Receptor Biochemistry and Signal Transduction

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Organisation

Lecture: Tuesday 8.30-10.00 Beck-Sickinger

Seminar: Mo 17-18.30 or Mo 8.30-10.00
  Introduction + 7 seminars April/May/June
  Isabelle Ziffert, M. Sc. Biochem/
  Victoria Behr, M Sc Biochem/

Lab Course: 2.4.2019 - 18.4.2019; 10:30-17h
  Dr. Karin Mörl + PhD students

Exam: oral exam by arrangement: July-September
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<td>Mo 29.04.2019</td>
<td>Signaling Pathways and Signal Complexes</td>
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<td>Mo 06.05.2019</td>
<td>GPCR – Structural Features</td>
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<td>Mo 13.05.2019</td>
<td>Ligand Design</td>
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<td>Crosstalk – Transactivation</td>
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<td>Receptor Internalization and Membrane Trafficking</td>
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<td>Mo 03.06.2019</td>
<td>Cancer and Inflammation</td>
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<td>Doping / Drugs-Biased-Signaling</td>
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Block Lecture

01.04. - 02.04.2019: Brüderstr 34

Mo 08:30-10:00 BeckmHS, EG
Mo 10:15-11:45 BeckmHS, EG
Mo 15:15-16:45 BeckmHS, EG
Tu 08:30-10:00 KHBBr, floor 2
Tu 10:30-12:00 KHBBr, floor 2

9. 4. 2019 – 4. 6. 2019 8:30-10:00 small lecture hall, Brü 34, floor 2

Script can be downloaded from: Campus online
https://biochemie.biphaps.uni-leipzig.de/en/study/
Login: students
Passwd: BCh18COnLine!!
Literature and used text books

Gerhard Krauss
Biochemistry of Signal Transduction and Regulation

Donald Voet, Judith G. Voet, Charlotte W. Pratt
Lehrbuch der Biochemie

Alberts et al.
Molekularbiologie der Zelle
Wiley-VCH, ISBN-10: 3-527-30492-4

Latest references and reviews
Receptor Biochemistry and Signal Transduction

1. Hormone, Transmitter, Cytokine
2. Introduction to Signal Transduction
3. Different Types of Receptors
4. Methods to Study and Investigate Receptors
5. Channels and Transporter
6. Cell Adhesion Molecules
7. Proteolytic Cleavage Signals
Hormone, Transmitter, Cytokine

Ernest Henry Starling
(* 17. April 1866; † 2. Mai 1927)
Engl. Physiologist,
Introduced in 1905 the name „hormone“.
Hormone (griech. ὁ ρόμαω hormáω „to push, to activate“).

He discovered that the gut releases a compound after HCl incubation, that stimulates the pancreas. He called the compound „secretine“

secretine


Isolated: 1961: Jorpes/Mutt (Karolinska Institut, Stockholm) 1 g from 1 km intestine
Confirmed by synthesis: 1967 M. Bodansky
Biochemical signals
transmit information between cells
intercellular within tissue
between neuronal cells via synapses
via gland/blood system

Accordingly, no difference between transmitter and hormone...
Classification

- Hormone production and release
- Chemical classes
- Hormone function/endocrinology
- Hormone receptors
Endocrinology


Hormones regulate
- Metabolism of carbohydrates and fat
- Regulation of food intake
- Regulation of sexual hormones
- Regulation of bone metabolism
- Anxiety and stress
- thyrotrope cycles
Hormone producing cells

- **Gland cells of** (pituitary gland, pineal gland, thyroid gland, adrenal gland, pancreas)
- **Sexual glands** (Theca- and Granulosa-cells in women and Leydig-cells in men)
- **Nerve cells** (Neurohormones, Transmitters)
- **Liver** (Angiotensin-precursor)
- **Gastro-intestinal tract (GI)**
- **Adipocytes**

**Responsible:**
**Specific enzyme pattern of each cell**
Hormone producing cells
Hypothalamus and RH

1. Hypothalamus produces releasing hormones (RH) and inhibiting hormones (IH) that directly influence anterior pituitary hormone secretion.

2. Hypothalamus produces two hormones (oxytocin and antidiuretic hormone) that are stored in the posterior pituitary.

3. Hypothalamus oversees the ANS, thereby helping to stimulate the adrenal medulla via sympathetic innervation.

Sympathetic preganglionic axons

Anterior pituitary

Posterior pituitary

Adrenal gland

Adrenal medulla

Secretion of epinephrine and norepinephrine
Pituitary Gland

Anterior lobe: LH/FSH, ACTH, Prolactin, GH, TSH
Posterior lobe: oxytocin, vasopressin
Released from nerve terminals
Thyroid Glands

Regulate the metabolic activity of the body
Feedback Loops

- Hypothalamus releases TRH
- Anterior pituitary releases TSH
- Thyroid gland releases T3 and T4

**HOMEOSTASIS DISTURBED**
- Decreased T3, T4 concentration in blood or low body temperature

**HOMEOSTASIS RESTORED**
- Increased T3 and T4 concentration in the blood
Pineal Gland and Melatonin

- Melatonin regulates the body's internal sleep-wake clock.
- Sleep-wake cycle influences hormonal secretions.

Numerous other inputs:
- Inhibits hypothalamic hormones.
- Inhibits ACTH & GH.

Hypothalamus:
- Regulates body's internal sleep-wake clock.

Growth hormone (GH):
- ACTH
- Liver
- IGF-1

Cortisol:
- DHEA
- Adrenal glands

Liver:
- Inhibits hypothalamic hormones

Pituitary gland:
- Growth hormone (GH)

Plasma and urine melatonin levels:
- Melatonin degradation

Graph showing melatonin levels in plasma and urine throughout the day.
Parathyroid Gland

Parathyroid hormone (PTH)
- most important endocrine regulator of calcium and phosphorus concentration in extracellular fluid
- opposite effect of calcitonin.
- stimulates osteoclasts which increases blood calcium levels.
- causes reabsorption of Ca$^{2+}$ from kidneys so it is not excreted in the urine
- stimulates synthesis of calcitriol (hormone made in the kidney which the active form of Vitamin D which increases Ca$^{2+}$ absorption from small intestine
Adrenal Gland

**Short-term stress response**
1. Glycogen broken down to glucose; increased blood glucose
2. Increased blood pressure
3. Increased breathing rate
4. Increased metabolic rate
5. Change in blood-flow patterns, leading to increased alertness and decreased digestive and kidney activity

**Long-term stress response**

**Mineralocorticoids**
1. Retention of sodium ions and water by kidneys
2. Increased blood volume and blood pressure

**Glucocorticoids**
1. Proteins and fats broken down and converted to glucose, leading to increased blood glucose
2. Immune system may be suppressed
Pancreas

Acini: Digestive enzymes
Islet of Langerhans: Hormones

They contain four types of cells - alpha, beta, delta and PP (pancreatic polypeptide) cells.
The alpha cells secrete glucagon: increases the level of blood sugar.
The beta cells secrete insulin: uptake of glucose.
The delta cells secrete somatostatin. It inhibits the release of other.
Pancreatic polypeptide inhibits food intake.
Tissue derived hormones

**Neuro hormones/neurotransmitters:** released from neurones
**Gut hormones:** regulate food intake
Hormones from kidney, heart, lung, etc.
**Cytokines** released from leukocytes
Adipose tissue releases **adipokines**
Chemical Classes of Hormones

Protein- und Peptidhormone

- **Neuropeptides of Hypothalamus**
  - Release hormones LH/FSH, TSH, ACTH, GH
  - Somatostatin
  - Agouti-related Peptid
  - Neuropeptide Y
  - Leptin
  - Ghrelin

- **Glycoproteinhormones of pituitary gland:**
  - Follikelstimulating Hormone Follitropin (FSH)
  - Luteinazing Hormon Luteotropin (LH)
  - Thyreotropin (TSH)
  - Adrenocorticotropin (ACTH)

- **additional hormones of the pituitary gland:**
  - Growth hormones: GH
  - Prolactin
  - Melanocyte stimulating hormone (MSH)
  - Galanin
  - Kisspeptin
Chemical Classes of Hormones

- Neuropeptide der Neuro pituitary gland:
  ~ Adiuretin (Vasopressin)
  ~ Oxytocin

- Hormone of the parathyroid gland
  ~ Parathormon
  ~ Calcitonin

- Hormone of the heart
  ~ Atrial-Natriuretic Peptide (ANP)

- Peptide hormones of the liver
  ~ Insulin-like growth factor (IGF)

- Proteine hormone of gonades
  ~ Inhibin und Aktivin
Chemical Classes of Hormones

- **Hormone of the pancreas:**
  - Insulin
  - Glucagon
  - Somatostatin (SST)
  - Pancreatic Polypeptide (PP)

- **Peptide hormones of the GI**
  - Cholecystokinin (CCK)
  - Secretin
  - Gastrin
  - Ghrelin
  - Vasoactive intestinale Peptide (VIP)
  - Gastro-inhibitoric Peptide (GIP)
  - Peptid Tyrosyl-Tyrosin (PYY)
Chemical Classes of Hormones

Amino acid derivatives
- Catecholamine
  - Adrenalin /Epinephrine
  - Noradrenalin /Norepinephrine
  - Dopamine
- Thyroxin (T4) and Triiodthyronin (T3)
- Serotonin und Melatonin

Steroidhormones
- Mineralocorticoids – as Aldosteron
- Glucocorticoids – as Cortisol
- Estrogenes – as Estradiol
- Gestagenea – as Progesteron
- Androgenea – as Testosteron

Arachidonic acid derivatives (Eicosanoide)
- Prostaglandine
- Leukotriene
- Thromboxane
Biosynthesis of Hormones

- Protein biosynthesis (ribosomal)
- Signalpeptide for translocation to ER
- Posttranslational Modification
  - proteolytic cleavage (MSH)
  - Disulfide bridges (Oxitocin, Insulin)
  - Glycosylation (TSH)
  - Sulfatation (CCK, gastrin)
  - Lipidisation (Ghrelin)
  - C-terminal Amidation (NPY, PP)
- Secretion by vesicles
Continuous and regulated release
Proopiomelanocortin
Biosynthesis of Angiotensin

Angiotensinogen
- Produced by liver
- α2 Globular protein

Renin
- Mainly kidney
- Aspartic acid protease

Angiotensin I
- Decapeptide

ACE inhibitor

Angiotensin converting enzyme
- Zn metalloprotease

Angiotensin II
- Octapeptide

Bradykinin

AT II antagonist

Angiotensin II

AT II receptors

Inactive products
Biosynthesis of Neuropeptide Y

Signal sequence (28 aa) \[ \rightarrow \] NPY (36 aa) \[ \rightarrow \] C-flanking peptide of NPY (33 aa)

Signal peptide

ProNPy

Prohormon convertase (PC1/3, PC2)

Carboxypeptidase B-like Enzyme

Peptidylglycine-α-amidating-monooxygenase (PAM)

NPY
C-terminal Amidation

C-terminal amidation of peptides: oxidative

Peptide\(\text{NH}_2\) \(\text{CO}\) \(\text{O}^-\)
\(\widehat{\text{H}_2\text{H}_2}\)
\(\text{PHM (Cu}^{1+}\)\)

Peptidyl-\(\alpha\)-OH-Gly

\(\text{O}_2\)
\(\text{H}_2\text{O}\)

\(\text{H}^+\)
\(\text{H}_2\text{O}\)

Peptide\(\text{NH}_2\) \(\text{CO}\) \(\text{O}^-\)

PAL:
peptidylamidoglycollate lyase

irreversible

Peptidylglycine-\(\alpha\)-hydroxylating monooxidase (PHM)
Biosynthesis of non-protein hormones

• Amino acid derivates
  – Decarboxylation of amino acids
  – Thyroid hormones (Tyr)
  – Catecholamine

• Steroid-Biosynthesis

• Eicosanoid-Biosynthesis
Amino acid derivatives

L-Tryptophan

O₂, Tetrahydrobiopterin

L-Tryptophan-5-Monoxygenase bzw.
Tryptophan-Hydroxylase (TPH)

Hydroxytetrahydrobiopterin

5-Hydroxy-L-Tryptophan (5-HTP)

Pyridoxal-phosphat

5-Hydroxy-Tryptophan-Decarboxylase bzw.
Aromatische-L-Aminosäure-Decarboxylase

Serotonin (5-HT)
Amino acid derivatives

- Serotonin (5-Hydroxytryptamine)
  - Arylalkylamine / N-Acetyltransferase (AANAT)
  - N-Acetylserotonin (N-Acetyl 5-hydroxytryptamine)
    - Hydroxyindole-O-methyltransferase (HIOMT)
    - Melatonin (N-Acetyl 5-methoxytryptamine)
Thyroid Gland Hormones

- Uptake of iodid by sodium/iodid transporter (cotransport)
- Thyreoperoxidase (TPO, Iodid-Peroxidase, or Iodid-hydrogenperoxide-Oxidoreductase) catalyzes introduction of iodid

\[
\begin{align*}
2 \text{ HO-CONH}_{3} & + 2 I^- + \text{H}_2\text{O}_2 \rightarrow 2 \text{ HO-CONH}_{3} & + 2 \text{H}_2\text{O} \\
2 \text{ HO-CONH}_{3} & + 2 I^- + \text{H}_2\text{O}_2 \rightarrow 2 \text{ HO-CONH}_{3} & + 2 \text{H}_2\text{O}
\end{align*}
\]

Iodid is oxidized to iodine, which immediately substitutes at tyrosine

Iodid is oxidized to iodine, which immediately substitutes at 3-I-tyrosine
Thyroid Gland Hormones

Why Iodination?

90 °-angle of aromatic rings lead to unique structure
Catecholamine