydrogen peroxide.[19] TPO is a selenoprotein (a protein with selenium incorporated into its tertiary structure). The regulation of the activity of this enzyme is quite complex, iodine being a very important factor. Exposure to excess amounts of iodine is known to block TPO activity, a phenomenon known as the Wolff-Chaikoff effect.[20] Clinically this can lead to hypothyroidism. However, over time thyrocytes can eventually overcome this blockade, and this can lead to increased production of thyroid hormone. This phenomenon is known as the escape from the Wolff-Chaikoff effect.[21] These events are characteristically seen in thyrocytes that are replete of iodine. By contrast, when a thyrocyte deplete in iodine is exposed to iodine, it increases production of thyroid hormone significantly, often leading to biochemical and clinical hyperthyroidism. This process is known as the Jod-Basedaw effect.[22] The mechanism for this phenomenon is unclear, but it is thought to be caused either by rapid iodination of poorly iodinated Tg or by the fueling of a subclinical autonomous functioning thyroid tissue, as in a "hot" nodule or in Graves disease.[23]

TPO also seems to be a target in the autoimmune processes such as Hashimoto thyroiditis. Detection of antibodies against TPO is diagnostic of thyroid autoimmunity, usually Hashimoto thyroiditis,[24] although they are detectable in the majority of patients with Graves disease as well.[25]

Another protein closely involved in the organification of iodine together with TPO is pendrin (see **Fig. 5**).[26] A rare genetic disorder called Pendred syndrome includes the clinical findings of sensorineural deafness and a goiter attributable to partial iodine organification defect.[27]

Tg, as already mentioned, is a large glycoprotein that represents the main storage form of thyroid hormone. When thyrocytes are stimulated by TSH, Tg is endocytosed and cleaved to release T_4 and/or (T_3). Tg is critical for the normal function of the thyroid gland and its measurement is a very important clinical tool, mainly in the management of thyroid cancer. It is one of the more immunogenic thyroid-related proteins, and

antibodies against Tg have been reported even in approximately 20% of people with no apparent thyroid pathology.

PERIPHERAL ACTIONS OF THYROID HORMONES

Thyroid hormones circulate in blood mainly bound to carrier proteins (less than 1% is circulating in a free unbound form). It is the small free amount of thyroid hormone that is thought to be metabolically active at the tissue level. More than 95% of the serum thyroid hormones are bound to 3 carrier proteins: thyroid-binding globulin (TBG), transthyretin, and albumin.[28] Thyroid hormone has also been shown to be bound to lipoproteins[29] and thyroid hormone autoantibodies of the immunoglobulin G class.[30] These carrier proteins function on one hand as an extrathyroidal depot of thyroid hormone, containing hormone that can be immediately available to peripheral tissues as needed, while on the other hand protecting them from exposure to excess amounts of thyroid hormone. The role of these carrier proteins is best illustrated in those unusual situations whereby genetic mutations lead to altered amounts and/or structures of these proteins and the resulting clinical and biochemical picture of the patients carrying these mutations. One such example is a condition known as familial dysalbuminemic hyperthyroxinemia, the result of mutations of the albumin gene, which leads to a 60-fold increase in the affinity of albumin for thyroxine.[31] Biochemically this results in an elevated level of serum thyroxine, a normal TSH, and a state of clinical euthyroidism.

Passive diffusion had been postulated to be the main mode whereby thyroid hormone(s) enter target cells. However, transporting proteins that seem to be critical in this process have now been identified. Members of this group include the monocarboxylate transporter 8 (MCT8), MCT10, and the organic anion transporting polypeptide 1C1 (OATP1C1).[32] Differential tissue expression has been documented, with OATP1C1, for example, being predominantly expressed in brain capillaries. OATP1C1 has a higher affinity for T_4 than for other iodinated compounds.[33] The clinical relevance of transporting proteins is again demonstrated in cases of genetic mutations. For example, mutations of the gene encoding MCT8 result in a clinical phenotype of severe psychomotor retardation and elevated levels of serum T_3.[34]

T_4 is often referred to as the prohormone, indicating that conversion to the active T_3 is required for biological activity. This conversion is catalyzed by a group of selenoproteins called diodinases. Three different isoforms have been described: D1, D2, and D3. Tissue-specific expression and different functions have been described for each of these.

Type 1 deiodinase (D1) has been shown to catalyze the conversion of T_3 to both the active triiodothyronine and its inactive counterpart, reverse T_3 (rT_3).[35] However, it seems to have an increased affinity for rT_3. As a result, it has been described a scavenger enzyme with a role of deiodinizing inactive iodothyronines, clearing them from the circulation, and recycling of iodine. A more recently noted function of D1 is in the biosynthesis of thyronamines, a class of endogenous compounds that appears to antagonize actions of thyroid hormone.[36] Although their exact role in thyroid physiology remains largely unknown, a promising therapeutic potential has already been described for thyronamines, as they represent the only endogenous compounds able to induce hypothermia as a prophylactic or for acute treatment of stroke.[37]

Type 2 deiodinase (D2) is the main thyroid hormone activator, converting the prohormone T_4 to the active T_3.[38] Furthermore, D2 regulates intracellular T_3 actions by regulating the availability of its nuclear receptors (thyroid receptors α and β). D2, together with D3, is the most important regulator of serum T_3 levels.

Type 3 deiodinase (D3) catalyzes the conversion of T_4 to the biologically inactive rT_3 and T_3 to 3,3′-diiodothyronine, which is also inactive. D3 likely represents the physiologic inactivator of thyroid hormones.[39] Rare cases of consumptive hypothyroidism have been described whereby D3 is overexpressed in hemangiomas. The result is a state of hypothyroidism caused by excessive degradation of T_3 and T_4.[40]

Thyroid hormones exert their actions mainly by binding and activating specific nuclear receptors. These receptors are transcriptionally active proteins that cause expression of thyroid hormone–responsive genes. The actions of thyroid hormones through these receptors are called genomic.

There are 2 major subtypes of thyroid receptors (TR): TRα and TRβ. However, there are several isoforms (TRα1, TRα2, TRβ1, TRβ2). Each isoform seems to have a tissue-specific function. For example, T_3-mediated cardiovascular effects are mediated by the TRα1 isoform,[41,42] whereas those on plasma cholesterol are mediated by TRβ1.[43] Recently, not only has manipulation of specific isoforms been shown to be clinically possible, but pharmacologic agents such as sobetirome or eprotirome, selective TRβ1 agonists, are currently entered in clinical trials for the management of hypercholesterolemia.[44]

More recently, nongenomic actions of thyroid hormone have been described that are mediated through either nonnuclear actions of these receptors[45–47] or novel cell-surface receptors.[48,49]

REFERENCES

1. Werner SC, Ingbar SH, Braverman LE, et al. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2000.
2. Sgalitzer KE. Contribution to the study of the morphogenesis of the thyroid gland. J Anat 1941;75(Pt 4):389–405.
3. De Felice M, Di Lauro R. Minireview: intrinsic and extrinsic factors in thyroid gland development: an update. Endocrinology 2011;152(8):2948–56.
4. Topaloglu AK. Athyreosis, dysgenesis, and dyshormonogenesis in congenital hypothyroidism. Pediatr Endocrinol Rev 2006;3(Suppl 3):498–502.
5. Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007;21(2):277–305.
6. Organ GM, Organ CH Jr. Thyroid gland and surgery of the thyroglossal duct: exercise in applied embryology. World J Surg 2000;24(8):886–90.
7. Klubo-Gwiezdzinska J, Manes RP, Chia SH, et al. Clinical review: ectopic cervical thyroid carcinoma—review of the literature with illustrative case series. J Clin Endocrinol Metab 2011;96(9):2684–91.
8. Toso A, Colombani F, Averono G, et al. Lingual thyroid causing dysphagia and dyspnoea. Case reports and review of the literature. Acta Otorhinolaryngol Ital 2009;29(4):213–7.
9. Oppenheimer JH, Schwartz HL. Molecular basis of thyroid hormone-dependent brain development. Endocr Rev 1997;18(4):462–75.
10. Haddow JE. The new American Thyroid Association Guidelines for thyroid disease during pregnancy and postpartum: a blueprint for improving prenatal care. Thyroid 2011;21(10):1047–8.
11. Spencer CA, LoPresti JS, Patel A, et al. Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. J Clin Endocrinol Metab 1990; 70(2):453–60.

12. Yamada M, Mori M. Mechanisms related to the pathophysiology and management of central hypothyroidism. Nat Clin Pract Endocrinol Metab 2008;4(12):683–94.
13. Losa M, Fortunato M, Molteni L, et al. Thyrotropin-secreting pituitary adenomas: biological and molecular features, diagnosis and therapy. Minerva Endocrinol 2008;33(4):329–40.
14. Davies TF, Yin X, Latif R. The genetics of the thyroid stimulating hormone receptor: history and relevance. Thyroid 2010;20(7):727–36.
15. Smith BR, Sanders J, Furmaniak J. TSH receptor antibodies. Thyroid 2007; 17(10):923–38.
16. Kleinau G, Krause G. Thyrotropin and homologous glycoprotein hormone receptors: structural and functional aspects of extracellular signaling mechanisms. Endocr Rev 2009;30(2):133–51.
17. Hingorani M, Spitzweg C, Vassaux G, et al. The biology of the sodium iodide symporter and its potential for targeted gene delivery. Curr Cancer Drug Targets 2010;10(2):242–67.
18. O'Neill CJ, Oucharek J, Learoyd D, et al. Standard and emerging therapies for metastatic differentiated thyroid cancer. Oncologist 2010;15(2):146–56.
19. Mansourian AR. Metabolic pathways of tetraidothyronine and triiodothyronine production by thyroid gland: a review of articles. Pak J Biol Sci 2011;14(1):1–12.
20. Markou K, Georgopoulos N, Kyriazopoulou V, et al. Iodine-induced hypothyroidism. Thyroid 2001;11(5):501–10.
21. Eng PH, Cardona GR, Fang SL, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology 1999;140(8):3404–10.
22. Woeber KA. Iodine and thyroid disease. Med Clin North Am 1991;75(1):169–78.
23. Ermans AM, Camus M. Modifications of thyroid function induced by chronic administration of iodide in the presence of "autonomous" thyroid tissue. Acta Endocrinol 1972;70(3):463–75.
24. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996; 335(2):99–107.
25. Chardes T, Chapal N, Bresson D, et al. The human anti-thyroid peroxidase autoantibody repertoire in Graves' and Hashimoto's autoimmune thyroid diseases. Immunogenetics 2002;54(3):141–57.
26. Scott DA, Wang R, Kreman TM, et al. The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet 1999;21(4):440–3.
27. Bizhanova A, Kopp P. Genetics and phenomics of Pendred syndrome. Mol Cell Endocrinol 2010;322(1-2):83–90.
28. Schussler GC. The thyroxine-binding proteins. Thyroid 2000;10(2):141–9.
29. Benvenga S, Gregg RE, Robbins J. Binding of thyroid hormones to human plasma lipoproteins. J Clin Endocrinol Metab 1988;67(1):6–16.
30. Benvenga S, Trimarchi F, Robbins J. Circulating thyroid hormone autoantibodies. J Endocrinol Invest 1987;10(6):605–19.
31. Pannain S, Feldman M, Eiholzer U, et al. Familial dysalbuminemic hyperthyroxinemia in a Swiss family caused by a mutant albumin (R218P) shows an apparent discrepancy between serum concentration and affinity for thyroxine. J Clin Endocrinol Metab 2000;85(8):2786–92.
32. Heuer H, Visser TJ. Minireview: pathophysiological importance of thyroid hormone transporters. Endocrinology 2009;150(3):1078–83.
33. Tohyama K, Kusuhara H, Sugiyama Y. Involvement of multispecific organic anion transporter, Oatp14 (Slc21a14), in the transport of thyroxine across the blood-brain barrier. Endocrinology 2004;145(9):4384–91.

34. Brockmann K, Dumitrescu AM, Best TT, et al. X-linked paroxysmal dyskinesia and severe global retardation caused by defective MCT8 gene. J Neurol 2005;252(6): 663–6.
35. Maia AL, Goemann IM, Meyer EL, et al. Deiodinases: the balance of thyroid hormone: type 1 iodothyronine deiodinase in human physiology and disease. J Endocrinol 2011;209(3):283–97.
36. Piehl S, Hoefig CS, Scanlan TS, et al. Thyronamines—past, present, and future. Endocr Rev 2011;32(1):64–80.
37. Doyle KP, Suchland KL, Ciesielski TM, et al. Novel thyroxine derivatives, thyronamine and 3-iodothyronamine, induce transient hypothermia and marked neuroprotection against stroke injury. Stroke 2007;38(9):2569–76.
38. Williams GR, Bassett JH. Deiodinases: the balance of thyroid hormone: local control of thyroid hormone action: role of type 2 deiodinase. J Endocrinol 2011; 209(3):261–72.
39. Dentice M, Salvatore D. Deiodinases: the balance of thyroid hormone: local impact of thyroid hormone inactivation. J Endocrinol 2011;209(3):273–82.
40. Jassam N, Visser TJ, Brisco T, et al. Consumptive hypothyroidism: a case report and review of the literature. Ann Clin Biochem 2011;48(Pt 2):186–9.
41. Johansson C, Vennstrom B, Thoren P. Evidence that decreased heart rate in thyroid hormone receptor-alpha1-deficient mice is an intrinsic defect. Am J Physiol 1998;275(2 Pt 2):R640–6.
42. Gloss B, Trost S, Bluhm W, et al. Cardiac ion channel expression and contractile function in mice with deletion of thyroid hormone receptor alpha or beta. Endocrinology 2001;142(2):544–50.
43. Gullberg H, Rudling M, Forrest D, et al. Thyroid hormone receptor beta-deficient mice show complete loss of the normal cholesterol 7alpha-hydroxylase (CYP7A) response to thyroid hormone but display enhanced resistance to dietary cholesterol. Mol Endocrinol 2000;14(11):1739–49.
44. Ladenson PW. Thyroid hormone analogues: ready for prime time. Thyroid 2011; 21(2):101–2.
45. Hiroi Y, Kim HH, Ying H, et al. Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci U S A 2006;103(38):14104–9.
46. Lei J, Nowbar S, Mariash CN, et al. Thyroid hormone stimulates Na-K-ATPase activity and its plasma membrane insertion in rat alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 2003;285(3):L762–72.
47. Moeller LC, Cao X, Dumitrescu AM, et al. Thyroid hormone mediated changes in gene expression can be initiated by cytosolic action of the thyroid hormone receptor beta through the phosphatidylinositol 3-kinase pathway. Nucl Recept Signal 2006;4:e020.
48. Bergh JJ, Lin HY, Lansing L, et al. Integrin alphaVbeta3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology 2005; 146(7):2864–71.
49. Davis PJ, Davis FB, Cody V. Membrane receptors mediating thyroid hormone action. Trends Endocrinol Metab 2005;16(9):429–35.