Synthesis, secretion and the effects of thyroid hormones

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Thyroid Gland

- Metabolically active hormones secreted by the thyroid gland
  - 93% thyroxine
  - 7% triiodothyronine

  } Difference in rapidity and intensity of action

- Triiodothyronine is about four times as potent as thyroxine, but shorter half life
  - About one half of the thyroxine is slowly deiodinated to form additional triiodothyronine
  - The hormone finally delivered to and used by the tissues is mainly triiodothyronine

Thyroid Gland

- Closed follicles(100 to 300 micrometers in diameter) filled with a secretory substance called colloid (glucoprotein thyroglobulin) and lined with cuboidal epithelial cells that secrete into the interior of the follicles

- High blood flow - five times the weight of the gland each minute

- C cells
  - secrete calcitonin → regulation of plasma calcium ion concentration

Iodine

- 1 mg/week of iodine
- Absorbed from the gastrointestinal tract into the blood
- One fifth are selectively taken by the cells of the thyroid gland
- Rapidly excreted by the kidneys

Formation of Thyroid Hormones

1.A. transport of iodides from the blood into the thyroid glandular cells and follicles (iodide trapping)

- sodium-iodide symporter
  - One iodide ion + two sodium ions
  - Secondary active transport
  - Concentration up to 30x compared to blood

1.B. Iodide is transported into the follicle by pendrin

- chloride-iodide ion counter-transporter

2. Epithelial cells synthesize and secrete thyroglobulin and enzymes into the follicle

Formation of Thyroid Hormones

- Thyroglobulin
  - Contains about 70 tyrosine amino acids
  - Precursor of thyroid hormones

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1. Oxidation of the Iodide Ion
2. Iodination of tyrosine and formation of the thyroid hormones—"organification" of thyroglobulin
   - thyroid peroxidase enzyme
3. Tyrosine iodized to monoiodotyrosine and diiodotyrosine
4. Coupled with one another
5. The major hormonal product is thyroxine (T4)

the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months

Release of Thyroid Hormones

1. Pinocytic vesicles are formed by apical surface of thyroid cells

2. Lysosomes form digestive vesicles

3. Multiple proteases among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine

4. T3 and T4 diffuse through the base of the thyroid cell into the surrounding capillaries

Release of thyroglobulin:

some thyroglobulin in the colloid enters the thyroid cell by endocytosis after binding to megalin and carried across the cell by transcytosis to the basolateral membrane and is released into the capillary blood

Transport of Thyroid Hormones to Tissues

- 99% of the thyroxine and triiodothyronine combines immediately with plasma proteins upon entering to the circulation
  - thyroxine-binding globulin
  - thyroxine-binding prealbumin
  - Albumin

- thyroid hormones are released to the tissue cells slowly (especially thyroxine)

- Upon entering the tissue cells, both bind with intracellular proteins
  - Stored in the target cells themselves, and used slowly over a period of days or weeks

Activity of Thyroid Hormones

- Thyroid hormones have slow onset and long duration of action

- Injection of a large dose
  - no effect for 2-3 days (long-latent period)
  - peak around 10-12th day
  - decreasing for 15 days

- Long latent period
  - Binding with proteins both in plasma and in the tissue cells
  - Signalling in the cells

Physiological Effects of the Thyroid Hormones

- Increase transcription of large numbers of genes
  - Activate nuclear transcription of large numbers of genes → increase in functional activity
  - Formation of a heterodimer with Retinoid X receptor (RXR) of thyroid hormone receptor at thyroid hormone response elements (TRE)
  - Binding with thyroid hormone and activation
    - mRNA, protein synthesis

Physiological Effects of the Thyroid Hormones

- Nongenomic cellular effects
  - Heart, pituitary, adipose tissue, etc.
  - Site of action plasma membrane, cytoplasm, some organelles (e.g., mitochondria)

  - Regulation of ion channels
  - Oxidative phosphorylation
  - Activation of intracellular secondary messengers (e.g., cAMP, protein kinases)

Physiological Effects of the Thyroid Hormones

- Increase in metabolic activity rate up to 60-100%
- Rate of utilization of foods is accelerated
- Increase of both protein synthesis and catabolism
- Growth rate is accelerated
- Mental processes are excited
- Activities of endocrine glands are increased

Physiological Effects of the Thyroid Hormones

- Celular metabolic activity
  - Increase in size and number of mitochondria → ATP production →energy → increased activity
  - Increase active transport of ions through cell membranes
    - activity of Na/K ATPase → heat production
    - Sodium leak channels

- Growth
  - Skeletal growth (epiphyses closing)
  - Brain development during fetal life and for the first few years

- Stimulation of carbonhydrate metabolism
- Stimulation of fat metabolism
- Decreases cholesterol, phospholipids, and triglycerides in the plasma, increases the free fatty acids

Physiological Effects of the Thyroid Hormones

- Requirement for vitamins (enzyme cofactor)
- Increased blood flow and cardiac output
- Increased heart rate
- Increased heart strength
- Normal arterial pressure
- Increased respiration
- Increased gatrointestinal motility
- Increased basal metabolic rate
- Decreased body weight

Physiological Effects of the Thyroid Hormones

- Central nervous system
  - Excitatory effects
  - increase rapidity of cerebration
  - Hyperthyroidism → irritability, anxiety, paranoia

- Muscle
  - Slight increase → increase in reaction
  - Excessive increase → weakening due to high catabolism
  - Decrease → sluggish and slow relaxation after contraction
  - Fine muscle tremor

Physiological Effects of the Thyroid Hormones

- Sleep
  - Hyperthyroidism : difficulty to sleep, constant tiredness
  - Hypothyroidism: extreme somnolence

- Increases rates of secretion of other ecdocrine glands

- Sexual function
  - Hyporthyroidism
    - Male: loss of libido
    - Female: menorrhagia, polymenorrhea, irregular periods or amenorrhea, decreased libido
  - Hyperthyroidism
    - Female: oligomenorrhea
    - Male: excess thyroid causes impotence

  - Mixed effects of mensturation