Department of medical physiology
9th week

Semester: summer
Study program: Dental medicine
Lecture: RNDr. Soňa Grešová, PhD.
The thyroid metabolic hormones, Calcitonin, Parathyroid hormone
The thyroid gland

- is one of the largest of the endocrine glands
- secretes two major hormones, *thyroxine* and *triiodothyronine*, commonly called T4 and T3
  - Increase the metabolic rate of the body
- Thyroid secretion is controlled primarily by *thyroid-stimulating hormone (TSH)*
- secretes *calcitonin*, an important hormone for calcium metabolism

![Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.](image)
Synthesis and secretion of the thyroid metabolic hormones

- 93 per cent of the metabolically active hormones secreted by the thyroid gland is *thyroxine*, and 7 per cent *triiodothyronine*

- Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine

- is composed of large numbers of closed *follicles* (100 to 300 micrometers in diameter) filled with a secretory substance called *colloid* and lined with *cuboidal epithelial cells*
  - glycoprotein *thyroglobulin*, (contains the thyroid hormones within its molecule)

Figure 76-1
Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

Synthesis and secretion of the thyroid metabolic hormones

- Prevention of iodine deficiency, (common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride)
- Iodides ingested orally are absorbed from the gastrointestinal tract into the blood
- from the circulating blood cells of the thyroid gland iodides are used for synthesis of the thyroid hormones
- the iodides are rapidly excreted by the kidneys

Figure 76-1
Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

Thyroglobulin, and chemistry of thyroxine and triiodothyronine formation

• Iodide pump (Iodide Trapping)
• Formation and secretion of thyroglobulin by the thyroid cells
• Thyroid peroxidase
  – Oxidation of the iodide ion
  – Iodination of tyrosine and formation of the Thyroid hormones—“Organification” of thyroglobulin
  – Coupling of iodine
Release of thyroxine and triiodothyronine from the thyroid gland

Figure 77-2. Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; ER, endoplasmic reticulum; I-, iodide ion; I₂, iodine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; RT₃, reverse triiodothyronine; T₃, triiodothyronine; T₄, thyroxine; T₉, thyroglobulin.

Transport of thyroxine and triiodothyronine to tissues

• Thyroxine and triiodothyronine are bound to plasma proteins
  – thyroxine-binding globulin
  – thyroxine-binding prealbumin and albumin

• Thyroxine and triiodothyronine are released slowly to tissue cells

• Thyroid hormones have slow onset and long duration of action
Physiologic functions of the thyroid hormones

• Thyroid hormones increase the transcription of large numbers of genes
  – most of the thyroxine secreted by the thyroid is converted to triiodothyronine
  – Thyroid hormones activate nuclear receptors (retinoid X receptor = RXR)

• Thyroid hormones increase cellular metabolic activity
  – Thyroid hormones increase the number and activity of mitochondria

• Thyroid hormones increase active transport of ions through cell membranes (Na-K-ATPase)

• Effect of thyroid hormone on growth
  • Structural proteins
Figure 76-5

Thyroid hormone activation of target cells. Thyroxine (T₄) and triiodothyronine (T₃) readily diffuse through the cell membrane. Much of the T₄ is deiodinated to form T₃, which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid hormone response element of the gene. This causes either increases or decreases in transcription of genes that lead to formation of proteins, thus producing the thyroid hormone response of the cell. The actions of thyroid hormone on cells of several different systems are shown. mRNA, messenger ribonucleic acid.
Physiologic functions of the thyroid hormones

- **Effects of thyroid hormone on specific bodily mechanisms**
  - Stimulation of carbohydrate metabolism
  - Stimulation of fat metabolism
  - Increased requirement for vitamins
  - Increased basal metabolic rate
  - Decreased body weight

- **Effect of thyroid hormones on the cardiovascular system**
  - Increased blood flow and cardiac output
  - Increased heart rate
  - Increased heart strength
  - Normal arterial pressure (MAP)
  - Increased respiration
  - Increased gastrointestinal motility
  - Excitatory effects on the central nervous system (nervousness, anxiety, worry, paranoia)
  - Effect on the function of the muscles (incr.: vigor, muscle tremor, excessive hormones - weakness, decreas.: sluggish)
  - Effect on sleep (incr.: tiredness, decreas.: somnolence)
  - Effect on other endocrine glands (pancreas, parathyroid hormone, adrenal glucocorticoids)
  - Effect of thyroid hormone on sexual function (decreas. men – loss of libido, women-menorrhagia)
Regulation of thyroid hormone secretion

- Anterior pituitary secretion of TSH is controlled by a hypothalamic hormone, *thyrotropin-releasing hormone (TRH)*- (phospholipase C-second messenger=Ca^{2+}, DAG)
- TSH - *thyrotropin* (from the anterior pituitary gland) increases thyroid secretion
  - *Increased proteolysis of the thyroglobulin*
  - *Increased activity of the iodide pump*
  - *Increased iodination of tyrosine*
  - *Increased size and increased secretory activity of the thyroid cells*
  - *Increased number of thyroid cells*
- Cyclic adenosine monophosphate mediates the stimulatory effect of TSH (cAMP=second messenger)
Regulation of thyroid hormone secretion

• Effects of cold and other neurogenic stimuli on TRH and TSH secretion (arctic region – increase 15-20% BMR)

• Various emotional reactions can also affect the output of TRH and TSH and therefore indirectly affect the secretion of thyroid hormones

• Feedback effect of thyroid hormone to decrease anterior pituitary secretion of TSH
Diseases of the thyroid

Hyperthyroidism

• Causes of hyperthyroidism (Toxic Goiter, Thyrotoxicosis, Graves’)

• Thyroid adenoma
Diseases of the thyroid
Hyperthyroidism

• **Symptoms:**
  1) a high state of excitability,
  2) Intolerance to heat,
  3) increased sweating,
  4) mild to extreme weight loss (sometimes as much as 100 pounds),
  5) varying degrees of diarrhea
  6) muscle weakness
  7) nervousness or other psychic disorders
  8) Extreme fatigue but inability to sleep, and
  9) tremor of the hands
  10) exophthalmos
Diseases of the thyroid
Hypothyroidism

- Endemic colloid goiter caused by dietary iodide deficiency
- Idiopathic nontoxic colloid goiter
- Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood
Parathyroid hormone, vitamin D, Calcitonin, calcium and phosphate metabolism
Parathyroid Hormone

• Parathyroid hormone provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating intestinal reabsorption, renal excretion, and exchange between the extracellular fluid and bone of these ions
Parathyroid glands

• Chief cells
  – Secretion PTH
    • Ribosomes – preprohormone,
    • Endoplasmic reticulum and Golgi apparatus – granules
    • Hormonal activity is caused by the fragments

• Oxyphil cells

Intestinal absorption and fecal excretion of Calcium

Figure 79-3

Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Effect of parathyroid hormone on calcium and phosphate concentrations

- In the extracellular fluid
  - 1) an effect of PTH to increase calcium and phosphate absorption from the bone
  - 2) a rapid effect of PTH to decrease the excretion of calcium by the kidneys
- Parathyroid hormone increases calcium and phosphate absorption from the bone
  - Rapid phase of calcium and phosphate absorption—osteolysis
  - Slow phase of bone absorption and calcium phosphate release—activation of the osteoclasts

Figure 80-5. Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to form receptor activator for nuclear factor κ-B ligand (RANKL) and to release macrophage-colony stimulating factor (M-CSF). RANKL binds to RANK and M-CSF binds to its receptors on preosteoclast cells, causing them to differentiate into mature osteoclasts. PTH also decreases production of osteoprotegerin (OPG), which inhibits differentiation of preosteoclasts into mature osteoclasts by binding to RANKL and preventing it from interacting with its receptor on preosteoclasts. The mature osteoclasts develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads all through the bone.

Effect of parathyroid hormone on calcium and phosphate concentrations

- Parathyroid hormone decreases calcium excretion and increases phosphate excretion by the kidneys
  - Cyclic adenosine monophosphate mediates the effects of parathyroid hormone

- Control of parathyroid secretion by calcium ion concentration

Figure 80-13. Summary of effects of parathyroid hormone (PTH) on bone, the kidneys, and the intestine in response to decreased extracellular fluid calcium ion concentration. CaSR, calcium-sensing receptor.

Control of Parathyroid secretion by calcium ion concentration

• the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes

• increasing the calcium ion concentration above normal cause decreased activity and reduced size of the parathyroid glands:
  – 1) excess quantities of calcium in the diet,
  – 2) increased vitamin D in the diet,
  – 3) bone absorption caused by factors other than PTH (for example, bone absorption caused by disuse of the bones
Vitamin D

• „Hormonal“ effect:
  – to promote intestinal calcium absorption
  – Promotes phosphate absorption by the interstines
  – Decreases renal calcium and phosphate excretion
  – Bone resorption and bone deposition

Figure 80-7. Activation of vitamin D$_3$ to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

Calcitonin

- Calcitonin, a peptide hormone secreted by the thyroid gland, tends to decrease plasma calcium concentration and, in general, has effects opposite to those of PTH.
- Increased plasma calcium concentration stimulates calcitonin secretion.
- Calcitonin decreases plasma calcium concentration.
- Calcitonin has a weak effect on plasma calcium concentration in the adult human.
Adrenocortical Hormones
Adrenal glands

• The two adrenal glands, each of which weighs about 4 grams, lie at the superior poles of the two kidneys

• is composed of two distinct parts, the adrenal medulla (epinephrine and norepinephrine) and the adrenal cortex (corticosteroids = mineralocorticoids and the glucocorticoids)
Function of the adrenal medullae

• Stimulation of the sympathetic nerves to the adrenal medullae causes large quantities of epinephrine (80%) and norepinephrine (20%) to be released into the circulating blood
  
  *the effects last 5 to 10 times as long*

• Norepinephrine causes constriction of essentially all the blood vessels of the body (increased activity of the heart, inhibition of the gastrointestinal tract, dilation of the pupils of the eyes, and so forth)

• **Epinephrine** and norepinephrine differ in the following respects:
  
  – 1. epinephrine, because of its greater effect in stimulating the beta receptors, has a greater effect on cardiac stimulation than does norepinephrine
  
  – 2. epinephrine causes only weak constriction of the blood vessels in the muscles
  
  – 3. Epinephrine has 5 to 10 times as great a metabolic effect as norepinephrine
Value of the adrenal medullae to the function of the sympathetic nervous system

- the organs are actually stimulated in two ways: directly by the sympathetic nerves and indirectly by the adrenal medullary hormones

- Norepinephrine and epinephrine are still released into the circulating blood and indirectly cause stimulation

- the adrenal medullae is the capability of epinephrine and norepinephrine to stimulate structures of the body that are not innervated by direct sympathetic fibers
Synthesis and secretion of adrenocortical hormones

- The adrenal cortex has three distinct layers
  1. The zona glomerulosa - these cells are the only ones in the adrenal gland capable of secreting significant amounts of aldosterone because they contain the enzyme aldosterone synthase.
  2. The zona fasciculata - secretes the glucocorticoids cortisol and corticosterone, as well as small amounts of adrenal androgens and estrogens (controlled by ACTH).
  3. The zona reticularis - secretes the adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione, as well as small amounts of estrogens and some glucocorticoids (controlled by ACTH and cortical androgen-stimulating hormone).

Synthesis and secretion of adrenocortical hormones

- Adrenocortical hormones are steroids derived from cholesterol
  - The LDLs, diffuse from the plasma into the interstitial fluid and attach to specific receptors contained in structures called coated pits on the adrenocortical cell membranes. By endocytosis, forming vesicles that eventually fuse with cell lysosomes and release cholesterol that can be used to synthesize adrenal steroid hormones

- Synthetic pathways for adrenal steroids
  - the formation of the important steroid products of the adrenal cortex: aldosterone, cortisol, and the androgens (the mitochondria and the endoplasmic reticulum)
Synthesis and secretion of adrenocortical hormones

• Mineralocorticoids
  – **Aldosterone** (very potent, accounts for about 90 per cent of all mineralocorticoid activity)
  – Desoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted)
  – Corticosterone (slight mineralocorticoid activity)
  – 9a-Fluorocortisol (synthetic, slightly more potent than aldosterone)
  – Cortisol (very slight mineralocorticoid activity, but large quantity secreted)
  – Cortisone (synthetic, slight mineralocorticoid activity)
Synthesis and secretion of adrenocortical hormones

• Glucocorticoids
  – **Cortisol** (very potent, accounts for about 95 per cent of all glucocorticoid activity)
  – Corticosterone (provides about 4 per cent of total glucocorticoid activity, but much less potent than cortisol)
  – Cortisone (synthetic, almost as potent as cortisol)
  – Prednisone (synthetic, four times as potent as cortisol)
  – Methylprednisone (synthetic, five times as potent as cortisol)
  – Dexamethasone (synthetic, 30 times as potent as cortisol)
Synthesis and secretion of adrenocortical hormones

- Adrenocortical hormones are bound to plasma proteins
  - *cortisol-binding globulin* or *transcortin* and,
  - to a lesser extent, to albumin
- Free forms, the hormones are transported throughout the extracellular fluid compartment

- Adrenocortical hormones are metabolized in the liver
  - in the liver and conjugated especially to *glucuronic acid* and, to a lesser extent, sulfates
  - these conjugates are excreted in the bile and then in the feces
  - remaining conjugates are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine
Functions of the Mineralocorticoids - Aldosterone

• Mineralocorticoid deficiency causes severe renal sodium chloride wasting and hyperkalemia
  – without mineralocorticoids, potassium ion concentration of the extracellular fluid rises markedly, sodium and chloride are rapidly lost from the body, and the total extracellular fluid volume and blood volume become greatly reduced

• Aldosterone is the major mineralocorticoid secreted by the adrenals (90%)
Functions of the Mineralocorticoids—Aldosterone

• Renal and circulatory effects of Aldosterone
  – Aldosterone increases renal tubular reabsorption of sodium and secretion of potassium (*principal cells of the collecting tubules*)
  – Excess Aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration
  – Excess Aldosterone causes hypokalemia and muscle weakness; too little Aldosterone causes hyperkalemia and cardiac toxicity
  – Excess Aldosterone increases tubular hydrogen ion secretion, and causes mild alkalosis (decreases the hydrogen ion concentration in the extracellular fluid)

• Aldosterone stimulates sodium and potassium transport in sweat glands, salivary glands, and intestinal epithelial cells
Functions of the Mineralocorticoids- Aldosterone

- **Cellular mechanism of Aldosterone action**
  - 1. its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells
  - 2. in the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic receptor protein
  - 3. the aldosterone-receptor complex or a product of this complex diffuses into the nucleus, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport
  - 4. the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation
    - 1) one or more enzymes
    - 2) membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane

- **Nongenomic actions of Aldosterone** (few seconds or minutes)
  - cAMP
  - PIP
Cellular mechanism of Aldosterone action

**Figure 78-4.** Aldosterone-responsive epithelial cell signaling pathways. Activation of the mineralocorticoid receptor (MR) by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block epithelial sodium channel proteins (ENaC).

Regulation of Aldosterone secretion

- The regulation of aldosterone secretion is so deeply intertwined with the regulation of extracellular fluid:
  - electrolyte concentrations, extracellular fluid volume,
  - blood volume, arterial pressure, and many special aspects of renal function
- Four factors are known to play essential roles in the regulation of aldosterone
  1. Increased potassium ion concentration in the extracellular fluid greatly increases aldosterone secretion
  2. Increased activity of the renin-angiotensin system (increased levels of angiotensin II) also greatly increases aldosterone secretion
  3. Increased sodium ion concentration in the extracellular fluid very slightly decreases aldosterone secretion
  4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions
Functions of the Glucocorticoids

• 95 per cent of the glucocorticoid activity of the adrenocortical secretions results from the secretion of cortisol, (hydrocortisone)

• a small but significant amount of glucocorticoid activity is provided by corticosterone
Functions of the Glucocorticoids

• Effects of Cortisol on carbohydrate metabolism
  – **Stimulation of gluconeogenesis** (formation of carbohydrate from proteins and some other substances)
    • *Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells*
    • *Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle*
  – **Decreased glucose utilization by cells** (*glucocorticoids depress the oxidation of nicotinamide-adenine dinucleotide (NADH) to form NAD*)
  – **Elevated blood glucose concentration and “Adrenal Diabetes”**

• Effects of cortisol on protein metabolism
  – Reduction in cellular protein
  – Cortisol increases liver and plasma proteins
  – Increased blood amino acids, diminished transport of amino acids into extrahepatic cells, and enhanced transport into hepatic cells
Functions of the Glucocorticoids

• Effects of Cortisol on fat metabolism
  – Mobilization of fatty acids
  – Obesity caused by excess cortisol (chest and head region)

• Cortisol is important in resisting stress and inflammation
  – Cortisol prevents the development of inflammation by stabilizing lysosomes and by other effects
Cortisol prevents the development of inflammation

• 1. Cortisol stabilizes the lysosomal membranes
• 2. Cortisol decreases the permeability of the capillaries
• 3. Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells
• 4. Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly
• 5. Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells
Regulation of Cortisol secretion by ACTH from the pituitary gland

• ACTH stimulates Cortisol secretion

• ACTH secretion is controlled by corticotropin-releasing factor from the hypothalamus

• ACTH activates adrenocortical cells to produce steroids by increasing cyclic adenosine monophosphate (cAMP)
Mechanism for regulation of glucocorticoid secretion

Figure 78-7. Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotropin hormone; CRF, corticotropin-releasing factor.