71. Principles of endocrine control systems.

72. Characterization of the hypothalamo-hypophyseal (neuroendocrine) system.

EXPLAINING ENDOCRINOLOGY

Arnold Adolf Berthold (1803-1861)
German physiologist

Berthold transplanted testes from intact birds into the capons’ abdomens, and showed that they redeveloped normal male characteristics. The testes had redeveloped their blood supply.

1902 Secretin
A scholar of ancient Greek suggested the word ‘ormao’, the Greek word for ‘excite’ – and thus the word ‘hormone’ entered the language.

THE HORMONE

William Bayliss (1860-1924)
Ernest Starling (1866-1927)
Hormones influence their target cells to respond in a specific way, to the benefit of the organism. It is part of the homeostatic response to an altered environment, whether external or internal.

„Chemical transmission” of information (almost all cells)
eg. adenosin → local vasodilatation

**Functions regulated by hormones:**

Metabolism
Adaptation to the environment (eg. stress)
Sexual functions
Growth
Signal transduction

**Endocrine System:**
- Effector cell
- Interleukin 1
- T-helper
- Interleukin 2
- B-lymphocyte
- + intracrine effect

**Paracrine System:**
- Synapse

**Autocrine System:**
- Macrophage
- Interleukin 4

**Immune System:**
- Endocrine system
- Nervous system
"Classic" endocrine glands

Anterior lobe of the pituitary gland (Adenohypophysis)

Thyroid gland
Parathyroid glands

"Diffuse" endocrine system

Central nervous system (Hypothalamus)

Thymus
Lung epithelial cells
Atrium of the heart
Kidney
Gastrointestinal tract
Fat tissue

Ovaries
Testes

Tissue hormones: prostaglandins

+ placenta
Chemical composition of hormones

1) Polypeptide and protein hormones (Glykoproteins)
   most hormones

2) Steroid hormones
   adrenal cortex, gonads, placenta, calcitriol

3) Amino acid (tyrosine)-derived hormones
   Catecholamines (adrenaline, noradrenaline, dopamine)
   Thyroid hormones (thyroxine, triiodothyronine)

Solubility of hormones

Water-soluble hormones: Polypeptide and protein hormones, catecholamines
Lipid-soluble hormones:Steroid hormones, thyroid hormones

Solubility of hormones determines their biological characteristics.
Biosynthesis of peptide hormones

DNA → mRNA → Preprohormone → Prohormone → Hormone
Insulin is released along with equimolar amounts of C-peptide. Concentration of C-peptide can be measured in the plasma. Its level provides an index of B cell function in patients receiving exogenous insulin.
1. Pre-pro-opiomelanocortin (POMC)

ACTH - Adrenocorticotropic hormone
MSH - Melanocyte-stimulating hormone
Biosynthesis of steroid hormones

Synthesis:
Smooth endoplasmic reticulum
Mitochondria

Enzymes:
Cytochrome P450
Hydroxysteroid dehydrogenases

DHEAS = Dehydroepiandrosterone sulfate
Cholesterol

Progesterone

Aldosterone

Cortisol

Testosterone

Estradiol
Sekretion of hormones

Polypeptide and protein hormones, catecholamines:
They are stored in vesicles, exocytosis results in expulsion of vesicle contents.

Lipophilic hormones:
They are synthesised on demand. Their release into the bloodstream is the consequence of the passive diffusion through the lipid membrane.

Cholesterol can be esterified and stored intracellularly in lipid droplets.

Thyroid hormones are stored in colloid.
Rhythm of hormone secretion

- **Minutes**: Circadian rhythm
  - Insulin
  - GnRH
  - Cortisol
  - STH
- **Hours**: Estradiol
  - LH
  - Testosterone
  - Growth hormone (GH)
  - Sleep
- **Weeks**: Ovulation
- **Lifespan**: Menstruation, LH, Estradiol
The half-life of a hormone in blood is defined as that period of time needed for its concentration to be reduced by half.

Hormone concentrations in the blood:
unstable $\approx 10^{-9} - 10^{-12}$ mol/l
It depends on the rate of production, secretion and degradation.

<table>
<thead>
<tr>
<th>Hormon</th>
<th>Proteinbindung (in %)</th>
<th>Halbwertszeit (in Minuten)</th>
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<tbody>
<tr>
<td>$T_4$</td>
<td>99,9</td>
<td>$\approx 10^4$ (7 Tage)</td>
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<tr>
<td>$T_3$</td>
<td></td>
<td>$\approx 1400$ (1 Tag)</td>
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<td>hCG</td>
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<tr>
<td>FSH</td>
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<td>ACTH</td>
<td>10</td>
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<td>Glucagon</td>
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<tr>
<td>ADH</td>
<td>$&lt; 1$</td>
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<td>Releasing/Inhibiting-Hormone</td>
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<td>Oxytocin</td>
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<tr>
<td>Adrenalin</td>
<td>$&lt; 2$</td>
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<tr>
<td>Bradykinin</td>
<td>$&lt; 1$</td>
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</tbody>
</table>
Measurement:
Bioassay

Radioimmunoassay (RIA)

Enzyme-linked immunosorbent assay (ELISA)
Activation of hormones in peripheral tissues

Thyroid hormones: Thyroxine $\rightarrow$ Triiodothyronine

Androgens: Testosterone $\rightarrow$ Dihydrotestosterone

Transport of hormones in the circulation

Water-soluble hormones: generally in a free form
Lipid-soluble hormones: free + protein-bound form

Transportproteins: prealbumin, albumin, globulins

Only free hormones are biologically active, but bound and free fractions are in equilibrium.
Breakdown of hormones

Liver, kidney (proteolysis of peptide hormones)
Liver (steroid hormones - reduction or conjugation with glucuronic acid)

Effects of hormones on target cells

Hormone receptor

1 hormone – more receptors (ADH – $V_1, V_2$)

1 receptor - more hormones

Autoantibodies (Basedow/Graves disease)
Hormone receptors:
1) Membranreceptors (Peptid- und Proteinhormone)
   - extracellular domain
   - membrane-spanning section
   - intracellular domain
2) Intracellular receptors of lipid-soluble hormones:

*in the cytoplasma* (glucocorticoids, mineralocorticoids, androgens, progesterone)

*in the nucleus* (thyroid hormones, calcitriol, estrogen)
General principle of negative feedback regulation

Increased blood glucose concentration

DIRECT NEGATIVE FEEDBACK

INTEGRATED STIMULUS

ENDOCRINE CELL

HORMONE

RESPONSE

(β-cell)

PANCREAS

Decreased blood glucose concentration

Increased glucose uptake by target cell (e.g. muscle cell)

Insulin
Negative feedback loops involving three endocrine glands

- **DIRECT NEGATIVE FEEDBACK**
  - Hormone A
  - Hormone B
  - Hormone C

- **INDIRECT NEGATIVE FEEDBACK**
  - Hypothalamus
  - CRH
  - Corticotropin (ACTH)
  - Adrenal cortex
  - Cortisol
Positive feedback regulation

Ovulation

LH (mU/ml)

menstruation

Estradiol

days

12–14

28
Neural control of endocrine functions

Autonomic innervation:
- direct
- regulation of blood flow

Neurosecretion:
hypothalamus, adrenal medulla

Permissive effect:
eg. requirement of glucocorticoids to be present for catecholamines to exert their effects.
Pathophysiology of hormone secretion

Hypofunction
Hormone or receptor?

Hyperfunction
- tumour
- stimulating autoantibodies
- disturbances of feedback regulation

Hormone therapy
Hormone replacement
Treatment
Glucocorticoids: anti-inflammatory and immunosuppressive agents
Estrogens, gestagens: hormonal contraception

Doping (growth hormone, androgens) side effects!
Hypothalamo-hypophyseal system

- **Portal vessels**
- **Circumventricular organs**
- **Adenohypophysis**
- **Neurohypophysis**
- **Hypothalamus**
- **Limbic system**
- **Third ventricle**
- **Eminentia mediana**
- **Releasing hormones**
- **Inhibiting hormones**

**Releasing hormones**
- GH
- ACTH
- TSH
- LH/FSH
- Prolactin

**Inhibiting hormones**
- Oxytocin
- ADH

**Autonomic function**
Hypothalamus

**Hypophysiotropic releasing and inhibiting hormones**
(Parvocellular neurons):
- Corticotropin-releasing hormone (CRH)
- Growth hormone-releasing hormone (GHRH)
- Gonadotropin-releasing hormone (GnRH)
- Thyrotropin-releasing hormone (TRH)
- Growth hormone-inhibiting hormone (Somatostatin)
- Prolactin-inhibiting hormone (Dopamine!)

**Supraoptic and Paraventricular nuclei**
(Magnocellular neurons):
- Vasopressin (Antidiuretic hormone - ADH)
- Oxytocin

**Other neuropeptides:**
- Enkephalin, Endorphin, Substance P, Calcitonin-gene related peptide etc.

**Adenohypophysis**

**Hormones acting on endocrine glands**
- Adrenocorticotropic hormone (ACTH)
- Thyroid-stimulating hormone (TSH)
- Gonadotropins: Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)

**2) Hormones acting on peripheral tissues**
- Growth hormone (GH)
- Prolactin (PRL)

**Neurohypophysis**

- 40% GH, 25% PRL
- 1 cell – 1 hormon (except for FSH/LH)