THYROID GLAND

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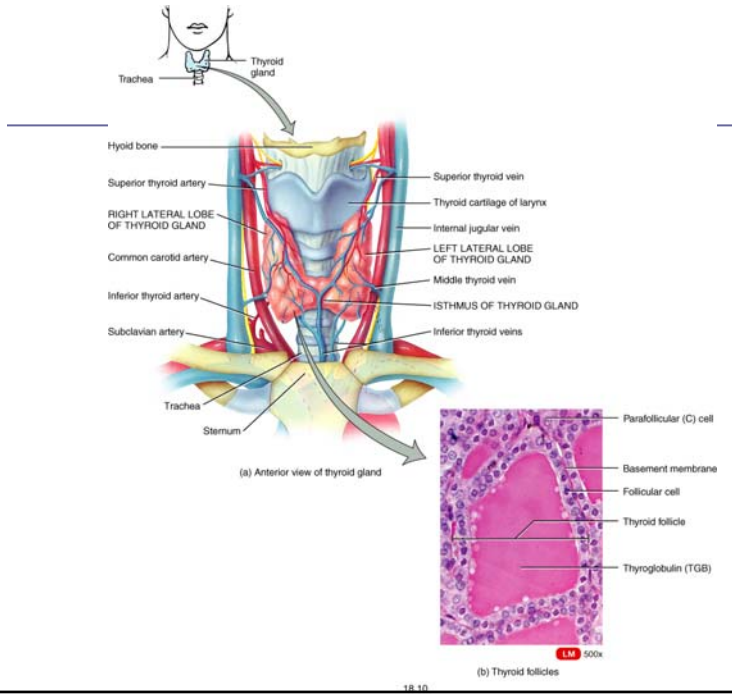


Thyroid Gland

- Richly vascular structure located in the anterior and lateral aspect of the trachea
- Composed of follicles filled with a clear, proteinaceous colloid which is the major constituent of the thyroid mass
- The follicle wall is lined by a single layer of packed cuboidal cell whose apical portions have microvilli extending into the colloid
- The cytoplasm of the follicular cells are rich in ER with microsomes, and dense granules called lysosomes
- Also contains parafollicular or C cells concerned with a hypocalcemic substance (calcitonin)

Steps for thyroid hormone synthesis:

- Active transport of iodide into the gland (Iodide uptake or trapping)
  - Iodide may enter the TG through
    - Diffusion
    - De-iodination of iodinated organic compounds of thyroglobulin
    - Iodide concentrating transport mechanism
  - The iodide pump found in the epithelial cell ensures adequate iodide for hormone formation

- Oxidation of iodide
  - The transported iodide is rapidly oxidized into an active form, in a reaction mediated by peroxidase
- Organic binding of Iodine
  - The oxidized form of iodide is transported to the apical portion of the cell to combine with the tyrosyl residues of thyroglobulin at the cell-colloid surface
  - The hormonally inactive mono-iodotyrosines and di-iodotyrosines are formed

IO + Tyrosine-TG ⟶ MIT-Tg

MIT-Tg + IO ⟶ DIT-Tg

- Coupling of iodotyrosines from the active hormones tri-iodothyronine (T3) and tetra-iodothyronine (T4)

DIT + MIT ⟶ T3 loss of alanine side-chain

2DIT ⟶ T4 loss of alanine side-chain

Storage and Release of Hormones

- The TG is also endowed with a large reservoir capacity to protect the individual against depletion of hormones should synthesis cease
- The gland contains about 8000 g of iodine, mostly stored in the form of thyroglobulin
- Stimulation of TG by thyrotropin (TSH) results in the engulfment of colloid materials by the pseudopodia in the apices of follicular cells

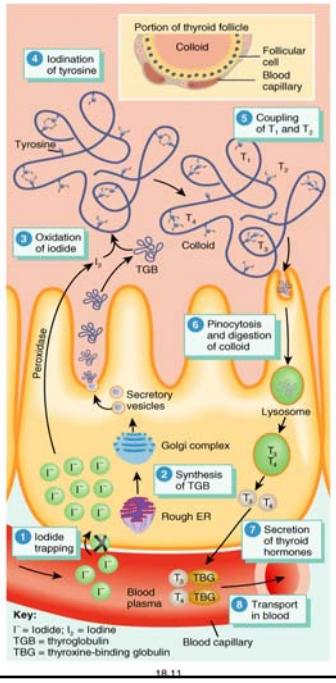
- Colloid droplets contain hormones bound to thyroglobulin
- Dense bodies (phagolysosomes) from the base of cell containing proteases move towards the apex and fuse with the droplets which results in hydrolysis of thyroglobulin → secretion of T3 and T4
- Microsomal iodotyrosine dehalogenase acts upon the MIT and DIT to liberate iodide from tyrosine
- Released iodide is either recycled for synthesis of new hormones or is lost in the urine
- The most recently synthesized are first to be secreted

Transport

- About 99% of the secreted hormones in the blood are bound to plasma proteins
  - Thyroxine Binding Globulin (TBG): this binds 75% of thyroxine and may also form weak bonds with about 60% of T3
  - Thyroxine-binding Pre-albumin (TBPA) – binds T4 more weakly and does not bind T3
  - Albumin – binds both thyroid hormones but with low affinity

- Protein-Bound-Iodine (PBI) – the circulating levels of thyroid hormones, expressed in iodide
  - Normal value in the plasma = 4-8 ug/100 ml
  - May be increased by potassium iodide ingestion and halogenated radiologic dyes
  - Estrogen and pregnancy elevate TBG, and thus increase PBI
  - Androgens decrease TBG without changing the concentration of free T3 and T4

- An equilibrium exists between the protein-bound and the free hormones, but binding is heavily favored so that only 1% of T3 and 0.1% of T4 are free
- It is the free hormones which is able to penetrate the target cell to initiate its effects
- T3 can diffuse out of the vascular compartment more rapidly
- T3 may be as much as 2 or 3x more biologically effective



Metabolism

- Half-life of thyroxine = 6-7 days
- Half-life of T3 = 1 day
- Liver – the principal site of thyroid hormone degradation
  - Hormones are conjugated with glucoronic acid or sulfuric acid and are excreted in the bile into the intestines
- Intestinal bacteria may disrupt the ester bridges so that some of the hormone is reabsorbed, the rest excreted in the stool

- Conjugation may also occur in the kidneys and the matabolites excreted in the urine
- Another route of hormone degradation is through deiodination
  - 33% of the daily production of T4 is converted to T3 through peripheral de-iodination

Factors which affect TH economy

- TSH
- Iodine
- Anti-thyroid drugs

- TSH – manufactured in the AP, and its effects on the thyroid gland include growth, hypervascularity and increased synthesis of hormones
  - Major regulator of thyroid function
  - Secretion is under the influence of TRH

Iodine

- Thyroid autoregulation
  - The thyroid has the intrinsic ability to modify its responsiveness to TSH depending on the availability of iodine
    - Iodine is low: thyroid becomes more responsive to TSH
    - In iodine deficiency, goiter may develop even if TSH is normal

Anti-thyroid drugs

- Reduce the level of circulating hormones by inhibiting the reactions which lead to their synthesis (goitrogens)
- The more common are:
  - Those that inhibit iodide transport: these are usually monovalent anions which compete with iodide (thiocyanate, perchlorate);highly toxic
  - Those that inhibit organic binding and coupling: thionamides (propylthiouracil, methimazole)

Other factors which affect thyroid economy

- Catecholamines – have a direct stimulant effect on thyroid hormone secretion
- Sex hormones
  - Estrogens probably inhibit endogenous TRH release so that serum levels of TSH are also depressed
  - Estrogen also brings about increase in TBG, thus elevate serum levels of T3 and T4
- Corticoids
  - Pharmacologic doses of ACTH and cortisols may decrease iodide uptake, clearance and turnover rate by suppressing TSH levels
  - Corticoids inhibit TRH secretion and release
  - Cortisone may temporarily increase clearance of iodide in the kidney

Peripheral effects of thyroid hormone

- Growth and maturation
  - TH are necessary for normal growth and maturation: congenital deficiency leads to dwarfness
  - TH also promote skeletal maturation
  - Hypothyroidism: the long bones remain infantile and closure of the epiphyses is delayed
  - Hyperthyroidism: there is premature closure of the epiphyses which may stunt growth
    - Bone demineralization and increased urinary loss of calcium and phosphate

Nervous system

- TH are required for normal development of the CNS; critical from time of birth till the first year of life
  - Deficiency leads to mental retardation
- TH are important in the development of the cerebrum, in nerve myelination, maturation of nerve cells, development of cell processes, and in influencing the size and vascularity of the brain
  - Learning performance is highly affected

- Behavioural Effect:
  - The effect of TH on the CNS are more serious the earlier they develop in an individual
  - Cretinous baby: somnolence, mental retardation, and sluggishness of physical activities
    - If untreated: irreversible
    - Deficiency both developmental and functional

Cardiovascular system

- TH increase metabolism of tissues, causes more rapid utilization of oxygen than normal and greater than normal quantities of metabolic end products to be released from the tissues → VD → increased BF
  - The rate of BF in the skin increases because of increased need of heat utilization
- The CO becomes proportional to the metabolic rate, increased CO as a result of an increase in both SV and HR
- Blood volume and SBP is proportional, the diastolic pressure normal or even lower secondary to local dilatation of vessels → wide PP

- Absence of TH: very low voltage deflections in ECG
- The circulation time is shortened in hyper and prolonged in hypothyroidism
- Arteriosclerosis develops faster in hypothyroids
  - Lack of TH increases the quantity of blood cholesterol because of diminished liver excretion of cholesterol in the bile

Gastrointestinal Functions

- Hypothyroids
  - Constipation: decreased activity of intestinal segments
  - Decreased intake of food
- Hyperthyroids
  - Increased food intake, an attempted adjustment to an increased caloric requirement
  - Diarrhea, increased rate of secretion of digestive juices and motility of the GIT
  - Increased absorptive capacity of the GIT
  - Hepatic dysfunction when severe
    - Hypoproteinemia, increased serum transaminase and alk phosphatase, mild BSP retention

Skeletal muscles

- Hyperthyroid:
  - Weakness – TH causes protein catabolism
  - Tremors – increased reactivity of neuronal synapses in the areas of the cord that control muscle tone
    - Relentless bombardment of the muscles by nerve impulses
- Hypothyroid:
  - Muscle sluggish and relax slowly after contraction

Effect of thyroxine on specific dietary substances

- Carbohydrates
  - Increases the rate of glucose and galactose absorption in the GIT
  - Increases the rate of glucose utilization by adipose tissue and muscle potentiates the effect of insulin in this respect
  - Large doses of T4 enhance gluconeogenesis by increasing the availability of precursors, such as lactate and glycerol
  - Increases insulin secretion

Fats

- Hypothyroid
  - Lipemia and hypercholesterolemia (excessive deposition of fats in the liver)
  - Hepatic cholesterol catabolism is markedly increased despite increase in cholesterol synthesis
  - Increased plasma concentration of cholesterol, phospholipids, and triglycerides
- Hyperthyroid
  - Decreased serum cholesterol
  - Decreased cholesterol, phospholipids, and triglycerides in the plasma

Proteins

- Thyroxine increases the rate of both protein anabolism because of increased enzymatic activities and quantity
- In smaller amounts it is a growth hormone (protein anabolism), in excess amounts it is catabolic
- When excess thyroxine has increased the catabolism of both CHO and fats, it turns to proteins and this substance becomes utilized in greater quantities

Vitamins

- Hyperthyroid – there is an increased requirement for water-soluble vitamin such as thiamine, riboflavin, B-12, and vitamin C and a reduction in tissue concentration
  - Vitamins are essential parts of some enzymes
  - TH increases need for vitamins → relative vitamin deficiency
- Hypothyroidism – the serum carotene concentration is increased and may give the skin a yellow tint and clinical manifestations of Vitamin A deficiency

Effect on water and electrolytes

- Hypothyroids: there is accumulation of water and electrolytes in the subcutaneous spaces
  - Administration of T4 and T3 results in loss of fluid from these spaces → diuresis

Clinical Correlation

Hypothyroidism: may be the end result of a number of disease of the TG, or it may be secondary pituitary failure (pituitary myxedema)

- Pituitary myxedema – the TG responds to the administration of TSH
- In complete absence of TH:
  - BMR falls to 40
  - Hair is coarse and sparse
  - Skin dry and yellow
  - Cold is poorly tolerated
  - Voice is husky and slow
  - Slow mentation and poor memory; severe mental symptoms in some (myxedema madness)

hypothyroidism

- Primary: ↑TSH ↓ T3T4
- Secondary: ↓TSH ↓T3T4
  - TG responds to administration of TSH
  - Pituitary myxedema
    - Cause: thyroiditis
    - Endemic colloid goiter
    - Idiopathic colloid goiter
    - Destruction of TG by irradiation
    - Surgical removal of the gland

Adult hypothyroidism

- May be primary (destroyed gland) or secondary hypothyroidism (no TSH)
- Syndrome is called myxedema
- Most common is primary type due to destruction or less of normally functioning thyroid tissue mass
  - 80% have thyroid antibodies due to an immune thyroiditis
  - 7x more common in females than in males
- Secondary is due to pituitary TSH insufficiency
  - A destructive lesion of the pituitary is usually present

Juvenile Hypothyroidism

- Probably the same etiology as in older patients
- Thyroiditis is a major etiologic factor
- Child may present as a dwarf with increased trunk limb ratio
- Because of decreased activity, excessive weight is common
- Patient looks younger than his chronological age

Cretinism

- A state of hypothyroidism from birth
- Victims are called cretins: dwarfed, large protruding tongues and pot bellies, increased trunk-limb ratio, large head, broad flat nose with widely set eyes, sparse hair, rough skin, malformed teeth, waddling gait and severe mental deficiency
- Most common cause: maternal iodine deficiency
- Preventable if treatment is started soon after birth
- Early symptoms: prolongation of physiologic neonatal jaundice, early feeding problem, failure to thrive, somnolence, hypothermia, constipation, hoarse cry

Hyperthyroidism

- May result from an excess of either or both T3 or T4
- Thyrotoxicosis
- Characterized by:
  - nervousness
  - Weight loss inspite of hyperphagia
  - Heat intolerance
  - Increased PP (high systolic but low diastolic)
  - Fine tremor of the outstretched fingers
  - Warm, soft skin
  - Metabolic rate of +10 to +100

- May be caused by a variety of thyroid disorders:
  - Benign and malignant neoplasms
  - Grave's disease (most common)
  - Exopthalmic goiter – the gland is diffusely enlarged and hyperplastic
    - There is protrusion of the eyeballs – exopthalmos
- Places a heavy load on the CVS, however thyrotoxic heart disease is curable

- Treatment:
  - Carbimazole and methimazole – inhibit production of TH; they have immunosuppressive actions
  - Monovalent anions and ouabain – inhibit the iodide trap
  - Thiocarbamide – inhibit iodination of tyrosyl residues
  - Sulfonamides – inhibit thyroid peroxidase (oxidizes iodine to iodide)