Lecture: Drugs affecting endocrine system
Drugs affecting hypothalamic and pituitary gland hormones. Drugs affecting thyroid hormones. Agents that affect bone mineral homeostasis.

Drugs affecting hypothalamic and pituitary gland hormones.

1.1. Hypothalamic hormones
1.1.1. Growth hormone-releasing hormone (GHRH)
Natural occurring GHRH exists as 44- and 40-amino-acid peptides (GHRH40 and GHRH44). In therapy are used synthetic analogues such as Sermorelin (a synthetic peptide corresponding to the 1–29 amino acid sequence of GHRH) and Hexarelin.

Sermorelin
- indications: - diagnosis of growth hormone deficiency (to test pituitary GH reserve),
  - treatment of growth hormone deficiency in children.
- adverse effects: facial flushing, reactions at the injection site (pain, erythema, swelling).

1.1.2. Growth hormone inhibiting hormone (Somatostatin)
Somatostatin inhibits growth hormone release in the CNS. Also inhibits the release of glucagon, insulin and gastrin, VIP and TSH.

Somatostatin has limited therapeutic usefulness because of its short duration of action (t1/2 = 1-3 minutes) and its multiple effects on many secretory systems.
In therapy are used: - a synthetic analogue of Somatostatin: Octreotide,
  - a growth hormone receptor antagonist: Pegvisomant.

Octreotide
- has similar properties to Somatostatin, but a longer duration of action (t1/2 = 80 minutes \(\rightarrow\) it is administered every 8 hours).
- indications: - acromegaly,
  - carcinoid tumours and other secretory neoplasms [such as VIPomas, glucagonomas, thymic carcinomas. The watery diarrhea hypokalemia achlorhydria syndrome (WDHA syndrome = pancreatic cholera) is due to a non-\(\beta\) cell pancreatic adenoma, referred to as a VIPoma, that secretes VIP and a host of other peptide hormones including pancreatic polypeptide, secretin, gastrin, gastrin-inhibitory polypeptide (also called glucose-dependent insulinotrophic peptide), neurotensin, calcitonin, and prostaglandins].
  - management of esophageal varices haemorrhage,
  - intestinal pseudoobstruction,
- other indications: - prevention of complications after pancreatic surgery,
  - HIV-associated diarrhoea,
  - diabetic diarrhoea,
  - antineoplastic chemotherapy associated diarrhoea,
  - gastrointestinal disorders including bleeding, refractory diarrhoea, fistulae, dumping syndrome, and nausea and vomiting secondary to bowel obstruction
- Somatostatin receptor scintigraphy with Octreotide is the most sensitive method for imaging lesions in patients with Zollinger-Ellison syndrome.

- adverse effects: - nausea, vomiting, steatorrhoea, abdominal cramps, flatulence,
  - changes in glucose tolerance test,
  - biliary sludge and gallstones may develop on long-term therapy (after 6 months of use).

Pegvisomant is indicated for the treatment of acromegaly refractory to other treatments.
1.1.3. Thyrotropin-releasing hormone (TRH = protirelin): TRH

Thyrotropin-releasing hormone (TRH = protirelin) stimulates the release of thyrotrophin from the anterior lobe of the pituitary. It also has prolactin-releasing activity.

In therapy is used Protirelin (synthetic TRH). It is rare used.
- indication: diagnostic purpose → to differentiate between primary and secondary hypothyroidism.
- adverse effects: an urge to micturate, flushing, metallic taste, headache, dizziness, nausea.

1.1.4. Corticotropin-releasing hormone (CRH = corticorelin): CRH

Corticotropin-releasing hormone (CRH = corticorelin) stimulates the release of ACTH from the anterior lobe of the pituitary.

In therapy is used Corticorelin (ovine or synthetic human CRH). It is rare used.
- indication: diagnostic purpose → to differentiate Cushing’s syndrome from ectopic ACTH secretion.
- adverse effects: flushing of the face, neck and upper chest.

1.1.5. Gonadotropin-releasing hormone (GnRH, LHRH): in therapy are used

Gonadotropin-releasing hormone GnRH is produced in the arcuate nucleus of the hypothalamus. Pulsatile GnRH secretion is essential to stimulate the gonadotroph cell to produce and release luteinizing hormone (LH) and follicle stimulating hormone (FSH). Continuous administration of GnRH or GnRH analogs inhibits the release of FSH and LH by the pituitary in both women and men, resulting in hypogonadism.

In therapy are used:
- synthetic gonadotropin: Gonadorelin (synthetic form of GnRH)
- synthetic gonadotropin analogues: Leuprolelin (Leuprolide), Nafarelin, Goserelin, Buserelin, Histrelin
- GnRH antagonists: Cetrorelix acetate, Ganirelix

Gonadorelin
- is a synthetic polypeptide hormone which stimulate the release of the LH from the hypothalamus.
- indications: - diagnosis of hypothalamic-pituitary-gonadal dysfunction
  - infertility related to hypogonadotrophic hypogonadism in both women and men
  - cryptorchidism,
  - prostate cancer,
  - precocious puberty.
- adverse effects: headache, nausea, flushing, dermatitis, hypersensitivity reactions (bronchospasm and anaphylaxis).
- contraindications: pregnancy and breast feeding.

Gonadotropin analogues: Leuprolelin (Leuprolide), Nafarelin, Goserelin, Buserelin, Histrelin
- mechanism of action: agonists on GnRH receptors that induce hypogonadism when given continuously.
- indications: - prostate cancer,
  - endometriosis,
  - uterine fibroids,
  - polycystic ovarian syndrome,
  - precocious puberty.
- adverse effects: - in women: hot flushes, sweats, headache, diminished libido, depression, ovarian cysts, breast atrophy, osteoporosis.
  - in men: serum testosterone levels increase, pain in men with bone metastases, hot flashes, sweats, edema, gynecomastia, diminished libido, decreased hematocrit and asthenia.
- contraindications: pregnancy and breast feeding.

GnRH antagonists: Cetrorelix acetate, Ganirelix
- mechanism of action: antagonists on GnRH receptors.
- indication: ovulation induction.
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- adverse effects: reactions at the injection site (erythema, pruritus, and swelling).
- contraindications: moderate to severe renal or hepatic impairment.

1.1.6. Prolactine inhibiting hormone (PIH).
Not used in therapy.

1.2. Hormones of the anterior pituitary gland:
1.2.1. Growth hormone (GH, Somatotropin)
Growth hormone produces growth of skeletal (at open epiphyses), muscular (produce growth of skeletal muscle), and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. It has a diabetogenic action on carbohydrate metabolism. Secretion is pulsatile and dependent on neural and hormonal influences: release is stimulated by Growth hormone-releasing hormone (GH-RH) and inhibited by Growth hormone inhibiting hormone (Somatostatin).
In therapy are used Somatropin (as recombinant human growth hormone = rhGH) and its analogue Somatrem.
- mechanism of action: directly (on target) or indirectly (mediated by somatomedines)
- indications: - GH deficiency in children (pituitary dwarfism, Turner's syndrome, in short children born small for gestational age, idiopathic short stature etc)
  - GH deficiency in adults
- adverse effects: - intracranial hypertension (headache, nausea, vomiting)
  - Creutzfeldt-Jakob disease after the use of GH from human cadaver pituitary gland
  - hypothyroidism
- contraindications: - patients with closed epiphyses
  - active neoplasms or intracranial lesions
  - hypothyroidism.

1.2.2. Thyrotropin (TSH): recombinant human TSH
Thyrotrophin is an anterior pituitary hormone that stimulates the thyroid to produce and synthesize thyroxine (T4), triiodothyronine (T3) and thyroglobulin.
In therapy is used Thyrotropin alpha (synthetic recombinant human TSH). It is rare used.
- indication: - diagnostic purpose → diagnosis of hypothyroidism and to differentiate between primary and secondary hypothyroidism.
  - stimulate uptake of radio-iodine for treatment of thyroid residual tissue after cancer thyroidectomy and metastatic differential thyroid cancer.
- adverse effects: headache, dizziness, nausea, flushing, an urge to micturate. High doses may produce hyperthyroidism (excessive thyroid stimulation explains angina, tachycardia or arrhythmias, dyspnea, sweating, nervousness and irritability).

1.2.3. Adrenocorticotropin (ACTH = corticotropin): ACTH
Corticotropin is a naturally occurring hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal glands to secrete adrenocortical hormones, especially cortisol (hydrocortisone), some mineralocorticoids such as corticosterone, and, to a lesser extent, androgens. It has little effect on aldosterone secretion, which proceeds independently.
In therapy are used: - Corticotropin (animal or synthetic human ACTH) – it is rare used
  - Tetracosactide (synthetic polypeptide with the first 24 residues of human ACTH).
- indications: - diagnostic purpose → to differentiate between primary (Addison’s disease) and secondary adrenal insufficiency.
  - infantile spasms (West syndrome).
adverse effects: similar to corticosteroids. Its mineralocorticoid properties can produce marked sodium and water retention, considerable potassium loss. Abrupt withdrawal of corticotropin may result in symptoms of adrenal insufficiency. Tetracosactide is less immunogenic than Corticotropin.

1.2.4. Follicle-stimulating hormone (FSH); luteinizing hormone (LH); human chorionic gonadotropin (hGC)

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are produced by gonadotroph cells in the anterior pituitary. FSH and LH regulate gonadal function. The principal function of FSH is to stimulate gametogenesis and follicular development in women and spermatogenesis in men. In ovary, FSH acts on the immature follicular cells and induces development of the mature follicle and oocyte. Both LH and FSH are needed for proper ovarian steroidogenesis. LH stimulates androgen production by these cells, and FSH stimulates androgen conversion into estrogens by the granulosa cells. In the testes, FSH acts on the Sertoli cells and stimulates their production of androgen-binding protein.

LH is primarily responsible for regulation of gonadal steroid hormone production. In men, LH acts on testicular Leydig cells to stimulate testosterone production. In the ovary, LH acts in concert with FSH to stimulate follicular development. LH acts on the mature follicle to induce ovulation, and it stimulates the corpus luteum in the luteal phase of the menstrual cycle to produce progesterone and androgens.

In therapy are used:
- menotropins (or human menopausal gonadotropin):
  - menotropins (hMG) is a purified extract of FSH and LH
  - urofollitropine (uFSH) is a purified preparation of human FSH
  - follitropin alpha (rFSH) is recombinant FSH
- human chorionic gonadotropin (hGC): Choriogonadotropin alfa is a recombinant form of chorionic gonadotrophin.

Menotropins (or human menopausal gonadotropin)
- obtained as extract of human postmenopausal urine.
- indications: infertility treatment (in male and female) due to hypogonadism. Human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation.
- adverse effects: ovarian enlargement (risk of hemoperitoneum due to rupture of ovarian cysts), hypovolaemia, multiple births, spontaneous abortion, gynecomastia in men.
- contraindications: pregnancy, abnormal genital bleeding, hormone sensitive malignancies (such as those of the breast, uterus, prostate, ovaries or testes), ovarian cysts or enlargement not caused by the polycystic ovary syndrome.

Human chorionic gonadotropin (hGC)
- is a hormone produced by the placenta and it is obtained from the urine of pregnant women.
- indications: infertility treatment (in male and female) due to hypogonadism, treatment of prepubertal cryptorchidism, delayed puberty due to hypogonadotrophic hypogonadism.
- adverse effects: headache, depression, edema, precocious puberty, gynecomastia, ovarian enlargement (risk of hemoperitoneum due to rupture of ovarian cysts), hypovolaemia.
- contraindications: carcinoma of the prostate or tumours of the breast, uterus, ovarian, testicular, hypothalamus, pituitary, thyroid, and adrenal glands, precocious puberty.
1.2.5. Prolactin
Prolactin amino-acid peptide hormone produced in the anterior pituitary, responsible for lactation. Prolactin secretion is stimulated by suckling and, for a few months after delivery, it has an inhibitory effect on the ovaries, acting as a natural contraceptive. Prolactin secretion may also be stimulated by methyl dodopa, metoclopramide, reserpine, opioid analgesics, and phenothiazine or butyrophenone antipsychotics.
A deficiency of prolactin is manifested by failure to lactate or by a luteal phase defect.

**Prolactin indications:** management of lactation disorders and some forms of menstrual disturbance. For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with dopamine agonists such as Bromocriptine, Cabergoline, Pergolide (these are ergot derivatives), Quinagolide (nonergot drug).

**Bromocriptine**
- is an ergot derivative,
Mechanism of action: agonist on dopamine D2-receptors
Indications: - to inhibit the secretion of prolactin:
  - prolactinoma and endocrinological disorders associated with hyperprolactinaemia
  - suppress puerperal lactation for medical reasons
  - Parkinson's disease
  - acromegalic patients (adjunct to surgery and radiotherapy to reduce plasma-growth hormone concentrations).
Adverse effects: - peripheral vasoconstrictor effect (because it is an ergot derivative): vasoospasm, Raynaud's syndrome, leg cramps, arrhythmias, exacerbation of angina, asymptomatic hypotension, very rarely hypertension, myocardial infarction,
  - psychiatric disorders
  - pulmonary and retroperitoneal fibrosis (because it is an ergot derivative)
Contraindications: - hypertension, coronary artery disease,
  - history of serious psychiatric disorders
  - pregnancy and breast-feeding.

1.3. Hormones of the posterior pituitary gland:
1.3.1. Oxytocin;
1.3.2. Vasopresin, desmopressin.

**Drugs affecting thyroid hormones.**
Thyroid gland synthesize thyroid hormones T3 and T4 following the steps:
- uptake of iodide from blood into thyroid gland (iodide is from ingested food, water or medication)
- iodide oxidation (oxidation of iodide to iodine by thyroidal peroxidase)
- iodide organification (iodinated thyrosine residues form monoiodothyrosine [=MIT] and diiodothyrosine [=DIT])
- coupling of iodothyrosines to result of thyroid hormones: T4 (by combination of 2 molecules of DIT), T3 (by combination of one molecule of DIT and one molecule of MIT).
Then thyroid hormones are released from gland into blood. Transport of thyroid hormones is by thyroxine-binding globulin.
2.1. Treatment of hypothyroidism → thyroid preparations:
- Liothyronine (T3),
- Levothyroxine (T4),
- Liotrix (a 4:1 ratio of T4:T3),
- thyroid desiccated.

Mechanism of action: thyroid hormones T3 and T4 are dissociated from thyroid-binding globulin → enter the cells by diffusion or possibly by active transport → T4 is converted to T3 by 5'-deiodinase, and the T3 enters the nucleus → in nucleus T3 binds to a specific T3 receptor protein → increased formation of RNA and subsequent protein synthesis.

Indications: - hypothyroidism (T3 is more active than T4, but has shorter half-life) – it is preferred Levothyroxine (T4),
- to suppress TSH production in the treatment of thyroid carcinoma,
- as a diagnostic agent for the differential diagnosis of hyperthyroidism.

Adverse effects: correspond to symptoms of hyperthyroidism (tachycardia, palpitations, cardiac arrhythmias, increase in blood pressure, anginal pain, headache, restlessness, insomnia, tremors, muscle weakness and cramps, heat intolerance, sweating, flushing, fever, weight loss, menstrual irregularities, diarrhoea, and vomiting).

Contraindications: cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension. Precaution in elderly patients.

2.2. Prophylaxy of endemic gout: Potassium iodide.

Indications:
- low doses taken by mouth: - prophylaxis and treatment of iodine deficiency disorders (eg, endemic gout, to prevent neonatal goitre and cretinism),
- radiation protection (to saturate the thyroid when uptake of radio-iodine by the gland is not desired),
- high doses: - pre-operative management of hyperthyroidism (reduce vascularity and friability of thyroid gland, increase thyroid firm).

Adverse effects: iodism (acneiform rash, drug fever, conjunctivitis, rhinorrhea, metallic taste, mucous membrane ulcerations).

2.3. Treatment of hyperthyroidism → antithyroid agents:
2.3.1. Thioamides: Methimazole (Thiamazole), Carbimazole, Propylthiouracil.

Mechanism of action: block the production of thyroid hormones by multiple mechanisms:
- block iodide oxidation,
- block iodide organification,
- block coupling of iodothyrosines.

Indications: - hyperthyroidism, including the treatment of Graves' disease,
- preparation of hyperthyroid patients for thyroidectomy,
- as an adjunct to radio-iodine therapy,
- treatment of thyroid storm.

Adverse effects: - skin rashes and fever → most common,
- mild leucopenia with neutropenia → the most frequent, agranulocytosis → the most serious.
- cholestatic jaundice, hepatitis,
- rare: limphadenopathy, arthralgia, vasculitis, lupus-like reactions, hypoprothrombinemia, nausea and vomiting, gastric discomfort, headache, pruritus.

Propylthiouracil is preferable in pregnancy (preferred to carbimazole or thiamazole) and in breast-feeding since it enters breast milk less readily.

2.3.2. Iodides: Potassium iodide.
2.3.3. **Anion inhibitors: Perchlorate, Pertechnetate, Thiocyanate.**
Mechanism of action: block uptake of iodide
Indications: drug induced hyperthyroidism (eg, Amiodarone-induced hyperthyroidism)
Adverse effects: aplastic anemia.

2.3.4. **Radioactive Iodine (I^{131}).**
Mechanism of action: destruction of thyroid parenchima.
Indications: treatment of thyreotoxicosis (hyperthyroidism, thyroid carcinoma).
Adverse effects: hypothyroidism.
Contraindications: pregnancy, breast-feeding, severe thyrotoxic heart disease.

2.3.5. **Iodinated contrast media: Ipodate, Iopanoic acid.**
Mechanism of action: inhibit the conversion of T4 to T3 in different tissues.
Indications: hyperthyroidism, thyroid storm.
Adverse effects: similar to iodides.

2.3.6. **Beta-blockers (Propranolol) or neurosympaticolytic drugs (Guanethidine, Rezerpine).**

2.4. **Treatment of thyroid cancer:**
- Radioactive Iodine (I^{131}),
- anticancer drugs: - cell cycle-specific agents: - antimetabolites: 5-Fluorouracil,
- antitumor antibiotic: Bleomycin,
  - cell cycle-nonspecific agents: - alkylating agents: Melphalan,
  - antracycline(antitumor antibiotic): Doxorubicin

### Agents that affect bone mineral homeostasis.

3.1. **Hormonal agents that influence bone mineral homeostasis:**
3.1.1. **Vitamin D:** cholecalciferol (D_{3}), ergocalciferol (D_{2}), 25(OH)D_{3} (calcifediol); 1,25-(OH)_{2}-D_{3} (calcitriol); 24,25-(OH)_{2}-D_{3} (secalcifediol); Dyhydrotachysterol (DHT); 1α(OH)D_{2} (doxercalciferol); 25-hydroxiisotachysterol; Isotachysterol.
Mechanism of action: stimulation of intestinal calcium and phosphate transport and bone resorption
Indications: treatment and prevention of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism.
Adverse effects:
- excessive intake of vitamin D → hyperphosphataemia, hypercalcaemia (hypercalcaemia is associated with hypercalcuria, ectopic calcification, and renal and cardiovascular damage).
- overdosage of vitamin D → anorexia, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo.
Contraindications: hypercalcaemia, patients with renal impairment or calculi or heart disease (risk of organ damage if hypercalcaemia occurred). Plasma phosphate concentrations should be controlled to reduce the risk of ectopic calcification.

3.1.2. **Parathyroid hormone (PTH):** Teriparatide (recombinant form of parathyroid hormone).
Indication: treatment of osteoporosis in patients with high risk of fractures (it is the only drug that stimulate bone formation).

3.1.3. **Calcitonin.**
Calcitonin is a hormone produced by mammalian thyroid parafollicular cells.
Mechanism of action: lower serum calcium and phosphate due to inhibition of osteoclastic bone resorption and increase urinary excretion of calcium and phosphorus

Indications:  
- osteoporosis (prevention and treatment),
- bone pain due to osteoporotic fractures,
- Paget's disease of bone,
- severe hypercalcaemia, especially that associated with malignancy.

Adverse effects:  
- rhinitis (after intranasal administration),
- abdominal pain, skin rashes of head and hands
- antibody formation (after long-term treatment with salmon/pork calcitonin).

3.1.4. Others:
- Glucocorticoids.
- Selective estrogen receptors modulators (estrogen-like drugs): Raloxifene.
- Thyroid hormones, somatotrop, androgens.

3.2. Non-hormonal agents that influence bone mineral homeostasis:

- **Biphosphonates: Etidronate, Alendronate, Pamidronate, Risedronate, Zolendronate, Ibandronate, Clodronate.**
  
  Mechanism of action: inhibit bone resorption by osteoclasts
  
  Pharmacokinetics: biphosphonates are poorly absorbed after oral administration (absorption is reduced by food, especially by products containing calcium or other polyvalent cations). Bioavailability in the fasting state is less than 10%. About 50% of an absorbed dose is sequestered to bones and retained in the body for prolonged periods. Excretion is in the urine, as unchanged drug.
  
  Indications:
  - osteoporosis (biphosphonates are first choice for prevention and treatment),
  - osteoporotic fragility fractures
  - Paget's disease of bone,
  - treatment of severe hypercalcaemia, especially when associated with malignancy.
  
  Adverse effects:
  - gastrointestinal disturbances: abdominal pain, nausea, vomiting, diarrhoea,
  - musculoskeletal pain,
  - disturbances in serum electrolytes (hypocalcaemia, hypophosphataemia),
  - oesophagitis and esophageal ulcer: low in Etidronate (to minimize this risk, patients should remain upright for 30 minutes after taking Alendronate, Risedronate, 60 minutes after taking Ibandronate),
  - osteonecrosis of the jaw,
  - osteomalacia after Etidronate administration.
  
  Contraindications: pregnancy.

- **Mithramycin (Plicamycin)**
  
  Mechanism of action: not well known
  
  Indications: hypercalcaemia and Paget disease

- **Thiazide diuretics, Loop diuretics**

- **Fluoride.**

- **Calcium preparations:**
  
  - parenteral preparations:
    - Calcium gluconate (0.45 mEq calcium/mL = 9% calcium)
    - Calcium chloride (0.68-1.36 mEq calcium/mL = 27% calcium)
    - Calcium gluceptate (0.9 mEq calcium/mL = 8% calcium)

  - oral preparations:
    - Calcium carbonate (40% calcium)
    - Calcium lactate (13% calcium)
- Calcium phosphate (25% calcium)
- Calcium citrate (21% calcium)
- Calcium acetate (25% calcium)
- Calcium glubionate (6.5% calcium)
- Tricalcium phosphate (39% calcium)

**Indications:**
- hypocalcaemia and calcium deficiency states (in simple deficiency states given by mouth, in severe acute hypocalcaemia or hypocalcaemic tetany given parenteral)
  - hyperkalaemia (calcium gluconate)
  - hypermagnesaemia (calcium gluconate)
  - hyperphosphataemia (calcium carbonate)
  - antiacids (calcium carbonate, calcium silicate)

**Adverse effects:**
- gastrointestinal irritation (calcium chloride is the most irritant)
- soft-tissue calcification (after parenteral administration)
- hypercalcemia.

**Contraindications:**
- renal lithiases,
- renal impairment,
- diseases associated with hypercalcemia (sarcoidosis, some malignancies).

**Interactions:**
- cardiac glycosides (calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication),
- thiazide diuretics decrease its urinary excretion,
- corticosteroids reduce calcium absorption,
- bisphosphonates, fluoride, some fluoroquinolones, tetracyclines (calcium salts reduce their absorption; doses should be separated by at least 3 hours).

**Treatment of hypocalcemia:** Vitamin D + Calcium preparations

**Osteoporosis treatment**
- Estrogens ± progestins; selective estrogen receptors modulators (estrogen-like drugs): Raloxifene.
- Calcitonin.
- Recombinant form of parathyroid hormone (PTH): Teriparatide.
- Fluoride.

**Treatment of Paget’s disease of bone**
- Calcitonin.
- Biphosphonates: Etidronate, Alendronate, Risedronate, Tiludronate.
- Mithramycin (Plicamycin).

**Treatment of hypercalcemia**
- Saline diuresis: rehydration with saline ± Furosemide.
- Other drugs: biphosphonates (Etidronate, Pamidronate, Zolendronate), Calcitonin, Gallium nitrate, Mithramycin (Plicamycin), phosphates (sodium or potassium salts), Glucocorticoids.
Lecture: Drugs affecting endocrine system
Drugs affecting sex hormones. Hormonal contraception.

Drugs affecting sex hormones.

Mechanism of action: bind to specific nuclear receptors → the complex hormon-receptor binds to DNA → stimulate specific protein synthesis.

1. Androgens
Natural androgens: testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone. Natural androgens have anabolic and androgenic properties.
Testosterone is the main androgenic hormone. It is formed in the interstitial (Leydig) cells of the testes and, in small quantities is derived from the metabolism of less potent androgens secreted by the adrenal cortex and ovaries.
Testosterone is converted to dihydrotestosterone by 5-alpha reductase in many target tissues (dihydrotestosterone is the major active androgen of these tissues). Some testosterone also undergoes peripheral conversion to estradiol.
Physiological effects of testosterone:
- normal maturation in men (controls the development of the male sex organs and secondary sex characteristics),
- stimulate and maintain sexual function in men (stimulate and maintain spermatogenesis),
- produces systemic anabolic effects: stimulate skeletal growth and accelerate epiphysial closure, increase synthesis of muscle proteins, increase retention of nitrogen, calcium, sodium, potassium, chloride, and phosphate,
- increases erythropoiesis.

In therapy are used:
1.1. Androgens and anabolic androgens
- Natural androgens: Testosterone (activity of natural testosterone is improved by esterification propionate, enantate, cypionate, undecanoate)
  - for i.m. administration: Testosterone propionate, Testosterone enantate, Testosterone cypionate, Testosterone undecanoate
  - for sublingual administration: Testosterone propionate
  - for transdermal administration: Testosterone

Indications:
- androgen replacement therapy in men (caused by testicular [→ primary hypogonadism] or pituitary deficiency [→ secondary hypogonadism; treatment should be started in puberty]),
- delayed puberty or growth in boys,
- premenopausal women with breast tumors,
- in combination with estrogens in postmenopausal women (eliminate endometrial bleeding),
- as anabolic (to reverse protein loss after trauma, surgery, or prolonged immobilization and in patients with debilitating diseases),
- anemia (in refractory anaemias, such as aplastic anaemia),
- as male contraceptives (high doses reduce spermatogenesis).

Adverse effects:
- retention of sodium and water, hypercalcemia,
- increase LDL-cholesterol, decrease HDL-cholesterol, increase haematocrit,
- large doses in adult men → suppress spermatogenesis, cause degenerative changes in the seminiferous tubules, gynaecomastia,
- large doses in adult boys in early puberty → closure of the epiphyses, stop linear growth, precocious sexual development,
- in women → suppression of ovarian activity and menstruation, virilism (hirsutism or male-pattern baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, increased libido, suppressed lactation). Masculinisation of the external genitalia of the female fetus may occur if androgens are given during pregnancy.

Contraindications: - pregnancy,
- neoplasms of the prostate or breast,
- infants and young children.

- **Semisynthetic androgens:**
  - Methyltestosterone, Fluoxymesterone: oral administration, but have hepatotoxic effects,
  - Mesterolone (is not metabolised to estrogens → not inhibit gonadotrophin secretion or spermatogenesis).

- **Androgens with anabolic activity (androgenic anabolic activity is compared to testosterone):**
  - Testosterone (1:1)
  - Nandrolone phenpropionate (1:3 – 1:6)
  - Nandrolone decanoate (1:2.5 – 1:4)
  - Ethylestrenol (1:4 – 1:8) (androgenic effect and slight progestational activity)
  - Stanozolol (1:3 – 1:6)
  - Drostanolone propionate (Dromostanolone) (1:3 – 1:4)
  - Methandienone (Methandrostenolone) (1:3) (anabolic, some androgenic and little progestational activity)
  - Oxymetholone (1:3)
  - Oxandrolone (1:13)

Indications: anabolic after debilitating illness

Adverse effects similar to testosterone.

**1.2. Androgen suppression and antiandrogens**

- **Androgen suppression:** Gn-RH analogues (Leuprolide, Nafarelin, Goserelin, Buserelin, Histrelin)
- **Antiandrogens:** - steroid synthesis inhibitors: Ketoconazole
  - 5-alpha reductase inhibitors (inhibits conversion of steroid precursors to androgens): Finasteride, Dutasteride
  - androgen receptors inhibitors:     - Cyproterone acetate,
          - Flutamide, Bicalutamide, Nilutamide
          - Spironolactone.

**Ketoconazole**

Indications: - antifungic drug.
  - for anti-androgenic effects: prostatic cancer, hirsutism, precocious puberty.

**5-alpha reductase inhibitors: Finasteride, Dutasteride**

Mechanism of action: inhibits 5-alpha reductase which convert steroid precursors to androgens

Indications: - benign prostatic hyperplasia
  - alopecia androgenetica in men

Adverse effects: decreased libido, erectile dysfunction, ejaculation disorders, gynaecomastia.

**Cyproterone acetate**

Mechanism of action: androgen receptors inhibitor (Cyproterone acetate has marked progestational effects)

Indications: - hirsutism in women,
  - control of libido (in men to decrease excessive sexual drive),
  - hormonal contraceptive.
Flutamide, Bicalutamide, Nilutamide
Mechanism of action: competitive antagonist at the androgen receptors.
Indications: prostatic carcinoma.
Adverse effects: gynecomastia, hepatotoxicity.

Spironolactone
Mechanism of action: competitive antagonist at the aldosterone receptors.
Indications: - potassium-sparing diuretic,
- refractory oedema associated with liver cirrhosis, nephrotic syndrome,
- ascites associated with malignancy,
- heart failure,
- primary hyperaldosteronism,
- hirsutism, particularly in the polycystic ovary syndrome.

2. Progestins
Natural progestins: progesterone.
Progesterone is the main hormone secreted by the corpus luteum.
Physiological effects of progesterone:
- acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase thereby preparing the uterus to receive the fertilised ovum,
- catabolic action
- causes a slight rise in basal body temperature during the secretory phase of menstruation,
- during pregnancy the placenta produces large quantities of progesterone, which suppresses uterine motility and is responsible for the further development of the breasts.

In therapy are used:
2.1. Natural and synthetic progestins:
- Natural: Progesterone.
- Synthetic progestins:
  - 21-carbon compounds:
    - progesterone derivatives: Hydroxiprogesterone, Medroxyprogesterone, Megestrol
    - 17-ethyniltestosterone derivative: Dimethisterone
  - 19-carbon compounds: Norgestrel, Desogestrel, Norethindrone (Noretosterone), Ethynodiol, Lynestrenol (Ethynylestrenol), Noretynodrel
  - other compounds: Allylestrenol, Dienogest, Gestodene, Norgestimate, Ethisterone (Ethynylestosterone), Norelgestromin, Etonorgestrel, Danazol

Indications: - replacement therapy (caused by primary hypogonadism),
- contraception (alone or in combination with estrogens),
- test diagnostic of estrogen secretion.
Adverse effects: - headache,
- depression,
- weight gain (for androgen-like progestins: Norgestrel, Norethindrone, Ethynodiol, Levonorgestrel, Lynestrenol),
- hirsutism (aggravated by the 19-nortestosterone derivatives: Norgestrel, Desogestrel, Norethindrone, Ethynodiol, Lynestrenol, Noretynodrel),
- changes in libido.
2.2. Inhibitors and antagonists of progestins:
- antagonist of progesterone and glucocorticoid receptors: Mifepristone.

Mifepristone
Mechanism of action: antagonist of progesterone and glucocorticoid receptors
Indications:  - contraception (emergency contraception),
- abortion,
- endometriosis,
- breast cancer,
- Cushing syndrome.
Adverse effects: prolonged bleeding, incomplete abortion.

3. Estrogens
Natural estrogens: estradiol, estrone, estriol.
Estradiol is the major secretory product of the ovarian follicles. Some estrone is produced in the ovary. Most estrone and estriol are formed in the liver from estradiol or in peripheral tissues (adipose tissue) from androstenedione and other androgens.
Physiological effects of estrogens:
- normal maturation in women (controls the development of the female sex organs and secondary sex characteristics),
- functions of the uterus and its accessory organs: endometrial development (proliferation of the endometrium, the development of the decidua), the cyclic changes in the cervix and vagina,
- induce synthesis of progesterone receptors.

In therapy are used:
3.1. Natural and synthetic estrogens:
- Natural: Estradiol, Estrone, Estriol.
  Oral activity of natural oestrogens is improved by esterification (estradiol valerate, estriol cypionate) or by conjugation (estrone sulfate).
- Semisynthetic and synthetic estrogens:
  - steroidal structure: Ethinyl-estradiol, Estropipate, Mestranol, Quinestrol
  - nonsteroidal structure: Diethylstilbestrol, Chlorotrianisene, Dienestrol, Methallenestrol, Hexestrol.

Indications:  - estrogen replacement therapy (caused by primary hypogonadism),
- postmenopausal hormone therapy (to reduce „hot flushes” and vaginal atrophy),
- contraception (in combination with progestins).
Adverse effects:  - uterine bleeding,
- risk of endometrial carcinoma,
- Nausea and breast tenderness,
- migraine headaches,
- cholestasis, gallbladder disease,
- hypertension.
Contraindications:  - estrogen-dependent neoplasms,
- undiagnosed genital bleeding,
- liver disease,
- history of thromboembolic disorder,
- heavy smokers.
3.2. Inhibitors and antagonists of estrogens:
- **Selective estrogen-receptor modulators:**
  - *Estrogen partial antagonist:* Tamoxifen, Toremifene
  - *Estrogen partial agonist-antagonist:* Raloxifene
  - *Estrogen partial agonist and inhibitor of endogenous estrogens:* Clomiphene
- **Estrogen receptor antagonist:** Fluvestrant
- **Inhibitors of aromatase:**
  - steroidal inhibitors: Testolactone (weak inhibitor),
  - nonsteroidal inhibitors: Anastrozole, Letrozole (selective inhibitors), Exemestane (irreversible inhibitor), Fadrazole

**Tamoxifen, Toremifene**
Mechanism of action: estrogen partial antagonist
Indications: breast cancer
Adverse effects: hot flushes, nausea, menstrual irregularities, vaginal bleeding.

**Raloxifene**
Mechanism of action: estrogen partial agonist-antagonist
Indications: osteoporosis and prevention of breast cancer in postmenopausal women.
Adverse effects: hot flushes, thrombosis.

**Clomiphene**
Mechanism of action: estrogen partial agonist and inhibitor of endogenous estrogens
Indications: induce ovulation.
Adverse effects: hot flushes, headache, enlargement of ovaries, multiple pregnancy.

**Fluvestrant**
Mechanism of action: estrogen receptor antagonist
Indications: breast cancer resistant to Tamoxifen

**Inhibitors of aromatase**
Classification: - steroidal inhibitors: Testolactone (weak inhibitor),
  - nonsteroidal inhibitors: Anastrozole, Letrozole (selective inhibitors), Exemestane (irreversible inhibitor), Fadrazole
Indications: breast cancer resistant to Tamoxifen

**Ovulation-inducing agents:**
- estrogen partial agonist and inhibitor of endogenous estrogens: Clomiphene
- menotropins (or human menopausal gonadotropin):
  - menotropins (hMG) is a purified extract of FSH and LH
  - urofollitropine (uFSH) is a purified preparation of human FSH
  - follitropin alpha (rFSH) is recombinant FSH
- human chorionic gonadotropin (hGC).
- synthetic gonadotropin: Gonadorelin
- GnRH antagonists: Cetrorelix acetate
Indications: induce ovulation.
Adverse effects: hot flushes, headache, enlargement of ovaries, multiple pregnancy.
Hormonal contraception.

Classification of hormonal contraceptives:

1. Chemical contraception in women:

1.1. Combinations of estrogens and progestins:

- Oral contraceptives:
  - Types of combinations:
    - monophasic (constant dosage of estrogens and progestins during the cycle)
    - biphasic (dosage of progestins is changed once during the cycle)
    - triphasic (dosage of one or both components are changed once or twice during the cycle)
  - contain:
    - Estrogens: Ethynil estradiol, Mestranol
    - Progestins: Norgestrel, Desogestrel, Norethindrone, Ethynodiol, Levonorgestrel, Lynestrenol, Noretynodrel, Norgestimate, Drospirenone
  - transdermal patch: Ethynyl estradiol + Norelgestromin
  - vaginal ring: Ethynyl estradiol + Etonorgestrel

1.2. Progestins only:

- Norethindrone, Norgestrel, Levonorgestrel.

2. Chemical contraception in men:

- Testosterone, Testosterone enantate
  - combinations: Testosterone + Danazol, androgens + progestins (Medroxyprogesterone acetate)
- Cyproterone acetate
- Gossypol
- Gn-RH analogues – in study.

Hormonal contraceptives in women are indicated for:

- contraception,
- endometriosis,
- menstrual disorders (severe dysmenorrhoea, premenstrual syndrome, menorrhagia),
- polycystic ovary syndrome,
- acne and hirsutism (those containing non-androgenic progestogens).

Progestogen-only oral contraceptives are indicated for women when an oestrogen component is contra-indicated.

Emergency contraception (postcoital contraception or “morning after pill”)
- is indicated within 72 hours of intercourse.
- prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function
- are used:
  - high doses of progestin (Levonorgestrel)
  - high doses of estrogens associated with progestins (Ethynylestradiol + Levonorgestrel)
  - Mifepristone (antagonist at progesterone and glucocorticoid receptors)

Adverse effects of oral contraceptives in women:

- severe adverse effects:
  - vascular effects: venous thromboembolic disease, myocardial infarction, cerebrovascular disease. This risk appears to be concentrated in women 35 years of age or older who are heavy smokers.
  - gastrointestinal disorders: cholestatic jaundice, gallbladder disease (including cholecystitis and cholangitis),
  - depression,
  - cancer: reduce the risk of endometrial and ovarian cancer, but increase the risk of cervical and breast cancer.
- **moderate adverse effects:**
  - breakthrough bleeding (most common for progestational agents alone),
  - breast fulness,
  - fluid retention (edema),
  - weight gain (common for combination containing androgen-like progestins: Norgestrel, Norethindrone, Ethynodiol, Levonorgestrel, Lynestrenol),
  - skin pigmentation (especially in dark-skinned women),
  - acne may be exacerbated by agents containing androgen-like progestins,
  - hirsutism (aggravated by the 19-nortestosterone derivatives: Norgestrel, Desogestrel, Norethindrone, Ethynodiol, Lynestrenol, Noretynodrel),
  - folic acid deficiency anemia,
  - vaginal infections,
  - amenorrhea (95% of patients \(\rightarrow\) for next few months, some \(\rightarrow\) for several years).

- **mild adverse effects:**
  - nausea, mastalgia, breakthrough bleeding, edema (related to the amount of estrogen),
  - headache,
  - changes in glucose tolerance,
  - oestrogen component increases triglycerides and HDL, but decreases LDL, whereas the progestogen component decreases HDL and increases LDL, particularly if it is androgenic.

**Contraindications of oral contraceptives in women:**
- pregnancy,
- thrombophlebitis, thromboembolic phenomena, cardiovascular and cerebrovascular disorders,
- estrogen-dependent neoplasm,
- liver disease, asthma, eczema, migraine, diabetes, hypertension, optic neuritis, retrobulbar neuritis, or convulsive disorders.

**Gossypol**
Mechanism of action: destroys elements of the seminiferous epithelium but does not alter the endocrine function of the testis.
Adverse effects: hipokaliemia (may lead to transient paralysis).
Hormones of the adrenal gland

The hormones of the adrenal gland:
- mineralocorticoid hormones (HMC) → zona glomerulosa;
- glucocorticoid hormones (hGC) → zona fasciculata;
- sex hormones → the zona reticularis.

The mechanisms of action: free hormones enter the cytosol → hormones cytosolic receptors couple to target cells (these receptors are related to a type of protein called "heat shock proteins" - "Hsp," that prevent complexation receptor nuclear sites) → hormones produce conformational changes of the receiver, the energy releasing, which detaches from the receivers Hsp proteins (particularly protein Hsp90) → complex form homodimers entering actively nucleus where it binds to the receptor sites for the glucocorticoid target gene (GRE) or other receptor sites of gene transcription → syntheses of specific proteins to the role of mediators.

Classification
• The natural glucocorticoids:
  - Cortisol
  - Hydrocortisone
• The glucocorticoid synthesis:
  2.1. Short term / medium duration of action:
    - hydrocortisone (hemisuccinate or the acetate);
    - Prednisone;
    - Methylprednisolone;
    - Meprednisone;
  2.2. medium duration of action:
    Glucocorticoid hormones
    - Triamcinolone
    - Paramethasone
    - Fluprednisolone
  2.3. long duration of action:
    - Betamethasone
    - Dexamethasone

Pharmacokinetics
- Administration → to the oral route by spraying the parenteral route, the topically, as ointments;
- secretion of glucocorticoid hormones → 20 mg / 24 hours (without stress) secretion is minimal after midnight;
- glucuronidation metabolism;
- the renal elimination.

The biological effects
a) Effects on metabolism:
- effects on carbohydrate metabolism:
  - glucocorticoids increases gluconeogenesis from protein;
  - glucocorticoids increase the deposition of glycogen in the liver;
Glucocorticoids increase blood glucose; glucocorticoids decrease the utilization of glucose in peripheral effects on lipid metabolism: Action permissive to the release of fatty acids from adipose tissue by catecholamines; the increase in lipid mobilization → changes in the distribution of adipose tissue; effects on protein metabolism: the increase in urogenèse; increase in the elimination of nitrogen; reduced affinity of insulin to insulin receptors; effects electrolyte metabolism: the increased sodium retention and the elimination of potassium, hypokalemic alkalosis l; channel setting to the elimination of water; the increase in renal elimination and reduction of intestinal calcium absorption.

b) The anti-inflammatory and immunosuppressive:
the increased synthesis of lipocortin macrocortine and → the inhibition of phospholipase A2 → the inhibition of lymphocytes, LTB4, others leukotrienes, prostaglandins, prostacyclins, thromboxanes (effects of the process inflammatory);
decrease in the number of circulating eosinophils and lymphocytes, particularly the number of Lyt;
the involution of the thymus and lymph nodes.

c) other effects:
the euphoria;
behavioral changes;
lower the threshold for seizures.

**Indications:**
a) replacement therapy:
Addison's disease;
the pituitary insufficiency;
adrenogenital syndrome.
b) therapy at doses large, supra-physiological
*o collagenosis:*
rheumatoid arthritis;
rheumatic fever;
polymyositis;
systemic lupus erythematosus;
ulcerative colitis;
polyarteritis nodosa dangerous;
the temporal arteritis, etc..
*o allergic diseases:*
allergic reactions to drugs;
contact dermatitis;
the angioedema (angioedema l);
allergic rhinitis;
the hives;
anaphylactic shock, etc..
eye diseases:
- the acute uveitis;
- allergic conjunctivitis;
- the choroiditis;
- optic neuritis;

gastrointestinal diseases:
- inflammatory gastrointestinal diseases;
- subacute hepatic necrosis;
- kidney disease:
  - nephrotic syndrome;

hematological diseases:
- idiopathic thrombocytopenic purpura;
- the autoimmune hemolytic anemia;
- leukemias;
- multiple myeloma;

pulmonary disease:
- the aspiration pneumonia;
- the bronchial asthma,
- syndrome respiratory distress in the newborn;

infections:
- septicemia with Gram-negative;

osteoarticular inflammation:
- arthritis;
- bursitis;
- tenosynovitis;

acute attack of gout;
post-traumatic lesions, cerebral edema s;

dermatological diseases:
- atopic dermatitis;
- dermatitis;
- seborrheic dermatitis;
- pemphigus vulgaris;
- psoriasis;
- mycosis fungoides;
- the eczema, etc..

cardiogenic shock and endotoxic shock;
hypercaldemia.

Contraindications:
- the peptic ulcer;
- diabetes mellitus;
- dyslipidemia;
- the osteoporosis;
- the hypertension +/- the heart failure;
- infections (herpetic lesions of the cornea);
- glaucoma;
psychoses;
children that the growth plates are not ossified.

Adverse reactions:
characteristic changes of hyperadrenocorticism: facies as "full moon", the hirsutism, acne, stretch marks, fatty deposits on the trunk, but not members;
the osteoporosis, loss of muscle mass;
the amenorrhea;
sodium retention, the hypertension, the worsening of heart failure;
dyslipidemia;
the necrotizing arteritis rheumatic patients, worsening the damage of cartilage growth, degeneration of the synovial folds;
diabetes mellitus (diabetes drug);
the gastro-intestinal ulcer;
the immunosuppression;
psychotic symptoms;
the atrophy of the adrenal gland;
the stunting among children.

Inhibitors of the synthesis of glucocorticoids and glucocorticoid antagonists

Classification
• inhibitors of the synthesis of glucocorticoids:
  metyrapone
  Aminoglutethimide
  Ketoconazole
  Mitotane
  Amphenone B
  Trilostane
  abiraterone
2. The glucocorticoid receptor antagonists
  Mifepristone

The pharmacological properties of inhibitors of the synthesis of glucocorticoids and glucocorticoid antagonists

Metyrapone
The mechanisms of action:
the inhibition of 11-hydroxylation at the adrenal → the inhibition of the production of cortisol and cortisone.

Indications:
diagnostic test for measurement of the ability of the anterior pituitary to the production of ACTH;
Cushing’s syndrome;
pituitary tumors;
syndrome ectopic ACTH secretion;
the adrenal hyperplasia;
the limitation of adverse effects of glucocorticoids;
the immunosuppression due to surgery or radiation therapy.

Adverse reactions:
minor side effects: dizziness, transient gastrointestinal disorders;
major adverse effects: edema (retention of sodium and water), the hirsutism.

Aminoglutethimide
The mechanisms of action: inhibition of the synthesis of all steroids.
Indications:
breast carcinoma (to decrease the production of estrogens and androgens);
association with Ketoconazole → Cushing's syndrome, adrenal cancer.

Ketoconazole
The drug is an enzyme inhibitor of drug metabolism.
Indications:
as antifungal;
as inhibitor of the synthesis of steroids;
Cushing’s syndrome.

Mitotane
Indications:
adrenocortical carcinoma.
Adverse reactions:
diarrhea, nausea, vomiting;
depression, drowsiness;
rashes.

Amphenone B
The mechanisms of action:
the inhibition of hydroxylation at position 11th, 17th and 21st.
Adverse reactions:
the increased production of ACTH;
the anterior pituitary hyperplasia;
deression;
for gastrointestinal disorders;
rashes;
disorders of liver function and thyroid function.

Trilostane
The mechanisms of action:
the inhibition of 3-beta hydroxysteroid dehydrogenase / isomerase of 5-4 at the adrenal → the inhibition of the production of mineralocorticoids and glucocorticoids.
Indications:
Cushing's syndrome;
the primary aldosteronism.
Adverse reactions:
for gastrointestinal disorders;
drowsiness.
Abiraterone
The drug is the latest inhibitors of steroid synthesis in clinical trials.
The mechanisms of action:
- the inhibition of the 17 α-hydroxylase (P450c17) and 17,20-lyase → decreased cortisol synthesis and gonadal steroids in steroids adrenal and gonadal steroids in the gonads.
Indications:
- abiraterone is a prodrug that is activated in the oral treatment of prostate cancer refractory to other treatments.

Mifepristone
The mechanisms of action → the partial agonist for the glucocorticoid receptor and progesterone.
Indications:
- Cushing's syndrome, as antiprogestin drug.

Mineralocorticoid hormones

Aldosterone, deoxycorticosterone (DOC)
factors that stimulate or regulate the secretion of aldosterone:
- ACTH;
- the hypovolemia by bleeding or dehydration by mass;
- receptor stimulation β1 - adrenergic presynaptic level of the renal juxaglomerular cells;
- diet without salt or salt restriction;
- the prolonged administration of diuretics that increase the elimination of Na + (thiazides, loop diuretics).
All these factors stimulate the synthesis and release of renin → the activation of the renin - angiotensin - aldosterone l.
The mechanisms of action → the mechanism of action is similar to that of glucocorticoid receptors in cytosolic and nuclear target cells (cells of the distal convoluted tubules, the loop of Henle, the cells of the epithelium carrier the urinary bladder and colon) → stimulation of Na + / K + - ATP - ase membrane → the passage of sodium ions in renal tubular cells, from the blood to the tubular space, the increased secretion of H + ions and K + in the peritubular space.
The pharmacokinetics of aldosterone
- secretion → daily 100-200 mg / 24 hours;
- hepatic metabolism → glucuronidation;
- the renal elimination in a partially unchanged;
- T1 / 2 = 15 - 20 minutes.
The excess aldosterone determines the following effects:
- the hyponatremia;
- the hypokalemia;
- the increase in plasma volume;
- the increase in blood pressure;
- edema;
- the hypokalemic metabolic alkalosis.
DOC:
The setting is made only of ACTH.

The substance is not influenced by the diet without salt or salt restriction.

The substance is released in large quantities in the adrenal carcinoma and hyperplasia in congenital adrenal.

T1/2 = 70 minutes.

In therapy → synthetic derivatives:

- deoxycorticosterone acetate (DOCA)
- Fludrocortisone

Indications:
- the lack of mineralocorticoid hormones;
- → Fludrocortisone treatment alternative to hypotension.

Adverse reactions:
- Fludrocortisone → high sodium retention.

mineralocorticoid antagonists

Classification

1. Competitive antagonists of aldosterone receptors
   1.1. Non-selective competitive antagonists of aldosterone receptors
       - Spironolactone
       - Prorenone

Mineralocorticoid antagonists

- Drosipirenone

1.2. Competitive antagonists selective for aldosterone receptor
    - Eplerenone

2. Physiological antagonists
   - Amiloride
   - Triamterene

Indications:
- as potassium-sparing diuretics;
- the primary and secondary hyperaldosteronism;
- Spironolactone → 1 congestive heart failure;
- drosipirenone → as an oral contraceptive.

The mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, contraindications, side effects → See chapter pharmacology of diuretic - potassium sparing diuretics.
Pancreatic hormones

Pancreatic hormones:
- Insulin - secreted by pancreatic beta cells;
- Glucagon - secreted by pancreatic alpha cells;
- insular amyloid polypeptide (IAPP) - secreted by pancreatic beta cells;
- Somatostatin - secreted by pancreatic delta cells;
- polypeptide hormone - secreted by pancreatic or liver cells.

Insulin

release is stimulated by:
- plasma glucose or other sugars;
- glucagon;
- amino acids (leucine, arginine);
- fatty acids;
- gastrointestinal hormones: gastrin, secretin, cholecystokinin, gastric inhibitory polypeptide (GIP) and enteroglucagon;
- beta2-adrenergic
- Sulphonylureas;
- ventrolaterale areas of CNS stimulation.

release is inhibited by:
- Somatostatin;
- diazoxide, minoxidil;
- phenytoin and other hydantoin;
- Vinblastine;
- Colchicine;
- presynaptic adrenergic alpha2 receptor agonists;
- alpha1 adrenergic receptor agonists;
- stimulation of ventro-medial areas of the CNS.

Insulin - mechanism of action

Insulin binds to a receptor on the cell surface enzyme to its target (liver, skeletal muscle, adipose tissue). This receptor is a glycoprotein composed of two subunits alpha and two beta subunits linked by disulfide bridges.
- alpha subunit coupling insulin activation of a tyrosine kinase receptor beta subunit structure portion autophosphorylation increases beta aggregation and stabilization of alpha and beta heterodimers activated state of the receptor tyrosine kinase phosphorylation as a result of repeated it activates a protein that is second messenger of biological signal transmission postreceptor.

Complex insulin - receptor is then internalized and then you dissolution occurs with insulin metabolism and recycling of cell surface receptors.

Insulin - mechanism of action (continued)

Elevated plasma insulin receptor causes down-regulation.
translocation and expression of glucose transporters to the cell surface is mediated calcium influx, while glucose transport is accomplished by activating adenylate cyclase.

glucocorticosteroids decrease its affinity insulin receptors, while growth hormone increases insulin affinity for these receptors.
There are 5 types of glucose transporters: GLUT-1 □ GLUT-5. Defect in GLUT-4 characterizes type 2 diabetes.

**Insulin - biological effects**
carbohydrate metabolism:
□ in the liver cells: decreases gliconeogeneza and glycogenolysis, increased glycolysis and glicogenogeneza;
□ in adipose tissue: increased glucose uptake, increased synthesis of glycerol;
□ the muscle tissue: increased glucose uptake, glycolysis, glicogenogeneza.
lipid metabolism:
□ in the liver cells: increased lipogenesis;
□ in adipose tissue: increased synthesis of triglycerides and fatty acids;
□ in muscle does not work.

Insulin - biological effects (continued)
metabolism protidic:
□ in the liver cells: cleavage of proteins decreases;
□ in adipose tissue does not act;
□ the muscle tissue: increased amino acid uptake and protein synthesis.

Other metabolic effects of insulin are:
□ increase in cell transport of K+, Ca2+, nucleosidelor and inorganic phosphate ion;
□ increase nucleic acids.

**Insulin Pharmacokinetics**
□ circulating free in plasma;
□ is degraded in acid;
□ t1/2 = 3-5 min;
□ is metabolized in the liver (predominantly endogenous insulin) and kidney (predominantly exogenous insulin).

Administration:
□ sc, iv infusion in a closed system, implantable pumps, external pumps, aerosol.

insulin species:
□ conventional preparations: the ox, pig, mixed (beef + pork)
□ human preparations: human insulin (recombinant DNA techniques, biosynthesis in E. coli), semi-synthetic insulin, human proinsulin (recombinant DNA techniques).

**Classification of insulin preparations**
ultra-fast acting insulin:
□ Insulin lispro;
□ Insulin aspart;
□ Insulin glulisine;
acting insulin: Insulin Regular;
intermediate-acting insulin:
□ Insulin slow;
Neutral protamine Hagedorn insulin □ (NPH Insulin or Insulin Isophane);
Long-acting Insulin;
Insulin glargine;
Insulin detemir.

Insulin combinations:
- 70% + 30% NPH Insulin Regular Insulin;
- 75% NPL insulin (neutral protamine lispro insulin) + 25% insulin lispro.

Pharmacokinetic features of insulin preparations

**Insulin**

**Indications:**
- diabetes type 1 (insulin-dependent patient, whose survival depends on exogenous insulin);
- type 2 diabetes who do not respond to oral agents because INFLUENCE stress, infection, surgery, pregnancy.

**Adverse effects:**
- hypoglycaemia;
- Type I immunological reactions (urticaria, anaphylaxis);
- insulin resistance (IgG antibodies antiinsulinici);
- Lipodystrophy at the injection site;
- Somogyi effect (nocturnal hyperglycemia);
- Dawn phenomenon (early morning hyperglycemia).

**Glucagon**

**Biological effects:**
- hyperglycemia, increased gluconeogenesis and ketogenesis;
- positive chronotropic and inotropic effect;
- intestinal smooth muscle relaxation.

**Indications:**
- in severe hypoglycemic states;
- poisoning with beta-blockers;
- cardiogenic shock;
- functional capacity for diagnosis of pancreatic beta cells and intestinal seating capacity.

**Adverse effects:**
- immediate-type immunologic reactions;
- abdominal discomfort, nausea, vomiting.

**Insular amyloid polypeptide (IAPP)**

Pramlintide
- Analog IAPP.
- Suitable: in emergencies, alternatively, in insulin-resistant diabetes.
Oral antidiabetics

Classification
4.1. Sulphonylurea:
   - Generation I: - tolbutamide
   - Chlorpropamide
   - Tolazamida
   - Acetohexamida
   - Generation II: - glyburide
   - Glipizid
   - Gliclazide
   - Glibenclamide
   - Glibormerid
   - Glisopexina
   - Gliquidona
   - Third Generation: - glimepiride.
4.2. Meglitinides: Repaglinide.
4.3. Phenylalanine derivatives: nateglinide.
4.4. Biguanides:
   - Feniletilbiguanide: Metformin.
   - Dimetilbiguanide: Fenformin.
   - Butilbiguanide: Buformin.
4.5. Alpha-glucosidase inhibitors: Acarbose, Miglitol, Vogliboza.
4.7. Aldozaeductaze inhibitors: Tolrestat.

4.1. Sulphonylurea
Mechanism of action: blocking receptor-dependent K+ channels.
Pharmacodynamic effects:
   - stimulating the release of insulin and somatostatin;
   - increase insulin receptor sensitivity in insulin target cells.
Generation I reduced hypoglycemic effect at the high dose, generation II and III increased hypoglycemic effect of low dose.
Indications: diabetes mellitus type 2 (treatment "traditional" choice in this type of diabetes).
Contraindications:
   - task;
   - renal failure;
   - hepatic impairment.
Adverse effects:
   - hypoglycemia;
   - Type I immunological reaction;

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teratogenicity;
- type Disulfiram-like effects;
- the Generation I:
  - diuretic (except chlorpropamide);
  - chlorpropamide: hyponatremia, transient leukopenia, thrombocytopenia, antidiuretic effect, jaundice, redness when combined with alcohol;
- the generation II: hepatotoxicity, nephrotoxicity.
NB: It is assumed that Ca\(^2\)\+ channel blockers could not antagonize effects of sulphonylureas. Diazoxide and minoxidil counteracts the effects of sulphonylureas.

4.2. Meglitinides: Repaglinide
Mechanisms of action:
- stimulate insulin secretion in a glucose-dependent mechanism;
- blocking K\(+\)-ATP channel-dependent membrane causing depolarization, opening of voltage-dependent Ca\(^2\)\+ channels by increasing intracellular Ca\(^2\)\+ influx, followed by the release of insulin;
- binding to sulfonylurea receptors in pancreatic beta cells (SUR1), but the other binding site.
Pharmacodynamic effects:
- Repaglinide induced insulin secretion appears early after drug administration and returned to baseline levels before the next dose.
Indication:
- Diabetes mellitus type 2 (uncontrolled by diet and exercise).
- type 2 diabetes patients found to failure after treatment with other oral antidiabetic agents.
Adverse effects:
- hypoglycemia;
- weight gain;
- nausea, diarrhea / constipation;
- arthralgia;
- headache;
- upper respiratory tract infections (sinusitis).

1.4. Biguanide
Metformin, Fenformin, Buformin
Are "euglicemiante" more than hypoglycemic.
Mechanism of action: decreases plasma glucose levels (not related to the presence of functional pancreatic beta cells).
Pharmacodynamic effects:
- slow intestinal glucose resorption;
- increase insulin binding to insulin receptors.
Pharmacodynamic effects:
- direct stimulation of glycolysis in tissues with increased glucose utilization in the periphery;
- decrease hepatic gluconeogenesis;
- reduce the absorption of glucose from the intestine;
- decreased plasma levels of glucagon.
Indications: diabetes mellitus type 2 (treatment "traditional" choice in this type of diabetes).
Contraindications:
alcoholism;
anoxic conditions (cardiovascular disease and chronic lung);
renal, hepatic;
elderly;
task.

Adverse effects:
lactic acidosis;
reduce the absorption of vitamin B12;
anorexia, nausea, vomiting, abdominal discomfort, diarrhea.

It is associated with generation sulphonylureas I.

1.5. Alpha-glucosidase inhibitors
Acarbose, Miglitol, Vogliboza
Mechanism of action:
by inhibiting alpha-glucosidase is delayed absorption of carbohydrates (dextrins, maltose, sucrrose, lactose not) of intestine reduces postprandial increase of blood glucose and increases the effect of insulin.

Adverse effects:
flatulence;
flatulence;
diarrhea.

It is associated with biguanides, sulfonylureas, insulin.

1.6. Thiazolidinediones
Troglitazone, pioglitazone, Englitazone, Ciglitazone, Rosiglitazone
Mechanism of action:
increased sensitivity to insulin receptor target cells.

Pharmacodynamic effects:
potentiates the action of insulin;
increase glucose uptake and glucose oxidation in muscle and adipose tissue;
reduce hepatic gluconeogenesis.

Indication:
type 2 diabetes;
patients resistant to therapy with insulin (common in patients with hypertension, hyperlipidemia, atherosclerosis);
prophylaxis to reduce the recurrence of diabetes in high-risk women with a history of gestational diabetes.

Adverse effects:
weight gain;
decrease in hemoglobin and hematocrit (dose-dependent);
changes in liver function tests (hepatotoxicity), abdominal pain, nausea, vomiting, anorexia, fatigue, or dark urine, increases in CPK and LDH are transient and have no pathological significance;
+ haemodilution fluid retention, peripheral edema;
other adverse effects (2% placebo): respiratory infections (11%), sinusitis, dental disease, headache, fatigue, dizziness, nausea, flatulence, constipation / diarrhea, visual disturbances,
arthralgia, pain in the back of the chest, myalgia, muscle cramps, numbness and tingling.

1.7. Inhibitors aldose reductase

Tolrestat

Mechanism of action:
- Aldose reductase is inhibited by inhibiting the conversion of glucose to fructose, and further, so the transformation of fructose into sorbitol enhances the toxic effects of glucose and increases the effect of insulin.

Indications: prevention or reduction of nephropathy, retinopathy, neuropathy in diabetes mellitus.

Side effects: nausea, vomiting.