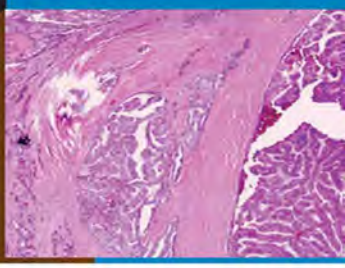
website www.jaypeebrothers.com, for detailed information on endocrinology books, visit our website www.jaypeebrothers.com

Principles and Practices of
THYROID Gland Disorders







Editors
Subhash K Wangnoo
Jamal Ahmad
Mohammad A Siddiqui

Foreword
JK Agrawal

JAYPEE

CONTENTS

1. **Anatomical and Functional Embryology and Histology of Thyroid Gland** 1
   Shehla S Shaikh

2. **Physiology of Thyroid Axis** 9
   Aditi D Pandit

3. **Laboratory Evaluation of Thyroid Functions: Dilemmas and Pitfalls** 22
   MK Garg, Namita Mahalle, KVS Hari Kumar

4. **Relevance of Thyroid Autoantibodies in Patients with Thyroid Dysfunction and in General Population** 32
   Shailesh U Pitale, Anagha V Sahasrabuddhe

5. **Manifestations of Thyroid Hormone Deficiency and Laboratory Evaluation** 45
   Subhankar Chowdhury, Soumik Goswami

6. **Hypothyroidism** 53
   Surya K Singh, Rahul K Singh

7. **Hypothyroidism and Pregnancy** 65
   Sarita Bajaj

8. **Congenital Hypothyroidism** 73
   Archana D Arya, Roopal N Pachani

9. **Subclinical Hypothyroidism** 92
   Jamal Ahmad

10. **Hashimoto's Thyroiditis** 100
    Surender Kumar, Roopal N Panchani

11. **Optimal Thyroid Replacement in Hypothyroidism** 113
    Narendra Kotwal

12. **Graves' Disease** 121
    Monashis Sahu

13. Radioiodine Ablation in Graves' Disease 136
Shivaprasad C, Prasanna Kumar KM

14. Hyperthyroidism in Pregnancy 146
Manash P Baruah

15. Neonatal Thyrotoxicosis 155
Anurag Bajpai

16. Pediatric Graves' Disease 160
Ayesha Ahmad, Radhika Jindal

17. Juvenile Thyrotoxicosis 169
Soham Mukherjee, Sanjay K Bhadada

18. Thyrotoxicosis without Hyperthyroidism 179
Nishant Raizada, Mohd A Ganie

19. Subacute Thyroiditis 191
Manoj Chadha, Sachin Mittal

20. Toxic Nodular Goiter and Adenoma 198
Mala Dharmalingam, Prashant U Kaduskar

21. Simple or Nontoxic Goiter: Diffuse and Multinodular—Pathogenesis, Evaluation, and Management 210
Bipin K Sethi, V Sri Nagesh

22. Approach to the Solitary Thyroid Nodule 224
Krishna G Seshadri

23. Differentiated Thyroid Carcinoma 235
Jubbin J Jacob, Kumaradoss F Jebasingh, Nihal Thomas

24. Medullary Thyroid Cancer 253
Vivek Mathew, Ganapathi Bantwal

25. Drugs Affecting Thyroid Function 264
Namita Sharma

26. Amiodarone-induced Thyroid Dysfunction 275
Ayesha Ahmad

27. Resistance to Thyroid Hormones 282
Deep Dutta, Yashwanth Poondla

28. Radioiodine in the Management of Benign Thyroid Disease 288
Sohaib Ahmad, Nadia Shirazi

29. **Thyroid Emergencies** 297
Dheeraj Kapoor, Ruchi Kapoor, Mona Dhingra

30. **Endocrine Disruptors and Thyroid Disease** 311
Manasi Shah, Shashank R Joshi

31. **Sick Euthyroid Syndrome** 322
Monika Sharma

Index *327*

CHAPTER 2

Physiology of Thyroid Axis

Aditi D Pandit

INTRODUCTION

Thyroid hormones play a very crucial role in the development, growth, and function of majority of the organ systems in the human body. Abnormalities of the function and anatomy of the thyroid gland constitute one of the commonest endocrine abnormalities of the body. This chapter provides an overview of the physiological and the biochemical functioning of the thyroid gland.

PHYLOGENY

The primary event in the phylogeny of the thyroid gland was the ability of the living organisms to trap iodine and bind it to protein which is closely linked with the gastrointestinal tract. Presence of monoiodotyrosine (MIT) and diiodotyrosine (DIT) can be detected in numerous invertebrate species but only cyclostomes (eel like jawless vertebrates) have a bonafide thyroid tissue with follicles in it.[1] Also, the morphological basis of thyroid function remains the same almost throughout all vertebrates, however, it differs significantly anatomically. The ontogeny of the thyroid has the same pattern in all vertebrates: the thyroid anlage arises from an outpouching of the primitive pharynx, migrates caudally, and reaches its definitive position.[2] The thyroid follicles of adult lamprey (cyclostomes) are derived from endostyle which is present only in the larval stage. The epithelium of the endostyle differentiates into different types of cells. A group of cells develops the ability to trap iodine, peroxidase activity, and expression of thyroxine (T4). These cells become "typical" follicular cells only after metamorphosis. The development of thyroid in higher vertebrates follows a slightly different pattern than that of cyclostomes but is closely related to endostyle.[3] These data suggest that during the evolution of protochordates, a group of genes whose function was to contribute to the specification of the anterior part of the gut were selected as part of the genetic program that leads to thyroid specification.

JAYPEE BROTHERS

ANATOMY AND EMBRYOLOGY

Thyroid gland is one of the largest endocrine gland. It is situated in the anterior part of the neck below the thyroid cartilage encircling the 3rd, 4th, and the 5th tracheal rings. The adult thyroid weighs 10–20 g. The normal thyroid gland consists of two lateral lobes joined by an isthmus. The dimensions of the lobes are approximately 2–2.5 cm in thickness and width and around 4 cm in length. The isthmus is around 0.5 cm thick, 2 cm in width, and 1–2 cm in height. The thyroid gland is mainly supplied by the superior thyroid artery, a branch of the external carotid artery and inferior thyroid artery, branch of the subclavian artery. The blood flow is approximately 4–6 mL/min/g of thyroid which can increase to up to 1 L/min/g in Graves' disease leading to the audible bruit.[4]

The thyroid gland originates as a diverticulum from the foramen cecum which is located at the base of the tongue at the level of the 2nd brachial arch. It is seen as early as the 3rd week of pregnancy. It migrates downwards at the root of the neck opposite 3rd and 5th tracheal rings which is the final position. The diverticulum expands laterally to form the lobes of the gland. The track which traces the connection of adult thyroid from its origin in the floor of the mouth by 5th week of pregnancy and totally disappears by 8th week is known as the thyroglossal duct. Fourth pharyngeal pouch also contributes to part of posterior position of the lobes of thyroid. The fusion of these thyroid precursors is identified as tubercle of Zuckerkandl, an important landmark to locate the recurrent laryngeal nerve. Components derived from the 5th pharyngeal pouch contribute to the development of the ultimobranchial body which are neural crest derived cells and migrate to upper third of thyroid and form the C cells secreting calcitonin.[5]

THYROID AXIS

Thyroid axis comprises of thyrotropin releasing hormone (TRH) released from the hypothalamus, thyroid stimulating hormone (TSH) from the pituitary, and the thyroid hormones ultimately secreted by the thyroid glands in response to TRH and TSH, and the delicate balance between them in response to both internal and external factors. Each part of the axis will be dealt with separately.

Thyrotropin Releasing Hormone

Thyrotropin releasing hormone is a tripeptide, (pyro)Glu-His-Pro(NH_2), and smallest hypophysiotropic hormone. It is a phylogenetically an ancient peptide and has been isolated from primitive vertebrates.[6] Thyrotropin releasing hormone is expressed in both central nervous system (CNS) and periphery, but it does not stimulate TSH release in these vertebrates. Therefore, TRH has multiple peripheral and central activities and considered as a hypophysiotropic factor during the evolution of vertebrates. Thyrotropin releasing hormone is needed for coordinated regulation of temperature homeostasis.

JAYPEE BROTHERS

Effects

Effects on pituitary

- Immediate rise of serum TSH within a few minutes, followed by rise of triiodothyronine (T3). Rise of T4 blood levels is not demonstrable because pool of circulating T4 is large (majority of which is bound to carrier proteins)[7]
- Thyrotropin releasing hormone is also a potent prolactin releasing factor.[7] The rise of serum prolactin levels and the dose response characteristics and suppressibility by thyroid hormones is parallel to that of TSH. It is not a physiological regulator of prolactin[8] but hyperprolactinemia is seen in some patients of primary hypothyroidism
- No demonstrable effect on pituitary hormones other than TSH and prolactin, however, it causes a rise of growth hormone (GH) levels in patients with acromegaly and of adrenocorticotropic hormone in patients with Cushing's disease. Release of GH due to TRH can be seen in some patients of the following:
  - Anorexia nervosa
  - Uremia
  - Hepatic disease
  - Psychotic depression
  - Children with hypothyroidism.[7]

Extrapituitary functions

Thyrotropin releasing hormone is present in almost all parts of brain,[9] and this extensive extrahypothalamic distribution, its localization on nerve endings, and presence of its receptors on brain tissue suggest a role of TRH as a neurotransmitter and neuromodulator.[10] It also acts as a general stimulator and induces increase in temperature suggesting a role in thermoregulation.[9]

Clinical Applications

- To differentiate between pituitary and hypothalamic causes of hypothyroidism; however, the test has lost favor because of the low specificity[7]
- To look for residual GH secretion from somatotropin secreting cells in acromegalic patients; which release GH in response to TRH before treatment
- Used for treatment of neurologic disorders like spinal muscular atrophy and amyotrophic lateral sclerosis (however, use in large centers have failed to confirm the efficacy)[9]
- Used for treatment of disorders like the West syndrome, Lennox-Gastaut syndrome, and intractable epilepsy[11]
- Proposed to be an analeptic agent.[9]

Thyroid Stimulating Hormone

Thyroid stimulating hormone is a glycoprotein hormone which is produced by the thyrotropic cells located in the anterior part of pituitary gland. It

JAYPEE BROTHERS

consists of a heterodimer of two noncovalently linked subunits, α and β. The α-subunit is common amongst other pituitary hormones like the luteinizing hormone (LH), follicle stimulating hormone (FSH), and also, human chorionic gonadotropin (hCG) secreted by the placenta. It is the β-subunit which grants the specificity to the TSH. Circulating TSH binds to specific cell-surface receptors present on the thyroid gland. It stimulates the production of thyroid hormones, T4 and T3, which act on multiple organs and subsequently resulting in a feedback inhibition of TSH output.

Biosynthesis

The TSH molecule is a heterodimeric glycoprotein. It has molecular weight of 28 kDa which is composed of the noncovalently linked α- and β-subunits. The α-subunit comprises of 92 amino acids, and the specific TSHβ-subunit has 118 amino acids. The biosynthesis of TSH comprises of the following steps:

Transcription and translation

The deoxyribonucleic acid (DNA) information contained in the TSHβ- and α-subunit genes is transcribed into a precursor ribonucleic acid (RNA) by a complex of enzymes. The transcribed RNAs undergo multiple splicing events at the exon-intron junctions which forms the mature messenger RNA (mRNA). The mRNA which is formed then exits the nucleus and is translated to protein in the cytoplasm. The mRNAs for the TSHβ- and α-subunits are independently translated by ribosomes in the cytoplasm. The first peptide sequences consist of formation of signal peptides. Further, translation into TSHβ- and α-presubunits continues into the lumen of the rough endoplasmic reticulum and cleavage of the signal peptide occurs before translation is completed. This results in the formation of 118 amino acid β-subunit[12] and 92 amino acid α-subunit.

Glycosylation

Glycosylation of TSH significantly impacts its biological activity.[13] The TSHβ-subunit has a single glycosylation site, the asparagine residue at position whereas the α-subunit is glycosylated in two sites.[14] Glycosylation of TSH is essential for it to attain normal bioactivity, a process that requires the interaction of TRH with its receptor on the thyrotrophs. Once TRH binds to its receptor on the thyrotrophs, TSH gets glycosylated into a biologically potent molecule. Glycosylation of the TSH molecule also results in rapid clearance of TSH from the circulation, raising the concept of "qualitative regulation of TSH secretion," which is mainly achieved through both transcriptional and post-transcriptional mechanisms involved in TSH glycosylation.[15]

Folding and storage

Folding is a critical step that allows correct internal disulfide bonding, which stabilizes the tertiary structure of the protein, allowing subunit combination. After folding, combination of TSHβ- and α- units takes place. The sequence of TSHβ-subunit from amino acid 27 to 31 [cysteine-alanine-

JAYPEE BROTHERS

glycine-tyrosine-cysteine (CAGYC)] is highly conserved and is essential for its combination with α-subunits. In case of point mutation in CAGYC as is the case in congenital hypothyroidism, TSHβ-subunit is unable to combine with α-subunits leading to lack of intact TSH production. Thyroid stimulating hormone is processed and then transported into secretory granules or vesicles. The secretory granules have a regulated secretory pathway which is influenced mainly by TRH. The free α-subunits are usually contained in vesicles which have a nonregulated secretory pathway.[16]

Thyroid Stimulating Hormone Secretion

The normal production rate of TSH is between 100 and 400 mU/day in healthy adult humans.[17,18] The distribution space of TSH is slightly greater than the plasma volume. In euthyroid subjects, the half-life of TSH in plasma is approximately 50 minutes, with a plasma clearance rate of approximately 50 mL/min. In hypothyroid subjects, TSH secretion rates increase by 10–15 times normal rates, and the clearance rate decreases slightly. In hyperthyroid subjects, TSH secretion is suppressed, and metabolic clearance is accelerated.

Ontogeny of thyroid stimulating hormone levels

- Eight to ten weeks of gestation → TRH measurable in hypothalamus[19]
- Twelve weeks → immunoreactive TSH cells present in the pituitary gland[19] and TSH detectable in pituitary and serum[20,21]
- Till 18 weeks gestation → low serum and pituitary TSH
- Twenty to forty weeks gestation → fetal T4 and TSH levels rise
- Last half of gestation and first 2 months of life → negative feedback develops.[22]

Patterns

Thyroid stimulating hormone is secreted from the pituitary gland in two ways consisting of basal secretion coupled with pulses occurring every 2–3 hours superimposed on it.[23] About 30–40% of secretion is accounted by the basal secretion and remaining 60–70% is by the pulses which directly stimulate T3 secretion. Thyroid stimulating hormone has a circadian pattern of secretion with peak TSH levels occurring between 11 PM and 5 AM with a nadir at 11 AM. This pattern is not seen in infants less than 4 weeks.[24] In cases of primary hypothyroidism, this nocturnal surge is preserved,[23] whereas in hypothalamic pituitary causes of hypothyroidism, nocturnal surge is lost.[25] Studies have reported that the normal early morning endogenous cortisol secretion suppresses the serum TSH and results in the observed TSH circadian secretion.[26,27]

Regulation

Hypothalamic

- Thyrotropin releasing hormone: Acute intravenous administration of TRH causes a dose related increase in TSH within 2 minutes and peak levels

JAYPEE BROTHERS

occurring at 20–30 minutes with return to basal levels at 2 hours.[28] A biphasic response occurs due to 2–4 hours infusions with initial rise because of stored TSH and the later phase because of newly synthesized TSH
- Somatostatin: Inhibits basal and TRH stimulated TSH secretion *in vitro* and *in vivo*; abolishes the circadian variation[29]
- Dopamine: Suppresses the TSH secretion[30,31]
- Opioids: Suppress the TSH secretion[32]
- Adrenergic: Alpha-adrenergic stimulation stimulates the TSH secretion.[33]

Peripheral

- Thyroid hormone: Blocks the pituitary secretion of TSH.[34] At pituitary level, they increase the activity of pituitary TRH degrading enzymes and also decrease the number of TRH receptors. Also, T3 stimulates the release of somatostatin from hypothalamic tissue
- Glucocorticoids: At pharmacologic doses or high endogenous cortisol levels (Cushing's syndrome) suppress basal TSH levels, blunt TSH responses to TRH, and diminish the nocturnal TSH surge in humans and animals[35]
- Leptin: Exogenous leptin increases the TSH levels by increasing the TRH gene expression[36]
- Cytokines: Administration of tumor necrosis factor (TNF) or interleukin-6 (IL-6) decreases serum TSH levels in healthy human subjects, and TNF and interleukin-1 (IL-1) decrease TSH levels in animals[37]
- Sex steroids: Do not play a major role in TSH secretion in humans. Estrogens administration to euthyroid rats do not have any impact on TSH levels[38]
- Others: Other factors, like neurotensin, galanin, substance P, epidermal growth factor, fibroblast growth factor, IL-1, and IL 6, all have effect on TSH levels.

Thyroid Hormones

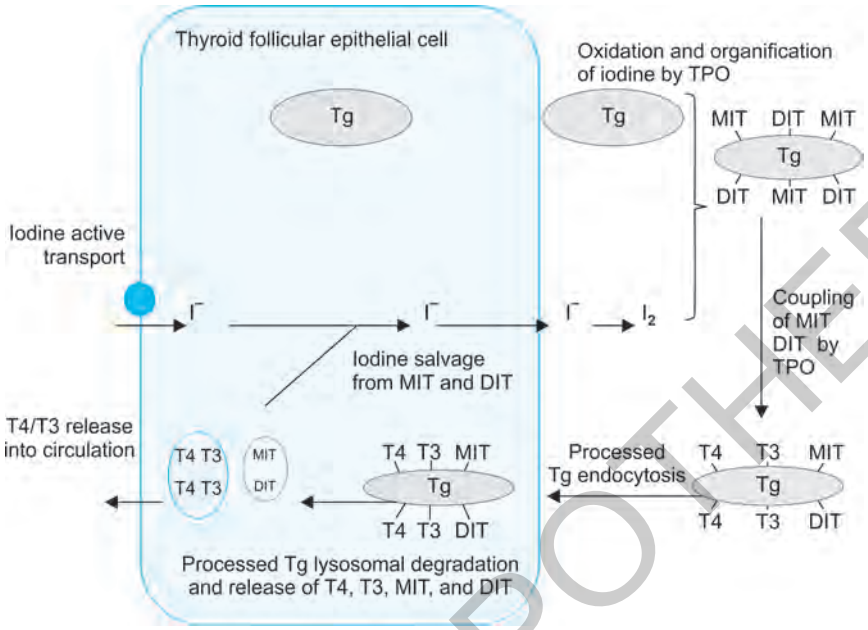
Synthesis (Fig. 1)

Thyroid hormones synthesis requires uptake of iodide actively, followed by thyroglobulin synthesis, oxidation and binding of iodide to thyroglobulin, and lastly, oxidative coupling of two iodotyrosines into iodothyronines.

Iodide uptake

Iodide is present in very low concentrations in the plasma. Sodium iodide symporter (NIS) located in the basolateral membrane helps the thyroid cell to concentrate the required amount of iodine.[39] It is encoded by the gene SLC5A5. Human NIS is a 643 amino acid glycoprotein with 13 membrane spanning domains. Iodine is transported actively depending on the presence of the sodium ion gradient across the basolateral membrane with a downhill transport of two sodium ions results in the uptake of one iodine atom against the electrochemical gradient. Iodide diffuses by a specialized channel (pendrin

JAYPEE BROTHERS



Tg, thyroglobulin; TPO, thyroperoxidase; T4, thyroxine; T3, triiodothyronine; MIT, monoiodinated tyrosine; DIT, diiodinated tyrosine.

Fig. 1: Synthesis of thyroid hormones

or another channel) from the cell to the lumen at the apical membrane.[40] Sodium iodide symporter is also located in the lactating mammary glands, choroid plexus, gastric mucosa, salivary glands, the syncytiotrophoblast, and the cytotrophoblast.[41] Sodium iodide symporter also transports pertechnetate (TcO_4^-), perchlorate (ClO_4^-), and thiocyanate (SCN^-) which accounts for the utility of radioactive TcO_4^- as a thyroid scanning tool and the capacity of $KClO_4^-$ to block iodide uptake.[42] Sodium iodide symporter has higher affinity for iodide than bromide and chloride. Sodium iodide symporter is required for concentration of iodine in thyroid and NIS gene mutation leads to congenital hypothyroidism.[43] There are many factors which control the NIS expression. Thyroid stimulating hormone upregulates the expression of NIS, whereas iodide directly decreases the NIS expression impairing the release and organification of thyroid hormones. Also, some drugs like hydrocortisone, dexamethasone, sex steroids, RU486, amiodarone, bromide, and ketoconazole are known to decrease the NIS expression. In contrast, adenosine and retinoic acid increase thyroidal iodide uptake and NIS expression.[44] In addition to active transport of iodide from the extracellular fluid, intracellular iodide is also generated by the action of the enzyme, iodotyrosine dehalogenase 1, also called iodotyrosine deiodinase (IYD). Transcription of IYD is stimulated by cyclic adenosine monophosphate (cAMP). Iodotyrosine deiodinase catalyzes nicotinamide adenosine dinucleotide phosphate dependent deiodination of MIT and DIT.[45] Iodide which exits from the apical membrane of the cell immediately reconstitutes with thyroglobulin which is newly synthesized.

JAYPEE BROTHERS

Iodide oxidation and organification

At the apical surface of the thyrocyte, the enzymes thyroperoxidase (TPO) and hydrogen peroxide generated by the calcium dependent dual oxidase 1 and 2 enzymes oxidize iodide and attach it to tyrosyl residues on thyroglobulin to produce MIT and DIT, the precursors of thyroid hormone.[46]

Iodothyronine synthesis

Thyroperoxidase then catalyzes the coupling of the phenyl groups of the iodotyrosines through a diether bridge to form the thyroid hormones. Linkage of two DIT molecules produces T4, and linkage of a MIT and DIT produces T3. Thus, T3 is structurally identical to T4 but has one less iodine (at the 5' position on the outer ring). Efficient synthesis of T4 and T3 in the thyroid requires thyroglobulin. There are 3–4 T4 molecules in each molecule of human thyroglobulin under conditions of normal iodination but only about one in five molecules of human thyroglobulin contains a T3 residue. In thyroglobulin from patients with untreated Graves' disease, the content of T4 residues remains approximately the same, but the number of T3 residues doubles to an average of 0.4 per molecule.

Storage and release of thyroid hormones

Secretion of thyroid hormone requires endocytosis of human thyroglobulin, its hydrolysis, and the release of thyroid hormones from the cell. Thyroglobulin can be ingested by the thyrocyte by three mechanisms.[47,48] The first mechanism is macropinocytosis in which the pseudopods are formed at the apical membrane[49] and the second is micropinocytosis by small coated vesicles that form at the apical surface.[50] Both processes are stimulated by TSH, with micropinocytosis thought to predominate in humans. A third (hypothesized) process is receptor mediated endocytosis; it would be enhanced in chronically stimulated thyroid cells.[51] The protein involved could be megalin and/or asialoglycoprotein. This process probably accounts for transcytosis of thyroglobulin. Whatever its mechanism, endocytosis is followed by lysosomal digestion, with complete hydrolysis of thyroglobulin. The main iodothyronine in thyroglobulin is thyroxine. However, during its secretion, a small fraction is deiodinated by type 1 5-deiodinases to T3, thus increasing relative T3 (the active hormone) secretion. The free thyroid hormones are released by an unknown mechanism, which may be transport or exocytosis. The iodotyrosines are deiodinated by specific deiodinases and their iodide recirculated in the thyroid iodide compartments.

Mechanism of Thyroid Action

All the thyroid cells express the TSH receptor (TSHR) which is a member of the glycoprotein G protein coupled receptor family. Thyroid stimulating hormone receptor contains a large extracellular N-terminal domain, seven membrane spanning domains, and an intracellular domain which

JAYPEE BROTHERS

transduces the signal. Guanosine diphosphate is exchanged for guanosine triphosphate on the α-subunit of G proteins. Thyroid stimulating hormone receptor couples to the stimulatory protein, Gs, when activated by high concentrations of TSH (100 times the physiologic level), it also couples to Gq/G11, activating the inositolphosphate diacylglycerol cascade.[52] The induction of signal via the phospholipase C and intracellular Ca^{2+} pathways regulates iodide efflux, H_2O_2 production, and thyroglobulin iodination, whereas the signal via the protein kinase A pathway mediated by cAMP regulates iodine uptake and transcription of thyroglobulin, TPO, and NIS mRNAs, leading to thyroid hormone production.

The TSHR also binds TSHR stimulating antibody, thyroid blocking antibodies, and neutral antibodies to the TSHR. The LH and hCG also bind to TSHR and activate it.[52] This causes the physiologic hyperthyroidism of early pregnancy. The TSHR is also expressed in osteoclasts, fibroblasts, and adipocytes, as well as retro-orbital adipocytes and skin besides the thyroid cells.

The thyroid hormone which is synthesized acts by binding to nuclear thyroid hormone receptor (TR) which, in turn, binds to DNA, usually as a heterodimer with retinoid X receptor (RXR) at specific sequences called thyroid hormone response elements; these sites are dictated by the DNA binding site preferences of the RXRTR (or TRTR)complex. Triiodothyronine has a 15 fold higher binding affinity for TRs than does T4, explaining its function as the active thyroid hormone. In humans, there are two TR genes, α and β, that are found on different chromosomes (chromosomes 17 and 3, respectively). There are several alternatively spliced gene products from each of these genes forming both active and inactive gene products. The active proteins are thyroid hormone receptor α1, β1, β2, and β3.[53] There are tissue specific preferences in expression of the various TRs, suggesting that they serve different functions in different tissues. It is as follows:

- Thyroid hormone receptor α1 (widely expressed and especially high expression in cardiac and skeletal muscles)
- Thyroid hormone receptor β1 (predominately expressed in brain, liver, and kidney)
- Thyroid hormone receptor β2 (expression primarily limited to the hypothalamus and pituitary)
- Thyroid hormone receptor β3 (expressed at low levels but is more abundant in liver, kidneys, and lungs).

Thyroid Hormone Metabolism

Thyroid hormones are poorly water-soluble and hence, are reversibly bound to plasma proteins. The major plasma proteins are thyroxine binding globulin (TBG), albumin, and transthyretin (TTR). More than two-third of T3 is bound by TBG and remainder by TTR and albumin. The TBG binding site has 20 fold less affinity for T3 than that for T4. Transthyretin is expressed in the choroid plexus and is the major thyroid hormone binding plasma protein in the cerebrospinal fluid. Binding of T4 and T3 by TBG is inhibited by certain

JAYPEE BROTHERS

drugs like phenytoin, salicylate, salsalate, furosemide, fenclofenac, and mitotane. Albumin has high concentration in the plasma and hence, binds 10% of the thyroid hormones even if the affinity of albumin for T4 and T3 binding is much lower than that of either TBG or TTR.[54]

The most important pathway for T4 metabolism is its outer ring (5') monodeiodination to the active thyroid hormone, T3. This reaction is catalyzed by type 1 and 2 deiodinases (D1 and D2) and is the source of more than 80% of the circulating T3 in humans. Inner ring deiodination, an inactivating step, is catalyzed primarily by type 3 deiodinase (D3), which inactivates T3 and prevents activation of T4 by converting it to reverse T3. Type 1 deiodinase is primarily located in the liver, kidney, and the thyroid; D2 is located mainly in the CNS; and D3 in placenta, CNS, and other locations.[55] Also, D1 is inhibited by propylthiouracil (PTU) and D2 is inhibited by excess levels of thyroid hormones, whereas D1 levels are increased by the thyroid hormones. Both, D1 and D2, form the active thyroid hormone T3. However, D2 is located in the endoplasmic reticulum, whereas both D1 and D3 are in the plasma membrane. The endoplasmic reticulum location of D2 gives the T3 formed by the catalytic process of D2 better access to the nucleus. Hence, D2 performs the important task of providing nuclear T3 from intracellular T4 in a cell specific fashion. This assumes special importance in the hypothalamo-pituitary-thyroid axis when D2 increases in response to decrease in serum T4. Also, in thyrotoxicosis, there is a 3–4 fold increase in D1 activity making D1 the primary source of T3. As D1 is inhibited by PTU, PTU is more rapid in reducing T3 levels in Graves' disease than methimazole. Type 3 deiodinase is the primary deiodinase inactivating T3. In infants with extensive hepatic lesions, D3 may overwhelm the secretory capacity of the infant's thyroid, causing hypothyroidism, a syndrome termed consumptive hypothyroidism.[56] Some drugs also interfere with the deiodination. Amiodarone inhibits the iodination of T4 by D1 due to its structural similarity with T4. Glucocorticoids in high dosage decrease the T3 by T4 ratio, whereas GH increases the circulating T3 by T4 ratio. In addition to deiodination, iodothyronines are metabolized by conjugation of the phenolic hydroxyl group with sulfate or glucuronic acid. Sulfation and glucuronidation are the so called phase II detoxification reactions, the general purpose of which is to increase the water solubility of the substrates and, thus, to facilitate their biliary and/or urinary clearance.

CONCLUSION

The thyroid axis compromising of TRH, TSH, and thyroid hormones is very intricately controlled by a myriad of factors. Thyrotropin-releasing hormone is the smallest tripeptide hypothalamic hormone exerting its control on TSH. It is a potent TSH and prolactin releasing hormone and plays an important role in thermoregulation and also works as an neurotransmitter and neuromodulator. Thyroid-stimulating hormone is a glycoprotein hormone produced by the pituitary stimulates the production of T3, T4, which act on multiple organs and subsequently provides negative feed back inhibition of

JAYPEE BROTHERS

TSH. It is a heterodimeric glycoprotein hormone with α and β units (92 and 118 amino acids, respectively) and is predominantly regulated centrally by TRH as well as by dopamine, somatostatin, and opiods amongst others. Thyroid hormone T3, T4 have various effects on the body by acting on the thyroid hormone receptors (α1, β1, β2, and β3) and metabolized into active and inactive forms by the three type of deiodinases (D1, D2, D3) located in the endoplasmic reticulum and plasma membrane.

REFERENCES

1. Verhaeghe EF, Fraysse A, Guerquin-Kern JL, Wu TD, Devès G, Mioskowski C, et al. Microchemical imaging of iodine distribution in the brown alga Laminaria digitata suggests a new mechanism for its accumulation. J Biol Inorg Chem. 2008;13(2):257-69.
2. De Felice M, Di Lauro R. Murine models for the study of thyroid gland development. Endocr Dev. 2007;10:114.
3. Ericson LE, Fredriksson G. Phylogeny and ontogeny of the thyroid gland. In: Greer M, editor. The Thyroid Gland. New York: Raven Press; 1990. pp. 1-35.
4. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. William's Textbook of Endocrinology, 12th ed. Philadelphia: Elsevier/Saunders; 2011.
5. Fisher DA, Dussault JH, Sach J, Chopra IJ. Ontogenesis of hypothalamic-pituitary-thyroid function and metabolism in man, sheep and rat. Recent Prog Hormone Res. 1976;33:59-116.
6. Yamada M, Radovick S, Wondisford FE, Nakayama Y, Weintraub BD, Wilber JF. Cloning and structure of human genomic DNA and hypothalamic cDNA encoding human preprothyrotropin-releasing hormone. Mol Endocrinol. 1990;4(4):551-6.
7. Jackson IM. Thyrotropin-releasing hormone. N Engl J Med. 1982;306:145-55.
8. Gautvik KM, Tashjian AH Jr, Kourides IA, Weintraub BD, Graeber CT, Maloof F, et al. Thyrotropin-releasing hormone is not the sole physiologic mediator of prolactin release during suckling. N Engl J Med. 1974;290(21):1162-5.
9. Gary KA, Sevarino KA, Yarbrough GG, Prange AJ Jr, Winokur A. The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. J Pharmacol Exp Ther. 2003;305(2):410-6.
10. Yarbrough GG, Kamath J, Winokur A, Prange AJ Jr. Thyrotropin-releasing hormone (TRH) in the neuroaxis: therapeutic effects reflect physiological functions and molecular actions. Med Hypotheses. 2007;69:1249-56.
11. Takeuchi Y, Takano T, Abe J, Takikita S, Ohno M. Thyrotropin-releasing hormone: role in the treatment of West syndrome and related epileptic encephalopathies. Brain Dev. 2001;23:662-7.
12. Pierce JG, Parsons TF. Glycoprotein hormones: structure and function. Annu Rev Biochem. 1981;50:465-95.
13. Thotakura NR, LiCalzi L, Weintraub BD. The role of carbohydrate in thyrotropin action assessed by a novel method of enzymatic deglycosylation. J Biol Chem. 1990;265:11527-34.
14. Magner JA, Weintraub BD. Thyroid-stimulating hormone subunit processing and V combination in microsomal subfractions of mouse pituitary tumor. J Biol Chem. 1982;257:6709-15.
15. Gupta V, Lee M. Central hypothyroidism. Indian J Endocrinol Metab. 2011;15(Suppl 2):S99-106.
16. Jameson JL, DeGroot LJ. Endocrinology: Adult and Pediatric, 6th ed. Philadelphia: Saunders/Elsevier; 2010.
17. Odell WD, Utiger RD, Wilber JF, Condliffe PG. Estimation of the secretion rate of thyrotropin in man. J Clin Invest. 1967;46(6):953-9.
18. Ridgway EC, Weintraub BD, Maloof F. Metabolic clearance and production rates of human thyrotropin. J Clin Invest. 1974;53:895-903.
19. Baker BL, Jaffe RB. The genesis of cell types in the adenohypophysis of the human fetus as observed with immunocytochemistry. Am J Anat. 1974;143:137-49.
20. Fisher DA, Polk DH. Development of the thyroid. Ballieres Clin Endocrinol Metab. 1989;3:67-80.

JAYPEE BROTHERS

21. Fisher DA, Klein AH. Thyroid development and disorders of thyroid function in the newborn. N Engl J Med. 1981;304:702-11.
22. Roti E. Regulation of thyroid stimulating hormone (TSH) secretion in the fetus and neonate. J Endocrinol Invest. 1988;11:145-55.
23. Samuels MH, Veldhuis JD, Henry P, Ridgway EC. Pathophysiology of pulsatile and copulsatile release of thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and α-subunit. J Clin Endocrinol Metab. 1990;71:425-32.
24. Mantagos S, Koulouris A, Makri M, Vagenakis AG. Development of thyrotropin circadian rhythm in infancy. J Clin Endocrinol Metab. 1992;74(1):71-4.
25. Samuels MH, Lillehei K, Kleinschmidt-Demasters BK, Stears J, Ridgway EC. Patterns of pulsatile pituitary glycoprotein secretion in central hypothyroidism and hypogonadism. J Clin Endocrinol Metab. 1990;70:391-5.
26. Samuels MH. Effects of variations in physiological cortisol levels on thyrotropin secretion in subjects with adrenal insufficiency: a clinical research center study. J Clin Endocrinol Metab. 2000;85:1388-93.
27. Samuels MH. Effects of metyrapone administration on thyrotropin secretion in healthy subjects—a clinical research center study. J Clin Endocrinol Metab. 2000;85:3049-52.
28. Chan V, Wang C, Yeung RT. Thyrotropin: alpha- and beta-subunits of thyrotropin, and prolactin responses to four-hour constant infusions of thyrotropin-releasing hormone in normal subjects and patients with pituitary-thyroid disorders. J Clin Endocrinol Metab. 1979;49:127-31.
29. Vale W, Brazeau P, Rivier C, Brown M, Boss B, Rivier J, et al. Somatostatin. Recent Prog Horm Res. 1975;31:365-97.
30. Ben-Jonathan N, Oliver C, Weiner HJ, Mical RS, Porter JC. Dopamine in hypophysial portal plasma of the rat during the estrous cycle and throughout pregnancy. Endocrinology. 1977;100(2):452-8.
31. Cooper DS, Klibanski A, Ridgway EC. Dopaminergic modulation of TSH and its subunits: in vivo and in vitro studies. Clin Endocrinol (Oxf). 1983;18(3):265-75.
32. Howlett TA, Rees LH. Endogenous opioid peptides and hypothalamo-pituitary function. Ann Rev Physiol. 1986;48:527-36.
33. Klibanski A, Milbury PE, Chin WW, Ridgway EC. Direct adrenergic stimulation of the release of thyrotropin and its subunits from the thyrotrope in vitro. Endocrinology. 1983;113(4):1244-9.
34. Larsen PR. Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. N Engl J Med. 1982;306(1):23-32.
35. Brabant G, Brabant A, Ranft U, Ocran K, Köhrle J, Hesch RD, et al. Circadian and pulsatile thyrotropin secretion in euthyroid man under the influence of thyroid hormone and glucocorticoid administration. J Clin Endocrinol Metab. 1987;65(1):83-8.
36. Ortiga-Carvalho TM, Oliveira KJ, Soares BA, Pazos-Moura CC. The role of leptin in the regulation of TSH secretion in the fed state: in vivo and in vitro studies. J Endocrinol. 2002;174(1):121-5.
37. Hermus RM, Sweep CG, van der Meer MJ, Ross HA, Smals AG, Benraad TJ, et al. Continuous infusion of interleukin-1 beta induces a nonthyroidal illness syndrome in the rat. Endocrinology. 1992;131(5):2139-46.
38. Farbota L, Hofmann C, Oslapas R, Paloyan E. Sex hormone modulation of serum TSH levels. Surgery. 1987;102(6):1081-7.
39. Nilsson M, Björkman U, Ekholm R, Ericson LE. Polarized efflux of iodide in porcine thyrocytes occurs via a cAMP-regulated iodide channel in the apical plasma membrane. Acta Endocrinol (Copenh). 1992;126(1):67-74.
40. Rodriguez AM, Perron B, Lacroix L, Caillou B, Leblanc G, Schlumberger M, et al. Identification and characterization of a putative human iodide transporter located at the apical membrane of thyrocytes. J Clin Endocrinol Metab. 2002;87(7):3500-3.
41. Wolff J. Perchlorate and the thyroid gland. Pharmacol Rev. 1998;50:89105.
42. Van Sande J, Massart C, Beauwens R, Schoutens A, Costagliola S, Dumont JE, et al. Anion selectivity by the sodium iodide symporter. Endocrinology. 2003;144(1):24752.
43. Bizhanova A, Kopp P. Minireview: the sodiumiodide symporter NIS and pendrin in iodide homeostasis of the thyroid. Endocrinology. 2009;150(3):108490.

JAYPEE BROTHERS

44. Shen DH, Kloos RT, Mazzaferri EL, Jhian SM. Sodium iodide symporter in health and disease. Thyroid. 2001;11(5):415-25.
45. Gnidehou S, Caillou B, Talbot M, Ohayon R, Kaniewski J, Noël-Hudson MS, et al. Iodotyrosine dehalogenase1 (DEHAL1) is a transmembrane protein involved in the recycling of iodide close to the thyroglobulin iodination site. FASEB J. 2004;18(13):15746.
46. Dunn JT. Thyroglobulin, hormone synthesis and thyroid disease. Eur J Endocrinol. 1995;132:603-4.
47. Dumont JE. The action of thyrotropin on thyroid metabolism. Vitam Horm. 1971;29:287-412.
48. Dumont JE, Boeynaems JM, Decoster C, Erneux C, Lamy F, Lecocq R, et al. Biochemical mechanisms in the control of thyroid function and growth. Adv Cyclic Nucleotide Res. 1978;9:723-34.
49. Deery WJ, Heath JP. Phagocytosis induced by thyrotropin in cultured thyroid cells is associated with myosin light chain dephosphorylation and stress fiber disruption. J Cell Biol. 1993;122(1):21-37.
50. Herzog V. Pathways of endocytosis in thyroid follicle cells. Int Rev Cytol. 1984;91:107-39.
51. van den Hove MF, Couvreur M, de Visscher M, Salvatore G. A new mechanism for the reabsorption of thyroid iodoproteins: selective fluid pinocytosis. Eur J Biochem. 1982;122(2):415-22.
52. Davies TF, Ando T, Lin RY, Tomer Y, Latif R. Thyrotropin receptorassociated diseases: from adenomata to Graves disease. J Clin Invest. 2005;115(8):197283.
53. Lazar MA. Thyroid hormone action: a binding contract. J Clin Invest. 2003;112:4979.
54. Bartalena L1, Robbins J. Thyroid hormone transport proteins. Clin Lab Med. 1993;13(3):583-98.
55. Visser TJ. Pathways of thyroid hormone metabolism. Acta Med Austriaca. 1996;23(1-2):10-6.
56. Köhrle J. Thyroid hormone deiodinases—a selenoenzyme family acting as gate keepers to thyroid hormone action. Acta Med Austriaca. 1996;23(1-2):17-30.

JAYPEE BROTHERS

or detailed information on endocrinology books, visit our website **www.jaypeebrothers.com**, for detailed information on endocrin

Principles and Practices of

THYROID Gland Disorders

Key Features

- A comprehensive resource, providing up-to-date information on various thyroid problems and their management
- Written by experts with an enormous knowledge- and clinical experience
- The book begins with chapters on physiology of thyroid axis, manifestations of thyroid hormone deficiency, and laboratory evaluation of various thyroid problems
- Subsequent chapters discuss benign and malignant thyroid disorders and their medical and surgical management
- Further chapters deal with toxic multinodular goiter and toxic adenoma followed by chapter on non-toxic goiter
- Special situations like neonatal and juvenile thyrotoxicosis, hyperthyroidism and hypothyroidism in pregnancy have been discussed in detail
- The book also features in-depth discussion on topics like Graves disease, Hashimoto disease, radioiodine ablation in Graves disease, pediatric Graves disease, subacute thyroiditis, and sick euthyroid syndrome
- In summary a must-read book with information that is useful in every day clinical practice for endocrinologists, physicians, postgraduate students, and nurse practitioners.

Subhash K Wangnoo MD DM FRCP FACE
Senior Consultant, Endocrinologist and Diabetologist
Apollo Centre for Obesity, Diabetes and Endocrinology (ACODE)
Indraprastha Apollo Hospital
New Delhi, India



Jamal Ahmad MD DM FCCP PhD FRCP DSc
Professor
Rajiv Gandhi Centre for Diabetes and Endocrinology
Jawaharlal Nehru Medical College Hospital
Aligarh Muslim University
Aligarh, Uttar Pradesh, India



Mohammad A Siddiqui MD MRCP
Consultant Endocrinologist
Apollo Centre for Obesity, Diabetes and Endocrinology (ACODE)
Indraprastha Apollo Hospital
New Delhi, India



Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
ENDOCRINOLOGY

ISBN 978-93-86056-25-2