Hormones

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HORMONES are body own substances, produced by endocrine glands which regulates biochemical processes.
HORMONES

- **use:**
  - *substitution drugs*
    - replace the missing hormone - insulin, menopause HRT
  - *drugs regulating endocrine and metabolic disorders*
    - treatment of osteoporosis by estrogens; p.o. contraceptives
  - *drugs regulating non-endocrine disorders*
    - treatment of bronchial asthma, immunosuppressants,
    - anti-inflammatory, anticancer
  - *diagnosis*
    - detecting the secretion of endocrine glands
      - administration of the parent hormone endocrine gland is to determine whether it is regulated by endocrine function
Regulatory Pathway of Tropic Hormones

- hypothalamus
  - releasing hormone (hormone 1)
    - pituitary gland
      - stimulating hormone (hormone 2)
        - target gland
          - target gland hormone (hormone 3)

Feedback inhibits release of hormone 1
Feedback inhibits release of hormone 2
Organs of the endocrine system (purple) and other organs containing tissues that secrete hormones (tan)

**Hypothalamus**
Secretes hormones involved with fluid balance, smooth muscle contraction, and the control of hormone secretion by the anterior pituitary gland.

**Pituitary Gland**
Secretes multiple hormones that regulate the endocrine activities of the adrenal cortex, thyroid gland, and reproductive organs, and a hormone that stimulates melanin production.

**Thyroid Gland**
Secretes hormones that affect metabolic rate and calcium levels in body fluids.

**Adrenal Glands**
Secrete hormones involved with mineral balance, metabolic control, and resistance to stress; the adrenal medullae release E and NE during sympathetic activation.

**Pancreas (Pancreatic Islets)**
Secretes hormones regulating the rate of glucose uptake and utilization by body tissues.

**Pineal Gland**
Secretes melatonin, which affects reproductive function and helps establish circadian (day/night) rhythms.

**Parathyroid Glands**
Secrete a hormone important to the regulation of calcium ion concentrations in body fluids.

**Organs with Secondary Endocrine Functions**
- **Heart**: Secretes hormones involved in the regulation of blood volume.
- **Thymus**: Secretes hormones involved in the stimulation and coordination of the immune response.
- **Digestive Tract**: Secretes numerous hormones involved in the coordination of system functions, glucose metabolism, and appetite.
- **Kidneys**: Secrete hormones that regulate blood cell production and the rates of calcium and phosphate absorption by the intestinal tract.
- **Gonads**: Secrete hormones affecting growth, metabolism, and sexual characteristics, as well as hormones coordinating the activities of organs in the reproductive system.
PEPTIDE HORMONES

- Building block of peptide hormones are **aminoacids**
- Except glycine, all proteinogenic **aminoacids** are L-enantiomers
Pituitary Hormones

• Anterior Pituitary
  – Growth hormone (GH)
    • stimulates growth
  – Corticotrophin (adrenocorticotropic hormone, ACTH)
    • regulate (stimulate) release of adrenal cortex hormones
  – Thyroid-stimulating hormone (TSH)
    • regulate (stimulate) release of thyroid hormones
  – Follicle-stimulating hormone (FSH)
    • female ovaries - stimulates follicle to mature an egg, estrogen production
    • male testes - stimulates sperm production
  – Luteinizing hormone (LH)
    • female ovaries - stimulates ovulation, progesterone production
    • male testes - stimulates testosterone production
  – Prolactin - Luteotropic hormone
    • mammary gland - milk secretion, growth of the mammary glands
    • corpus luteum formation, secretion of progesterone
    • support the growth of testicles and prostate
Pituitary Hormones

- Pineal gland (middle pituitary gland)
  - melanocyte-stimulating hormones (melanotropins, MSH)
    - produce melanin - causes decoloration of the skin and dark hair responsible for the activation of the melanocytes and formation of brown pigment
    - their antagonist is produced by the pineal gland hormone melatonin, which causes:
      1) shrinking the melanocytes, resulting in lightening the skin
      2) regulates the rhythm of sleep

- Posterior Pituitary
  - vasopressin – antidiuretic hormone (ADH)
    - in kidney - stimulates retention of water
  - oxytocin
    - uterus - stimulates contraction during labor
    - breast - stimulates contraction to express milk
Thyroid hormones

- thyroxine = levothyroxine (T4), triiodothyronine = liothyronine (T3)
- for their production is important iodine
- they increase tissue oxidation and basal metabolism
- effect: T3 >> T4
- in peripheral tissues, there is the conversion of T4 to T3

- hyperproduction of T4
  - Basedow syndrome (Graves disease)
  - increase in basal metabolism - weight loss

- hypoproduction of T4
  - insufficient production of hormones
  - therapy: substitution with thyroid hormones – T4

- hypoproduction from a iodine deficiency - treatment: iodine, iodides
  - Goitre disease
Antithyroid drugs

Hyperthyroidism is characterized by increased secretion of levothyroxine and liothyronine.

**Treatment:**
- a) surgery - removes part of the body
- b) radiotherapy radioiodine $\text{I}^{131}$
- c) therapy with Antithyroid drugs (thyreostatics)
  - reduce the formation of thyroid hormones

**SAR:** cyclic thioureides

- KClO$_4$
  - Potassium perchlorate

- carbimazole
- methimazole
- methylthiouracil
- propylthiouracil
Thyroid gland hormones

• regulation of Ca metabolism

• C - thyroid cells
  – calcitonin (polypeptide – 32 amino acids)
    • action – reduce the concentration of blood (Ca$^{2+}$)

• parathyroid glands
  – parathyroid hormone (polypeptide - 84 amino acids)
    • action - increase the concentration of blood (Ca$^{2+}$)
HORMONS of PANCREAS

• alfa – cells:
  – glucagon
    • antagonist of insulin
    • regulation of blood glucose: increase level of glucose

• beta – cells:
  – INSULIN
    • lowers levels of blood glucose and allows utilization of glucose by cells
**Insulin**

3D structure of insulin
- Chain A (21 AA) – blue colour
- Chain B (30 AA) – red colour

**Human insulin** – is a peptide (51 AA), formed by chain A (21 AA) and chain B (30 AA). Chains are connected by disulphide bond between A7 and B7 and between A20 and B19.

**Crystals of insulin**
INSULIN

• nomenclature by the speed of onset and duration of action
  – fast and short-acting insulins
    • aqueous solutions of crystalline insulin
  – moderately long-acting
    • suspension applied s.c. / i.m.
  – long-acting
    • suspension of crystals with a slow absorption s.c. / i.m.

• prolongation of insulin action

• complexes
  • zinc – insulin
  • protamine – zinc – insulin
  • isophan – insulin
  – amorphous insulin → faster onset of action
  – crystalline suspensions → slower onset of action
Insulin analogues

• insulin with rapid onset and short action
  – insulin aspart (NOVORAPID®, NOVOMIX®)
    • s.c. the effect occurs within 20 min, the maximum occurring at 1 h, 3-5 h (just before eating)
  – insulin lispro (HUMALOG®)
    • the effect occurs within 15 min, reaching a maximum within 1 h, it takes 2-5 h (just before eating)
  – insulin glulisine (APIDRA®)
    • faster onset and shorter effect than human

• insulins with delayed onset and longer action
  – insulin glargine (LANTUS®)
    • constant concentration of 24 hours
  – insulin detemir (LEVEMIR®)
    • under the effect of dose up to 24 h (daily dose 1/2x)
Oral antidiabetics – Biguanides

\[
\begin{align*}
&\text{NH} & & \text{NH} \\
&\text{C} & & \text{C} \\
&\text{N} & & \text{NH}_2 \\
&\text{CH}_3 & & \\
\end{align*}
\]

metformin

**Biguanides SAR**

N-alkylbiguanides:
- most active => N-methylbiguanide
- higher alkyl => activity decreases
Oral antidiabetics – Sulfonylureas

SAR

- hydrogen on sulfamoyl fragment is a requirement, its N-methylation interrupt activity
- \( R = \text{methyl/Cl/acyl} \)
  - change of this groups to another position, or their change for polar groups (\(-\text{OH/COOH}\)) cause dystherapeutically
- variability on N3-nitrogen sulfonylurea (\( R_1 \))
  - alkyl
  - cycloalkyl
  - N-heterocycles

Sulfonylureas

Gliclazide
Oral antidiabetics – Sulfonylureas

Sulfonylureas bind to an ATP-dependent $K^+(K_{ATP})$ channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated $Ca^{2+}$ channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro)insulin.
Oral antidiabetics - meglitinides

Repaglinide

Nateglinide
Oral antidiabetics - thiazolidinediones

SAR

- basic part is thiazolidin-2,4-dion with p-substituted benzyl on carbon atom at position 5
- different substituents on benzyl
  - useful are polar aromatic/heterocyclic systems

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated hemoglobin in the bloodstream.
Inhibitors of dipeptidyl-peptidase IV (DPP-IV)

Glucagon increases blood glucose levels, and DPP-4 inhibitors reduce glucagon and blood glucose levels. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.
Glucagon-like peptide-1 analog (Incretin mimetics)

- **Exenatide (Byetta)**
  - treatment of diabetes mellitus 2

- **Liraglutide**
  - Liraglutide is a long-acting acylated human glucagon-like peptide-1 (GLP-1) receptor agonist, with a 97% amino acid sequence identity to endogenous human GLP-1.
  - Like GLP-1, liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells.
  - Liraglutide increases intracellular cyclic AMP (cAMP), leading to insulin release in the presence of elevated glucose concentrations.

His-Gly-Glu-Gly-Thr-Phε-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Tip-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂
Steroid hormones

- the steroid nucleus is **gonane** (cyclopentanoperhydrophenanthrene)
- by substitution of gonan by one or two methyl C10 and C13, or ethyl or higher alkyl on C17 are formed basic structure s of the different types of steroids
- configuration of circles of all steroid hormones - trans-trans-trans (derivates of 5-alpha-gonane).
Estrogens

- Estrogens play a role:
  - In the development of the female reproductive system and creation of secondary sexual characteristics
  - Together with progesterone regulate the menstrual cycle, are essential for maintenance of pregnancy
  - Calcium metabolism affect the construction of bones, supports the production and storage subcutaneous fat, thereby providing a female body shape

- The use of estrogen:
  - Replacement therapy of estrogen deficiency caused by decrease of production (natural - menopause, artificially - surgery, the prevention of osteoporosis, often in combination with progestogens
NATURAL ESTROGENS AND THEIR DERIVATES

- low bioavailability
  - low solubility
  - bad absorption
  - fast first past effect
- prolongation of action
  - esterification of C_3 -OH and/or C_{17} -OH
- ↑↑ of p.o. activity
  - C_{17} ethynilation (blocking of metabolic deaktivation to estrone)
- p.o. effect is positively influenced by blocking of -OH with etheric bond
- substitution of estrane in another positions is not suitable

Estradiol

Estrone

Ethinylestradiol

Mestranol

Estriol
Syntetic estrogens

- diethylstilbestrol
  - **use**: prostate cancer
• **ANTIESTROGENS** (antagonists of the estrogen receptor)

**SAR:** high antiestrogenic activity
- alkaline-like substitution on the connecting bridge of phenyl
- Cl atom on clomifene can be substituted for \(-\text{CH}_2\text{CH}_3 / -\text{CH}_2\text{CH}_2\text{Cl}\)

• clomifene
  
  **use:** female infertility

• tamoxifen
  
  **use:** breast cancer

• raloxifene
  
  **use:** prevention of osteoporosis in postmenopausal women
  
  Selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast

• fulvestrant
  
  **use:** breast cancer (inj. monthly)
  
  **MOA:** degrading the estrogen receptor
Inhibitors of aromatase

- inhibition of **aromatase**
  (aromatization of ring A in the last phase of estrogens biosynthesis) = **blockade of estrogens synthesis**

- **use**: anticancer drugs (breast cancer)
- exemestane, formestane are covalently bounded to the enzyme = irreversible blockade

![Chemical structures of Aminoglutethimide, Letrozole, Anastrozole, Exemestane, Formestane]
Progestogens

- the second group of female sex hormones

Progesterone

- Is produced by the corpus luteum in ovaria
- with estrogen regulates female reproductive processes of the body, maintains pregnancy
- Its use is limited by short half-life, because when is administration p.o. is quickly reduced by first-pass metabolism to a pregnan-3,20-diol.

- use:
  - Together with estrogens are used as substitution drugs of different disorders of menstrual cycle
  - The hormone therapy of conditional cancer, especially breast cancer and cervical cancer
  - contraception
Progesterone and its pregnane analogues

- ↑ of activity by subst. on C₁₇ -OH (hydroxyprogesterone) / -CH₃, + carbon C₆ substituted by -CH₃ / -Cl (medroxyprogesterone), or + with double bond between C₆ a C₇

- analogues of 17-hydroxyprogesterone → esters, ↑lipophilicity markedly prolongate the effect

- for maintaining progestogens activity is not necessary on -CH₃ C₁₀ on bacis skeleton of pregnane

progesterone  17-hydroxyprogesterone caproate  chlormadinone-acetate

medroxyprogesterone  megestrol  dydrogesterone  nomegestrol-acetate
Derivates of testosterone and 19-nortestosterone (nandrolone)

**SAR** derived from norethisterone: androgenic activity suppresses by removing of methyl on C<sub>10</sub>

- C<sub>3</sub> -carbonyl is not provided, may be missing / replaced by -OH (-OH met. \(\rightarrow\) =O effective 3-oxo-compounds)

- optimal activity is linked to C<sub>17</sub> ethinyl substitution (norethisterone) as its replacement with ethylen enhances androgen and anabolic activity

- suitable is bioizosteric substitution by cyano-metyl group (**dienogest**)

- activity is not lossed, when double bond is transferred from C<sub>4</sub> to neighbor carbons, or the introduction of next conjugated double bond (**dienogest**)

- suitable is subst. of C<sub>7</sub> by -CH<sub>3</sub> / C<sub>11</sub> =CH<sub>2</sub> (methylene) (probably ↑ metab. stability)
Derivates of 13-ethyl-18,19-nortestosterone

- convenient substitute of C₁₃ -CH₃ → by ethyl
- without loss of activity is change of C₃ =O → to hydroxyimine-group
- metabolic sensitive carbonyl group on C₁₁ can be changed by methylene group
- activity does not interfere with the introduction of additional double bonds: double bond on C₁₅ levonorgestrel significantly increases activity (gestodene)
- levonorgestrel – active levorotatory enantiomer of norgestrel (C₁₃ carbon)
- usage: contraceptives, especially in combination with estrogens (especially ethinylestradiol)
Androgens

- Male sex hormones - control growth and development of male sexual characteristics, and functions of genital organs (spermatogenesis, potency, libido)
- The primary endogenous androgen testosterone is produced by testicles
- Testosterone is poorly absorbed after oral administration and is body rapidly metabolically degraded.
- Prolongation of its effect is achieved eg. By administration in the form of esters of fatty acids.
- Testosterone is in the body bound in 98% to a specific globulin (SHBG, sex hormone binding globulin).
- Testosterone induces effects by binding to the receptors.
- More efficient than Testosterone is only as dihydrotestosterone.
- Main effects of testosterone: ensuring gonadal function - androgenic effect
  stimulation of biosynthesis of proteins and protein increased growth of tissue - anabolic effect
testosterone  dihydrotestosterone
pharmaceutical researchers wanted separated these two main effects of androgens, but they were only partly successful, and therefore separation of male sex hormones to androgens and anabolic steroids is approximate only, according to predominant activity.

-substitution of testosterone by methyl on C$_{17}$ ensure better metabolic stability (methyltestosterone), also by subst. on C$_1$ was ensured better metabolic stability - mesterolone

Use of androgens:
androgen deficiency in men (infertility, male hypogonadism)
in oncology for breast cancer
Anabolics

- Androstane derivatives:
  - mestanolon, oxandrolone, oxymetholone, methandriol, metandienon, stanozolol

- 19-nortestosterone derivatives:
  - Nandrolone (19-nortestosteron)

- Anabolic androgens effects -
  - Positive nitrogen balance as a result of increased production of proteins and nucleic acids, retention of calcium ions, potassium and phosphate.
  - External expression of the anabolic effect is muscle growth.

- Use:
  - Disease states with a negative nitrogen balance, osteoporosis and regeneration after trauma and infections (e.g., poorly healing fractures) in oncology in breast cancer
  - Abuse by athletes, bodybuilders
• nandrolone is one of the chemical derivatives of 19-nortestosterone
• only nandrolone is used as a anabolic drug (in European Pharmacopoeia as nandrolone decanoate)
Antiandrogens

- binding in target organs, they block the effect of androgens. These drugs are used in androgen-dependent diseases, prostate cancer and Benign prostatic hyperplasia
- from a chemical point of view are non-steroidal and steroidal compounds character

Steroid compounds: cyproterone acetate

cyproterone acetate - an anti-androgen, which has also partial gestagenic action
- blocks the effect of testosterone by competitive antagonism on androgen receptor.

use:
- Men - to suppress the hypersexuality of deviants, cancer therapy prostate
- Women - hirsutism, acne, seborrhea
Non-steroidal compounds: flutamide, nilutamide, bicalutamide

Anti-androgenic effect is explained by the ability to inhibit intake androgens or inhibiting their bound in the target organs.

Unlike steroid cyproterone acetate, these drugs have no effect on testosterone levels, and therefore do not cause erectile dysfunction or loss of sexual interest (libido).

Use: prostate cancer
• Drugs used for treatement of benign prostatic hyperplasia
  (inhibitors of 5α-reductase)

  – in the development of prostatic hyperplasia have primary role the endogenous androgens
    testosterone and dihydrotestosterone. Testosterone in prostate cells transformed by 5-
    alpha -reductase enzyme to more effective dihydrotestosterone. Dihydrotestosterone
    bounded to the receptor induces proliferation of prostate tissue. Therefore, the
    preferably use drugs are selective inhibitors of 5-alpha reductase:

  • finasteride
  • dutasteride

![Chemical structures of finasteride and dutasteride]
Adrenal corticosteroids hormones

- corticosteroid hormones
  - Mineralocorticoids
  - Glucocorticoids
  - This division is only by dominant character of the effect.

- Production and secretion of corticosteroids in the adrenal cortex is stimulated by pituitary corticotropin hormone (adrenocorticotropin, ACTH). Substrate for their biosynthesis is cholesterol, from which the first phase of the side chain degradation occurs progesterone, a precursor of both types of steroids.
Biosynthesis of **Mineralocorticoids** takes place in the top layer of the adrenal cortex (zona glomerulosa)

- they provide the body's electrolyte balance by regulating the transport and excretion of ions of sodium, potassium, chloride and bicarbonate -> regulate the distribution of water in the tissues.
- they increase the absorption and excretion of sodium and potassium ions

![Chemical structures]

The strongest mineralocorticoid is the aldosterone, in the body occurs in equilibrium with half-acetal (masked free C11-hydroxyl group)

Use: low production of corticosteroids (Addison's disease)
Glucocorticoids

- biosynthesis of glucocorticoids takes place in the middle layer of the adrenal cortex (zona fasciculata)
- they regulate metabolism of carbohydrates, fats and proteins
- they increase gluconeogenesis, increase degradation of proteins (catabolic effect), increase blood glucose and glycogen formation in the liver.

- **Antiphlogistic** effect - reduce the formation of interleukins, interference with phospholipase A2, blocks the release of oxygen. arachidonic acid (precursor of inflammatory mediators, prostaglandins, leukotrienes),

- In therapy:
  - rheumatoid arthritis, inflammation locally in dermatology, ophthalmology, **otolaryngology**
  - Immunosuppressive - block proliferation of T-lymphocytes
**Glucocorticoids**

- Basic pregn-4-en-3-on skeleton of hydrocortisone has on C\textsubscript{11} subst. -OH / =O

- (an important finding was that, the introduction of the second double bond between carbons C1 and C2 results in pregnadien analogues, that have an even stronger effect of glucocorticoid)

**SAR  ↑↑ glucocorticoids activity:**

- second double-bond on C\textsubscript{1} → prednisone, prednisolone
  - subst. -F on C\textsubscript{6}/C\textsubscript{9} → der. of prednisolone
  - subst. -OH on C\textsubscript{16} → der. of triamcinolone
  - subst. -CH\textsubscript{3} on C\textsubscript{16} → der. of dexamethasone
Hydrocortisone and its derivates

- activity is not changed by subst. on C₆ with -CH₃
- activity is not changed by subst. on C₂₁ with -OH / -SH / -Cl
- subst. on C₆ / C₉ with -F → fludrokorzgR;wzon (15x ↑ glucocort. activity as hydrocortisone)
- der. HCZ – DERM- lipophilic esters 17-butyrate, 21-acetate; inj. 21-natrium-succinate

Hydrocortisone is the most important of the body's own glucocorticoid with partial mineralocorticoid activity

- Use of HTZ - substitution therapy for renal insufficiency, anti-inflammatory drug in ophthalmology, rheumatology and dermatology. Cortisone in the body is metabolized to active hydrocortisone.
Derivates of prednisolone

- **SAR:** advantage – methylsubstitution on C₆
  - suitable subst. C₆ / C₉ -F
  - possible is also modification of -OH on C₂₁ → removed, replaced by basic subst.
  - even deeper variations in subst. on C₁₇ dont influence the activity
  - prednisone is effective only after metabolic activation of prednisolone
- prednisolone has 4-5x ↑ glk. activity as hydrocortisone, is a moderate anti-inflammatory corticosteroid effective
Derivates of triamcinolone

- use:
  - triamcinolone (4/5 x more potent as hydrocortisone) = system (p.o.)
  - triamcinolone-acetonide (10x ↑ potent as triamcinolone)= dermatoses
  - budesonide, ciklesonide = allergies, rhinitis, asthma
Derivates of dexamethasone

SAR:

- possible replacement of $C_{16}$ methyl with methylene group $=CH_2$
- for the activity of „methasones“ is not necessary $C_{17}$ -OH (removing significantly change anti-inflammatory activity)
- possible modification of prim. alcohol group on $C_{21}$, that can be metabolised by oxidation
- possibility of condensation another ring on $C_2$ a $C_3$

- Use: dermatosis, arthritis, severe allergies, rhinitis, asthma

![Chemical structures of dexamethasone and its derivatives](image-url)