Introduction to the thyroid: anatomy, histology, hierarchy, feed-back regulation, effect of T3-T4 on Na/K ATPase and uncoupling proteins

Biosynthesis of T3-T4: thyroglobulin, iodide pump, iodination and coupling reactions, lysosomes

T3-T4 effects: metabolism, T°C/F control, growth / development, reproduction, tertiary hypometabolism (starvation, hibernation)

mechanism of action: T4 to T3, T3 receptor, nuclear / mitochondrial sites, increase enzymes, Na/K ATPase, uncoupling proteins

Pathology: goitrogens, hypo and hyperthyroidism, thyroid hormone resistance

Introduction

Thyroid & its “story lines”

For each hormone, the student should know
1. Its cell of origin
2. Its chemical nature, including
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excess secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion
   a. How those signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action
Introduction

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

The human thyroid is located at the base of the neck wrapped around the traquea.

The thyroid is controlled by feedback systems that include the hypothalamus and the AP gland.
Introduction

• Thyroid gland
• Biosynthesis
• Effects
• Mechanism of action
• Pathologies

Introduction

TSH secretion is controlled by TRH, whose neuronal terminals are located in the ME.

Metabolism of T4

The half-life of the thyroid hormones T3 and T4 is different.

The half-life of the thyroid hormones T3 and T4 is different.
Introduction

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

TSH secretion is controlled by TRH, whose cell bodies are located in the PVN

TSH secretion is controlled mainly by a negative feedback of T3 - T4

T3 implanted unilateral in left PVN
Introduction

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

TSH secretion is controlled mainly by a negative feedback of T3 - T4

TRH stimulates the secretion of TSH and of Prl from the AP
Introduction

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

The hypothalamic - pituitary - thyroid axis is controlled by negative feedbacks

Scanning electron micrographs of the luminal microvilli of dog thyroid follicular cells. A. TSH secretion suppressed by feeding thyroid hormone; magnification 36,000x. B. At 1 hr after TSH; magnification 16,500x.
Thyroid hormones (T3 - T4) derived from the amino-acid tyrosine

Biosynthesis of T3 - T4

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid hormones and related compounds

Thyroid hormones (T3 - T4) derived from the amino-acid tyrosine

Thyroid hormones (T3 - T4) derived from the amino-acid tyrosine

Thyroid hormones (T3 - T4) derived from the amino-acid tyrosine
Biosynthesis of T3 - T4

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid hormones (T3 - T4) derived from the amino-acid tyrosine
Biosynthesis of T3 - T4

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid hormone biosynthesis and secretion. Iodide (I–) is transported into the thyroid follicular cell by the sodium/iodide symporter (NIS) in the basal membrane and diffuses passively into the lumen through the iodide channel called pendrin (P). Thyroglobulin (TG) is synthesized by microsomes on the rough endoplasmic reticulum (ER), processed in the cisternae of the ER and the Golgi where it is packaged into secretory granules and released into the follicular lumen. In the presence of hydrogen peroxide (H2O2) produced in the luminal membrane by thyroid oxidase (TO), the thyroid peroxidase (TPO) oxidizes iodide, which reacts with tyrosine residues in TG in the follicular lumen to produce monoiodotyrosyl (MIT) and diiodotyrosyl (DIT) within the peptide chain. The TPO reaction also catalyzes the coupling of iodotyrosines to form thyroxine (T4) and some triiodothyronine (T3, not shown) within TG. Secretion of T4 begins with phagocytosis of TG, fusion of TG-laden endosomes with lysosomes and proteolytic digestion to peptide fragments (PF), MIT, DIT, and T4. T4 is released from the cell at the basal membrane. MIT and DIT are deiodinated by iodotyrosine deiodinase (ITDI) and recycled.

Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Models of the effects of thyroid hormone receptor (TR) on gene transcription. A. In the absence of T3 the TR in heterodimeric union with the retinoic acid receptor (RXR) binds to the thyroid hormone response element (TRE) in DNA. The unliganded TR also binds to a corepressor, in this case the silencing mediator retinoic acid and TR (SMRT), which recruits factors that remodel chromatin such as histone deacetylase (HDAC), histone demethylase (HDM), and histone methyl transferase (HMT) and other factors that interfere with attachment of the RNA polymerase in the general transcription complex to the TATA box in the promoter of a thyroid hormone regulated gene. B. Upon binding T3, the TR changes its conformation, sheds the corepressor complex and replaces it with a coactivator, in this case steroid receptor coactivator-1 (SRC-1), which recruits such chromatin remodeling factors as histone acetylase (HA) and other coactivators that make the gene accessible to the polymerase complex. Effect of treatment of normal young men with thyroid hormones for 3 to 4 weeks on the response of the pituitary to thyrotropin-releasing hormone (TRH) as measured by changes in plasma concentrations of thyroid-stimulating hormone (TSH). The six subjects received 25 mg of TRH at time 0 as indicated by the green arrow. Values are expressed as means ± SEM. (From Snyder, P.J. and Utiger, R.D. (1972) Inhibition of thyrotropin response to thyrotropin releasing hormone by small quantities of thyroid hormones.)
Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

**Physiological effects of thyroid**

**TABLE 13.1** Some physiological roles and actions of thyroid hormones in mammals

- Feedback inhibition of hypothalamic TRH and pituitary TSH secretion
- Permissive to the action of many other hormones
- Enhances lipolytic response of adipose tissue to hormones
- Required for the growth-promoting activity of GH
- Increases activity of the sympathetic nervous system
- Regulates basal metabolic rate
- Increases mitochondrial oxidative phosphorylation
- Required for hepatic conversion of carotene to vitamin A
- Required for bone growth and maturation
- Required for nervous system differentiation in early development
- Required for pituitary products and growth hormone synthesis
- Increases the rate of intestinal glucose absorption
- Increases human red blood cell Ca²⁺-ATPase activity

Induces enzyme synthesis:
- Na⁺/K⁺-ATPase (a protein component or activator of the sodium pump)
- Carcollac phosphatase (a phosphomonoesterase)
- Lactate dehydrogenase (lactate synthase system present)
- Hepatic pyruvic carboxylase (converts pyruvate to oxaloacetate)
- Catabolic protein kinase
- Mitochondrial α-glycerophosphoric dehydrogenase
- Malic dehydrogenase (converts malic acid to oxaloacetate)
- Glycogenolysis (activates intracellular glycogen phosphatase)

Induction of cellular proteins (rather than enzymes):
- Proteins, growth hormone, lung surfactant, heat shock factor (HSP)

T3 - T4 have multiple physiological effects

**T3 - T4 increases oxygen consumption and body weight, two metabolic indices**
Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

Effects of thyroxine on oxygen consumption by various tissues of thyroidectomized rats. Note in A the abscissa is in units of hours and in B the units are days.

T3 - T4 increases oxygen consumption and body weight, two metabolic indices

Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

Effects of thyroid therapy on growth and development of a child with no functional thyroid tissue. Daily treatment with thyroid hormone began at 4.5 years of age (green arrow). Bone age rapidly returned toward normal, and the rate of growth (height age) paralleled the normal curve. Mental development, however, remained infantile.

T3 - T4 increases bone age, height age and mental age in a child with no thyroid tissue
Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
  - Effects
  - Mechanism of action
  - Pathologies

Effects of glucose and T3 on the induction of malic enzyme (ME) in isolated hepatocyte cultures. Note that the amount of enzyme present in tissues was increased by growing cells in higher and higher concentrations of glucose. Blue bars show effects of glucose in the presence of a low (10^-10M) concentration of T3. Red bars indicate that the effects of glucose were exaggerated when cells were grown in a high concentration of T3 (10^-8M).

T3 - T4 increases carbohydrate metabolism in liver

Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
  - Effects
  - Mechanism of action
  - Pathologies

Hypothalamic or tertiary hypometabolic states: fasting and hibernation

A change in the set-point alters the level at which the whole system operates

- variable under control
- set point or CS
- feedback detector
- comparator
- common language
- error signal
- amplifier

Long negative feedback loop

Thyroid hormones

A tertiary hypometabolic state is useful to understand various thyroid functions

e.g. fasting, hibernation

Page 12
Physiological effects of thyroid

- Thyroid gland
  - PVN, link to ME and ANS

- Biosynthesis
  - POA, t°C/F Integration site

- Effects
  - ANS, neuronal link to thyroid
  - Thyroid control of Na/K ATPase and uncoupling proteins

- Mechanism of action
- Pathologies
  - e.g. fasting, hibernation
  - A tertiary hypometabolic state is useful to understand various thyroid functions

Physiological effects of thyroid

- Thyroid gland
  - T3-T4 (low)
  - TSH (low / normal)
  - TRH mRNA (low)
  - UC proteins (low)
  - TRH-induced TSH release (high)
  - TRH release (low)
  - SS inhibits TSH release
  - Insulin (low)
  - Glucagon (high)
  - Cortisol (high)
  - Epinephrine (high)
  - LH/FSH (low)
  - Leptin (low)
  - Cas, NPY, aMSH, arcuate thermogenesis (low)
  - energy expenditure (low)

- Effects
- Mechanism of action
- Pathologies
  - e.g. fasting, hibernation
  - Thyroid hormones control the expression of the Na/K ATPase and uncoupling proteins
Physiological effects of thyroid

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid hormones control the expression of the Na/K ATPase and uncoupling proteins. e.g. fasting, hibernation

TRH / TSH mechanism of action

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

TRH and TSH mechanism of action are associated with a GCPR.
**TRH mechanism of action**

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

TRH mechanism of action is associated with a GCPR linked to PLC

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**TSH mechanism of action**

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

TSH mechanism of action is associated with a GCPR linked to AC
TSH mechanism of action

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

TSH hormone signal can be increased by rising cAMP or by decreasing phosphodiesterase.

TSH mechanism of action is associated with a GCPR linked to AC.
T3-T4 mechanism of action

- Thyroid gland
- Biosynthesis
- Effects
  - Mechanism of action
- Pathologies

T3 - T4 mechanism of action is associated with intracellular receptors (genomic effect)
T3-T4 mechanism of action

- **Thyroid gland**
- **Biosynthesis**
- **Effects**
  - **Mechanism of action**
  - **Pathologies**

T3-T4 mechanism of action is associated with intracellular receptors (genomic effect)

T3-T4 have permissive effects

- **Thyroid gland**
- **Biosynthesis**
- **Effects**
  - **Mechanism of action**
  - **Pathologies**

T3 - T4 mechanism of action is associated with intracellular receptors (genomic effect)
Some endocrine pathologies can be visualized in a tropic / target diagram or in a photography.
Diseases of the thyroid axis

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid gland - Thyroid gland

Biosynthesis - Biosynthesis

Effects - Effects

Mechanism of action - Mechanism of action

Pathologies - Pathologies

Thyroid gland - Thyroid gland

Biosynthesis - Biosynthesis

Effects - Effects

Mechanism of action - Mechanism of action

Pathologies - Pathologies

Characteristic symptomatology of adult hyper and hypothyroidism

Hyperthyroidism, nervousness, irritability, emotional instability, pounding heart, fatigue, heat intolerance, weight loss despite normal or increased food intake, tachycardia, atrial arrhythmia, even congestive heart failure.

Adult hypothyroidism, slow onset, tiredness, lethargy, constipation, slow mental and motor function, cold intolerance, menstrual abnormalities, infertility, sc accumulation of mucopoly-sacharides (mixedema).

Twin sisters, one has hypo and the other hyperthyroidism.

Characteristic symptomatology of adult hyper and hypothyroidism.

Diseases of the thyroid axis

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid gland - Thyroid gland

Biosynthesis - Biosynthesis

Effects - Effects

Mechanism of action - Mechanism of action

Pathologies - Pathologies

Hypothyroidism in infancy leads to cretinism. Severe T3/T4 deficiency cause mental and growth retardation.

Infancy hypothyroidism leads to cretinism if it is not treated.

Diseases of the thyroid axis

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Thyroid gland - Thyroid gland

Biosynthesis - Biosynthesis

Effects - Effects

Mechanism of action - Mechanism of action

Pathologies - Pathologies

Hypothyroidism in infancy leads to cretinism. Severe T3/T4 deficiency cause mental and growth retardation.

Infancy hypothyroidism leads to cretinism if it is not treated.
Diseases of the thyroid axis

- Thyroid gland
- Biosynthesis
- Effects
- Mechanism of action
- Pathologies

Characteristic symptomatology of hyper and hypothyroidism