PHYSIOLOGY OF THE GASTROINTESTINAL TRACT (GIT)

Main function: The GIT provides the body with a supply of water, nutrients, electrolytes, vitamines.

Actions:

1) Digestion of the food
2) Absorption of the products of digestion

Ad 1) Digestive processes: - mechanical
- chemical

Mechanical methods: - mastication (chewing)
- swallowing (deglutition)
- movements of the GIT (motor functions)

Chemical means (secretions): - saliva
- gastric juice
- pancreatic juice
- intestinal juice
- bile

PHYSIOLOGY OF MOUTH

Functions:
1/ Mechanical and chemical digestion of the food
2/ The source of the unconditioned reflexes
3/ Control of physical and chemical properties of the food

Ad 1 a Mechanical activity – mastication
The anterior teeth – a cutting action
The posterior teeth – a grinding action

Thee maximal **closing force** - incissors 15 kg
- mollars 50 kg

Inervations of the muscles of chewing – 5th, 8th, 12th cranial nerves
Centers – near the brain stem and cerebral cortex centers for taste

Act of mastication:
The movement of the lower jaw down:
- Contraction of m. biventer mandibulae (m.digastricus), m. pterygoideus ext., m.m. infrahyoidei →

The movement – up: *the drop initiates a stretch reflex*
Contraction of m. masseter, m. temporalis, m. pterygoideus
Rebound of antagonists- inhibition – the jaw drops +
compression of the bolus of the food against the linings of the mouth - rebound – repetitive actions.....
Mastication reflexive and voluntary
Function of the mastication: - grinding the food
- mixing with saliva
- prevention of excoriation of GIT
- makes easy swalowing

- aids subsequent digestion

SALIVATION

Ad 1 b) Adjustment of the food by the saliva

The salivary glands: - parotid
- submandibular
- sublingual
- buccal

Secretion of the saliva: - basal - 800 – 1500 ml/day
- during intake of food

Regulation of salivary secretion
– nervous - parasympathetic
- sympathetic

Unconditioned reflexes:
Taste and tactile stimuli increase 8-20 times the basal rate of secretion
Conditioned reflexes:
Visual, olphactoric, acoustic stimuli
Centers: salivatory nuclei (at the juncture of the medulla and pons):
superior – submandibular (70%), sublingual (5%)
inferior – parotid (serous saliva)

Parasympathetic nerves: n.VII, n.IX – stimulation of the salivation.
Parasympathetic nerves – acetylcholine – kallikrein – alpha 2 globuline (plasma) – bradykinine – vasodilatation – stimulation of the secretion of saliva (serous)

Sympathetic nerves: stimulation of the secretion of the mucinous saliva

Composition of the saliva

99.5 % - water; 0.5 % substances – organic – 0.3 %
- anorganic – 0.5 %

Organic substances: Mucin, digestive enzymes – ptyalin, lingual lipase, proteolytic enzymes, cytochromoxidase, carbanhydrase, phosphatase, IgA, lysozyme, blood groups s....
Cells: leukocytes,epithelial cells,...
Anorganic substances: Na^+, K^+, Cl^-, HCO_3^-

Functions of saliva

Saliva - keeps the mouth moist, aids speech
- facilitates swallowing
- serves as a solvent for the molecules that stimulate the taste buds
- serves a solvent for irritating foods - helps wash away the pathogenetic bacteria,
- destroy bacteria (thiocyanate ions, proteolytic enzymes),by proteins antibodies

can destroy oral bacteria, lysozyme = antibacterial
- keeps the mouth and teeth clean

Deficient salivation = xerostomia

Swallowing (Deglutition)

Three stages:

1) **oral** – voluntary – the food is squeezed into the pharynx by tongue
2) **pharyngeal** – automatic – cannot be stopped (1 s)

Involuntary contraction in the pharyngeal muscles – that pushes the food into the oesophagus.
Concomitant actions: Inhibition of respiration, closing of the posterior nares by the soft palate, pulling the larynx upward (enlargement the opening of the oesophagus), glottic closure

Control of the pharyngeal stage of swallowing -**swallowing reflex**:
Swallowing center – in the medulla and lower pons
Afferent nerves – Vth, VIIth, IXth, Xth
Coordination of the swallowing with respiration

3) oesophageal stage of swallowing:

Oesophagus - the first third striated muscle
- the last third smooth muscle
- the middle – mixed

Innervation – n. vagus, sympathetic nerves and others endings
Function – to transport food from the pharynx to the stomach by gravity and by peristalsis

Peristalsis – primary = a continuation of the peristaltic wave from pharynx
- secondary waves result from distention of the oesophagus by the retained food. Speed 4 cm/s

The swallowing time – for a compact food 6-9 s
a fluid 4-5 s

Regulation of the oesophageal peristalsis:
- by intrinsic neural circuits – myenteric and submucosal plexus
- by vagal efferent fibers

Functions of the upper and lower oesophageal sphincters
Upper – pharyngoesophageal junction – 3 cm segment – with high resting tone – relaxes reflexly upon swallowing
Lower – cardia – sphincter cardiae – 2-5 cm above the juncture of the oesophagus with the stomach. Circular muscle – tonically constricted.
Receptive relaxation – allows propulsion of the swallowed food into the stomach. The relaxation through VIP.

Disorders of the swallowing:
- **dysphagia** – pain

- **achalasia** – weak oesoph. peristalsis, accumulation of the food in the oesophagus – dilatation, increased tonus of cardiae. Pneumatic dilatation or myotomy
  - lower oes. sphincter incompetence – **gastrooesophageal reflux** (GER). Surgical treatment.

STOMACH

Anatomy and histology

- Cardia
- Fundus
- Corpus
- Antrum
- Pyloric sphincter

The smooth layers: - longitudinal – ext.
- circular - med.
- transversal - int.

Each muscle layer functions as a syncytium – gap junctions

Innervation: - myenteric plexus – outer between the longitudinal and circular layers
- submucosal plexus – inner

Vagal and sympathetic control

Gastric motility

The motor functions of the stomach:
1) storage of food
2) mixing – " – with gastric secretions – semifluid form – chyme
3) emptying of the food into duodenum

1) Storage: receptive relaxation of the stomach (P = 6 mmHg) by
   - a plasticity of the smooth muscle layers
   - nervous action – reduction of vagal tone
   - humorally (gastrin)

Food forms concentric circles. A limit about 1.5 l.

Storage time: Fats – 6 hours, proteins – 4 hours,
sacharides – 2 hours

2) Mixing: Gastric slow waves – basal electric rhythm – 3/min – pacemaker cells – the circular smooth muscle of the fundus
Velocity – 1- 4 cm/s – weak propulsion to move the chyme toward the antrum.
Raising intensity – peristaltic constrictor rings.

Hunger contractions – when the stomach is empty fora long time (12 hours ...) – intensive contractions – most intense in young people – feeling of hunger – regulation of the food intake.

3) emptying of the stomach

Antral peristaltic contractions – P – 50-70 mmHg pressure against the pylorus.
Pylorus – circular muscle –sphincter – receptive relaxation - after passage of a bolus – contraction – pyloric pump.

Regulation of the emptying:

- **Stretching** of the stomach wall peristalsis inhibits the pylorus
- **Gastrin** – stimulates gastric motility. Acid in the antrum (G-cells) inhibits gastrin secretion – a negative feedback. It enhances the activity of the pyloric pump.
- Duodenal factors:
Enterogastric reflex – distention of the duodenum, activity of „duodenal osmoreceptors" – inhitition in gastric motility through the enteric nervous system

Hormonal feedback – the stimulus – mainly fats in the duodenum hormones:
GIP, CCK – a competitive inhibitor of the gastrin

Disturbances of the gastric emptying
Pylorostenosis – congenital – hypertrophy of the circular layer. Incidence 1:200- boys, 1:800- girls
Symptoms – vomiting – metabolic alkalosis, dehydratation Treatment – surgical – myotomy

Pylorospasm – functional – hyperexcitability of parasympathetics. Symptoms –like pylorostenosis
Treatment – anticholinergic drugs (atropine)

V o m i t i n g

Expulsion of the gastric – gut contents through oesophagus and mouth/nose out.
Vomiting: - peripheral
- central
1) Peripheral: protective reflex against:
- a presence of irritants in the GIT
- an overdistention of GIT
The most sensitive portion – duodenum

2) Central: effect of some drugs (emetic) – e.g. apomorphine, emetin, nikotine, digoxine or hypoxia, ischemia, bacterial endotoxines on the cells of the chemoreceptor trigger zone (near the area postrema). Psychic influences.

The vomiting centre – CNS – RF lies near the tractus solitarius
The vomiting act
Nausea – subjective feeling – a necessity to vomit, pale, sweating, salivation – hyperactivity of the autonomic nervous system
Antiperistalsis of the small intestine, pyloroconstriction, stomach is relaxed.

The vomiting act:
1) a deep inspiratory breath
2) closing of the glottis
3) lifting of the soft palate

4) strong downward contraction of the diaphragm along with contraction of all the abdominal muscles – squeezing the stomach, intragastric P to a high level.
5) Contraction of the stomach, relaxation of the lower oes. sphincter – expulsion of the gastric content through a passive oesophagus.

Complications – alkalosis, dehydration ...

Gastric secretion

2.5 – 3 l of gastric juice daily

Components: - Hydrochloric acid (HCl) – parietal cells
- Pepsinogens – pepsins – chief cells
- Lipase
- Intrinsic factor – parietal cells
- Mucus – neck cells

1) **Hydrochloric acid secretion**
Acid solution containing 150-160 mmols/l, pH = 0.8 – 1.0

a) Cl^- is actively transported from the cytoplasm of the parietal cells into the lumen of canaliculus
b) H_2O is dissociated into hydrogen and hydroxyl ions in the cell cytoplasm. H^+ ions are actively secreted into the canaliculus in exchange for potassium ions.

$$H^+ + Cl^- \Rightarrow HCl$$

HCl – free and attached to the mucin and proteins

Functions of HCl in gastric juice:
1) Activation of pepsinogen
2) Coagulation of proteins
3) Change ferric state of iron (Fe^{3+}) to ferrous form (Fe^{2+}) – for absorption – with ascorbic acid
4) Antibacterial effect

Pepsin:
The chief cells → pepsinogens (precursors) without digestive activity
Pepsinogen + HCl – pepsin – active proteolytic enzyme (and + active pepsin); pH optimum 1.8 – 3.5
Derivates: - Pepsin C (gastricsin, cathepsin) – pH opt. 3.8 – 4.7 in newborns and sucklings
- Chymosin – pH 5.3 – milk

Lipase:
Carnivores – fatsplitting action

Intrinsic factor:
The parietal cells. Glycoprotein.
Essential for aabsorption of vit. B_{12} from distal ileum. B_{12} – for erythropoesis.
Pernicious anemia with megaloblasts.

Mucus:
Neck and surface mucous cells (pyloric mucosa). Glycoprotein.

Film 0.5 – 1.5 mm. pH 7.0. HCO_3^-

Regulation of gastric secretion

Local, neural and humoral mechanisms
Phases: Cephalic, gastric, intestinal

1) Cephalic phase:
Unconditioned reflexes – tactile and chemical stimuli in the mouth
Conditioned reflexes – the sight, smell, acoustic stimuli, phantasy ...
via the dorsal motor nuclei to the vagi – vagal afferent pathway to the gastric glands
Cephalic phase is responsible for 1/3 –1/2 the gastric secretion

2) Gastric phase:
Contact of the food with the gastric mucosa
Intake ⇒ the distention – mechanoreceptors – release of the gastrin from G-cells
⇒ the increase of pH – the release of the gastrin
(The decrease of pH – inhibition of the gastrin secretion)

3) Intestinal phase:
Inhibitory influences:
The presence of AA, fats ... secretion of GIP, VIP and secretion – GIT hormones – blood – inhibition of the gastric secretion

Drugs that influence gastric secretion
Histamine – (H_2 receptors) – cAMP
Alcohol, coffeine
ACTH – glucocorticoids – stimulate secretion of HCl and inhibit secretion of mucus !!

Disturbances of the gastric secretion

Hyposecretion - the decrease of the gastric functions –
- impaired storage and digestive and other functions

Postgastrectomy syndrome – dumping – hyperosmolar chyme in the duodenum – hypoglycemia

Hypersecretion – dysbalance in HCl: mucus ratio – ulceration – autodigestion

Zollinger – Ellison sy.: Gastrinomas-tumors in stomach, duodenum, pancreas – secrete gastrin – the increase in HCl production - ulcers

PHYSIOLOGY OF THE SMALL INTESTINE

Movements of the small intestine

Anatomy of the intestinal wall:
Layers (from the outer surface inward):
- the serosa
- a longitudinal muscle layer – myenteric nerve plexus
- a circular muscle layer – Meissner´s plexus – the submucosa –

- the mucosa

= 2 layers of the smooth muscles, 2 neural plexus

Motility:
Local contractions: - segmentation – ring like – circular muscle layer
- pendular – circular + longitudinal muscles
- villious

Propulsive – peristalsis: Peristaltic waves – analward at a velocity 0.5 – 2 cm/s to 3.5 – 10 cm.

Transport of the chyme 1 cm/min = 3 – 5 hours for passage of chyme from the pylorus to the ileocaecal valve.
Rotation of the chyme.

Regulation of the intestinal motility

Neural:
Myenteric reflex – mechanical stimulation of the duodenum – distention – serotonin
Gastroenteric reflex – distention of the stomach – through myenteric plexus
Parasympathetic +, sympathetic pars -

Humoral:
Acetylcholine +
Pilocarpin, physostigmine (inhibitors of cholinesterase) +, serotonin +, thyroxine +, CO_2 +.

Secretion of the small intestine
Intestinal digestive juice: colorless, alkaline (pH 7-9) fluid
Volume: 2 – 3 l per day
Product of: - Brunner´s glands – mucous glands secret mucus
- the crypts of Lieberkühn

Enzymes:
1) Proteolytic – peptidases - for splitting small peptides into AA
(enteropeptidase – for activation of the trypsinogen)
2) Intestinal lipase – neutral fats into glycerol and FA
3) Enzymes for splitting disaccharides – sucrase, maltase, isomaltase, lactase

Regulation of small intestinal secretion:
1) Local stimuli – tactile, irritative, chemical (the presence of the chyme, HCl, saccharides ...)
2) Neural – through parasympaticus

Valve ileo – caecalis (ileocaecal sphincter)
Function: Prevention backflow of fecal contents from the colon into the small intestine.
Sphincter slows the emptying of ileal contents into the caecum.

Receptive relaxation – neural + gastrin

Feedback control of the sphincter by reflexes from the caecum:
The distention of the caecum intensifies the contraction of the sphincter.

An irritation of the caecum (inflammation of appendix) – can cause intense spasm and paralysis of the ileum - by way of the myenteric plexus.

Movements of the colon

Movements: - mixing – haustrations – for better exposition of the fecal material to the surface of the large intestine
- propulsive - 2-3/day – transport down the colon

Gastrocolic and duodenocolic reflexes – distention of the stomach and duodenum – initiation of mass movements

Defecation

Tonic constriction of 1) internal anal sphincter – smooth muscle
2) external anal sphincter – striated muscle –under voluntary control S_2 -S_4

Distention of the rectum P – 40-50 mmHg – **defecation reflex**
Center S_2 –S_4 : activation of parasympathetic nerve fibers (pelvic nerves) $\Rightarrow$ intensification of the peristaltic waves, relaxation of the internal anal sphincter.

Voluntary relaxation of the external sphincter. Deep breath, closing the glottis, contraction of the abdominal wall muscles – expulsion the fecal content.

PANCREATIC SECRETION

The pancreas: - endocrine portion – hormones
- exocrine portion – the pancreatic juice

The pancreatic juice: 1-2 1/24 hours, colorless, viscous fluid
(1-2 % of substances), alkaline (pH = 7.5 – 8.5),with a high HCO_3^- content – from gastric venous blood.

The most important **pancreatic digestive enzymes:**

1) The proteolytic enzymes:

Proenzymes – in inactive form –initial step by enteropeptidase in the duodenum.
Trypsin inhibitor – in the cytoplasm of the pancreatic cells. It prevents activation of trypsin both inside the secretory cells and in the acini and ducts.

Prevention of autodigestion.

2) The pancreatic lipase - steapsine – the most important lipase in the GIT.

Secretion in active form – enhancement in the duodenum by Ca^{+2}, amino acids...
The necessity of emulsification of fat.
Patients with deficit of the p. lipase have impaired digestion and absorption of fat = fatty stool = steotorrhea.

3) The pancreatic alpha-amylase – splits starch.

Small amount in the blood – a rise – indicator of acute pancreatitis.

Regulation of pancreatic secretion:
- neural,
- hormonal

1st – neural – 1-2 minutes – after the start of the feeding – via n. vagus ⇒ the juice containing a high concentration of the enzymes - up 10%.

Unconditioned and conditioned reflexes from the mouth ...
Blockade with atropine.

2nd – Neural + hormonal – gastric – distention – n. vagus
- gastrin – large quantities of the enzymes

3rd – Hormonal – also in denervated pancreas - via GIT hormones:

- Secretin – from „S cells" – duodenum – stimulation of secretion of large quantities of fluid with $NaHCO_3$

- Cholecystokinin – pancreozynin – duodenum – by way of the blood to pancreas – causes secretion of quantities of the pancreatic enzymes

- Chymodenin – chymotrypsinogene

- VIP – $NaHCO_3$

LIVER AND BILIARY SYSTEM

Blood Flow: 25 % of CO = 1.5 l/min
- Nutritive – a. hepatica (P = 100 mmHg)
- Functional – v. portae (P = 10 mmHg)

Volume of Blood in liver = 20-30 ml/100 g
Insufficiency of RV – increase of the volume = Hepatosplenomegaly
Increase in P – ascites

Regulation of the Flow and Volume –
Sympathetic nerves – Th_{3-11} – vasoconstriction
reservoir function for blood volume – haemorrhage ...

Metabolic functions of the liver

1) Carbohydrates – storage of glycogen –
1 – 4 % of the liver weight – glycogen
- Gluconeogenesis
- Glycogenesis
- GLUCOSTATIC FUNCTION OF THE LIVER

2) Metabolism of fat – fatty acid oxidation
- formation of ketone bodies
- formation of cholesterol
- formation of phospholipids
- synthesis of lipids

3) Metabolism of proteins – oxidative deaminations
- urea formation
- manufacture of plasma proteins (50 g/day)
- formation of the clotting factors (fibrinogen, prothrombin, proaccelerin, almost all – vit. K – II, VII, IX, X)

4) Cholesterol metabolism – synthesis from acetate
- excretion – in the bile – in the free form and as bile acids.

5) Metabolism of hormones – angiotensinogen
- inactivation of adrenocortical and gonadal steroid hormones
- inactivation of erythropoietin

6) Iron and vitamins metabolism –
- storage of ferritin (apoferritin = globular protein) + iron – in ferric form)
- Vit. A, B, B_{12}, synthesis of 25-hydroxycholecalciferol (from vit. D_3 – reabsorption of Ca^{++} in kidneys)

Detoxification function of the liver

Excretion of bilirubin
- " - of cholesterol → bile salts
Detoxification of the ammonia, indole, skatole, alcohol, nikotine ...

Thermoregulatory function of the liver
Heat production

THE BILE

- product of the liver modified by the gall-bladder
Daily amount: 700 – 1200 ml
Composition of Bile
The bile secreted continually by the liver is stored in the gallbladder (V = 20-60 ml) – where water, Na^+, Cl^- ...

are absorbed – concentrating the bile constituents.
Concentration about 5-fold up to 20-fold.

1) Bile pigments – biliverdin + bilirubin
1 g Hb → 40 mg Bi

2) Bile salts
- Cholic acid
- Deoxycholic acid
- -

bacteria - Chenodeoxycholic acid
colon Lithocholic acid

Conjugation with glycine/taurine:
Salts: Glycocholic acid form sodium and
Taurocholic acid potassium salts

200 – 250 mg of the bile salts/day

Actions:
- Reduction of surface tension – a detergent function.
Breaking the fat globules into minute sizes = emulsifying function
- Forming minute complexes – the bile salts + lipids = micelles – better absorption of FA, cholesterol, lipids from intest. tract.

Without the presence of bile salts – up to 40 % of the lipids are lost into the stool = acholic stool -
-steatorrhoea
Enterohepatic circulation of bile salts
(3-10 x/day, lost 5-10 % per 1 circulation)

3) Cholesterol (0.06%) – proportion
x CH: bile salts 1 : 20-30
If the ratio is < 1 : 13 – formation of the cholesterol gallstones

x Inflammation of the gallbladder –
excessive absorption of water – CH begins
precipitate – small crystals

x Ca^{2+} - bilirubinate gallstones - deconjugation of the Bi by beta – glucuronidase (bacteria) –

4) Anorganic salts NaCl, $NaHCO_3$ –
pH – 8 – 8.6 - alkaline

Regulation of Biliary Secretion

- Neural – parasympathetic +

- Humoral – CCK – duodenum → blood → gallbladder
Constriction + relaxation of Oddi sphincter

Functions of the bile

1) Neutralisation of gastric HCl
2) Help for digestion and absorption of fat and for metabolism of vitamins soluble in fat (A, D, E, K)
3) Excretory function – bile pigments, anorganic substances (copper, zinc, mercury), toxins, some drugs ...

REGULATION OF FOOD INTAKE

Motivation: „hunger" – subjective feeling

Centers: in HYPOTHALAMUS

Lateral - feeding (hunger) center (FC)
- constantly active, inhibited by satiety center
- if stimulated – subject looks for the food
↑ food intake

Ventromedial – satiety center (SC)
- when stimulated ⇒ stop eating

Corpus mamillare – coordination of feeding reflexes

Stimuli:

1) *glucostatic cells* → monitoring of glycemia (blood glucose) – if ↓ glycemia – FC is stimulated
2) *afferentation from GIT*- distention of organs ⇒ reflex activation of SC and depression of FC
3) *ambient temperature*: cold: enhances eating
warm: ↓ food intake
4) *blood temperature*
5) *metabolic condition of the body* (exhaustion, long-term stress, adaptation) - enhances eating
6) *limbic system (emotions)* (+/-)
7) *brain cortex* – voluntary influences (+/-)
8) *hormones*

CONTROL OF WATER BALANCE

1) Control of water intake

Motivation: subjective feeling of „thirst"
Center: lateral hypothalamus (next to *ncl.paraventricularis*)
Stimuli from:
1) *osmotic receptors*: directly in hypothalamus
2) *volumoreceptors*: low-pressure baroreceptors in RA (type B)

3) *periphery*: dry mucosa in oral cavity, increase level of angiotensin

2) Control of renal water excretion

- stimulation of osmotic receptors and volumoreceptors- information into neurohypophysis: ADH- acts at distal tubules and collecting ducts → reabsorption of water

HYPOTHALAMIC LESIONS

Bilateral lesion of <u>lateral</u> hypothalamus

- ↓ food intake – anorexia, ↓ water intake, extreme passivity

Bilateral lesion of <u>ventromedial</u> hypothalamus

- ↑ food intake (hyperfagia), ↑ water intake
- hyperreactivity, brutality, bursts of anger

<u>Consequences</u>:

- cachexia (extreme loss of b.w.)
- obesity
- mental anorexia
- bulimia – pathological feeling of hunger

NUTRITIONAL ASPECTS IN SPECIAL GROUPS

1) Newborns and sucklings (0-12 months)

- highest caloric requirements/kg b.w.
- <u>Intake</u>: fats – 40-45%, sugars – mainly lactose, proteins 2-2.2 g/kg/day
- in lack of iron ⇒ anemia (1 yr.of age)
- vit.D - supplement
- fluid intake ! 150 ml/kg/day
- period of complete milk diet (0-6 months)

2) Children (1-10 years)

- high caloric requir. (⇐ increased moving activity)
- fat intake < 30 %
- if disproportion in E intake: E output ⇒ obesity
- <u>nutritional habits-forming period</u> !

3) Children and teenagers (11-18)

- <u>acceleration</u> in growth and development ⇒ ↑ E demands
- <u>gender differences</u> in BMR: boys – more muscles with higher metabolic activity⇒ increased nutritional requirements
- <u>hormonal changes</u> → anabolic reactions
- need of Ca (bone mass) and Fe (blood, muscles)
- experiments with diets; „body building“, mental anorexia

4) Pregnancy

a) before pregnancy: 8-12 weeks before stop with diets, well-balanced food

b) pregnancy

- in last 2/3 - ↑ requirements
- ↑ caloric intake by 1200 kJ, body weight – optimum increase by 10-12 kg
- fetus growth and development: proteins, folic a., Fe, Ca
- reduce alcohol and caffeine intake
- ↑ fibre intake

5) Lactation

- caloric requir. ↑ by 2100 kJ (500 kcal)/day
- carbohydrates, fats; proteins 1,5 g/kg
- Ca – teeth, bones !
- ↑ fluid intake – milk production !

6) **Elderly people**

- teeth condition, secretion and motility of GIT is ↓
- proteins: 1 g/kg b.w., to reduce cholesterol
- active fluid´s intake (subjective feeling of „thirst" is reduced)

7) Sportsmen and physically active people

- light food, ↑ E output !
- carbohydrates: first source of E; 1g/17.1 kJ (4.1 kcal)
- utilization of sugars also in anaerobic exercise
- fats: richest in E; 1g/38.9 kJ (9.3 kcal)
- proteins: inefficient source of E; 1g/17.1 kJ (4.1 kcal)

Principles: ↑ E intake, fats < 30%; sugars (2/3-3/4) for glycogen renewal in endurance sports,
proteins: depending on kind of exercise (1.2 – 2g/kg)

- loss of fluids by sweating (water + minerals!)

METABOLISM

Control of energetic balance

Break-down of organic molecules – energy for different forms of „biological work": Muscle contraction, active transport, synthesis of new molecules....

Energy of organic substances E= H + W

H = heat (60%) – to keep body temperature
W = work (40%)

Biological work:
external – skeletal muscles – movement of the subject
internal – all other forms (heart activity, HCl secretion, plasma proteins synthesis, storage of energy – macroergic bind. – in ATP, CP...)

Total energy expenditure = produced heat + external and internal work
(incl. energy storage)

Total energy expenditure/time = metabolic rate – MR

Basal metabolic rate (BMR)
Minimum amount of energy necessary to keep the vital functions (heart activity, respiratory muscles, liver function, kidneys, brain) in basal conditions:
Quiet, relaxed state (psychic, emotional, physical)
Indifferent room temperature – thermoneutral zone 15-25 °C
Postabsorption state (12-16 hrs after last food intake, 3 days protein-reduced diet)**; specific-dynamic effect** (proteins up to + 30%).

(During sleep – even lower BMR)

Factors influencing MR
- age (growth, development)
- gender
- body size (b.w., height, surface)
- body temperature
- ambient temperature – thermoregulatory activities
- emotions-psychic state, mude
- physical activity
- food intake (+10-20% after eating) – postprandial thermogenesis
- sleeping– nonREM/REM
- hormonal levels

Hormones influencing MR
Thyroid gland hormones (TH):

TH icrease oxygen consumption and heat production by most of the tissues (except brain) = calorigenic effect – the exact mechanism not known

Hyper/hypo/thyroidizmus

Adrenalin - calorigenic effect via stimulation of catabolism of glycogen and triacylglycerol.

Measurement of BMR/MR
Direct calorimetry: amount of the heat released by the body surface
– calorimetric chambers

Indirect calorimetry: calculated according to the amount of consumed O_2 and produced CO_2

Indirect methods:
1) Krogh´s metabolimeter – based on oxygen consumption
2) Douglas method - O_2 consumed vs.CO_2 produced

In both methods – amount of energy, released in the body using 1 litre of oxygen depends on the type of nutrients oxidized = **energetic equivalent**.

Respiratory quotient
RQ = volume of produced CO_2/volume of used O_2
Carbohydrates = 1.0, proteins = 0.8, lipids = 0.7

BMR in adults = 2000 kcal = 8400 kJ/24 hrs
(f = 4.184)

Men = 40 kcal (167 kJ)/m^2/hrs) Women by 5-7% less

Calculated MR – to compare with standard MR – tables
(gender, age, b.w., height)

Values in percentage +/- 100% .

Measurement of working MR

Direct/indirect (Douglas) method
MR/shorter time for a particular kind of activity-work

ONTOGENY OF DIGESTIVE SYSTEM

1. **Prenatal period**

- Histotrophic nutrition
- Hemotrophic – placenta – from 9.-10.w.

Activity of digestive system – from 16.-20.w. – swallowing of amniotic fluid (mainly regulation of its volume)
- if atresia (closure) – *polyhydramnion*

Motility:
- spontaneous periodic activity missing
- tonic contraction of anal sphincter ! – no defecation i.u.

IMPORTANT: during asphyxia (hypoxia) of fetus – intestinal content can be released and aspirated (inhaled) ⇒ meconium aspiration syndrome

2. **Postnatal period**

a) lactotrophic nutrition

- breast-feeding + supplementation after 6.m. ⇒ mixed nutrition
- sucking reflex
- salivation – reduced in newborn, later hypersalivation (teeth)

- swallowing r. – well developed

Sucking reflex

- unconditioned: receptors in lips and perioral area – n.V, VII, IX ⇒ MO, and V, VII, XII ⇒ muscles
- later becomes conditioned
- **1st phase**: negative pressure 13-20 kPa.
- **2nd phase:** movements of the jaw - milk in to the mouth
- Breast – active, contractions of myoepithelial cells to mechanical stimulation through oxytocin

Stomach: in newborns 5-10 ml, 1 yr.-250-300 ml, cardia - low tone ⇒ easy to belch
Secretion:
chymosin – causes milk proteins to clump together, transport is slow
gastric lipase – to digest milk fat
fetal pepsin – stronger in milk digestion
intrinsic f.
Gastric evacuation: maternal milk after 2-3 hrs, artific. 3-4 hrs
Small intestine: lower amount of villi, ↑ activity of enzymes

Large intestine: defecation: 5-7x/day, 1 yr.1-2x

b) **definite nutrition**
– by own (intraluminal) enzymes of GIT

LIVER

In fetus – hematopoesis
Storage (mainly glycogen) – fast E source after birth

Excretory and detoxication
- immature liver – insufficient after physiological hemolysis in newborns

Biotransforming reactions– lower activity ⇒ prolonged response to farmacological treatment in newborns

METABOLISM

In comparison to adults:
1) each deviation in metabolism is dangerous
2) predominance of anabolic reactions
3) immature enzymes

BMR/kg b.w. is increased
Demand: newborns 500 kJ/kg/day (adults 3x more)
Brain utilizes 2/3 of BMR, in adults ¼ - 1/5

Proteins intake: sucklings 2.5 g/kg/day (adults 1g/kg/day)

GIS IN ELDERLY PEOPLE

Oral cavity

- Hyposalivation/xerostomia
- Mastication disorders – teeth !

Swallowing

- Disorders of motor function of esophagus, missing secondary perist.waves, present terciary w. – no transport.func.
- Sphincters: cardia - ↓ food passage,
- in laying position – incompetent ⇒ GER **presbyesophagus**

Stomach

- ↓ Motility and HCl secretion
- ↓ iron and B_{12} resorption
- Possible atrophic gastritis = anemia

Small intestine

- ↓ surface for absorption–
- ↑ fibrotic tissue

Large intestine

- Low motility ⇒ constipation
- Often – *colon irritable*
- Insufficient control of sphincters

Liver

Liver blood flow ↓ by 35 %

- Slow metabolic rate in liver - ↓ elimination of medications
- ↑ cholesterol and ↓ bile acids secr. ⇒ ↑ production of bile stones

↓ BMR by 2-3% per decade

Nutrition

- Optimal proteins intake: 1 g/kg,
- Water intake: reduced feeling of thirst - *(negative water balance)*

THERMOREGULATION

- maintainance of the balance between heat production and heat loss.

1) Heat production -
   a) in chemical reactions – metabolism
   b) during the contraction of skeletal muscles
2) Transport of the heat – in the blood and tissues
   Liver +1ºC, lungs -2ºC – of average temperature
3) Heat loss -
   a) Radiation – transfer of heat from one object to another at a different temperature without direct contact (by infrared electromagnetic radiation)
   b) Conduction – heat exchange between objects in contact
   c) Convection – the movement of molecules away from the area of contact.Wind, draught ...
   d) Vaporization - perspiratio insensibilis (the insensible water loss) – 50 ml/h
      - sweating
      - increased ventilation (panting)

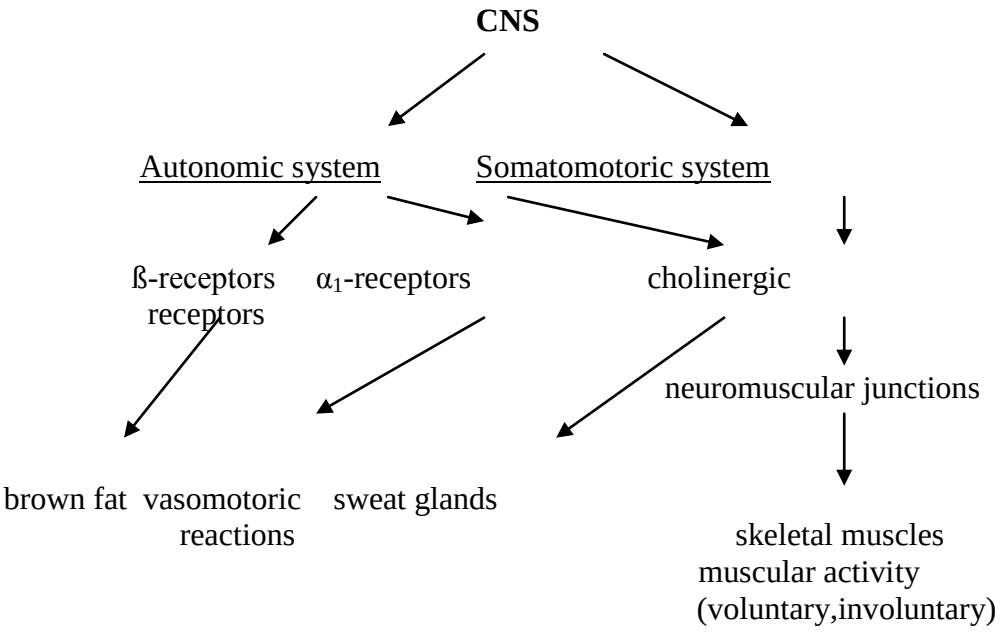
Temperature – regulating mechanisms

Neural – reflexes – immediate responses
Humoral – long-term adaptation

Neural thermoregulation

Center – hypothalamus – temperature-regulating centers
Afferents – temperature-sensitive cells in the anterior hypothalamus
- cutaneous temperature receptors

Efferents - autonomic nerves
- motor neurons



Body temperature

- manifestation of the thermoregulation efficiency

Species - poikilothermic – „cold-blooded“
- homeothermic – „warm-blooded“

Temperatures:
1) central – organs: brain, hypothalamus ...
constant = 37.0 ˚C
2) core – skin – varies with the changes in environmental T +
changes in perfusion.
Average = 33.0 ˚C

Diurnal rhythm – lowest at about 6 a.m.
Changes of the basal temperature (oral or rectal) in ovulation – the increase due to a secretion of progesteron (thermogenic effect).

Reactions of the adult humans in cold environment

A) The increase heat production and B) The decrease heat loss

Ad A)
1. The increase in metabolic rate
2. Food intake (specific dynamic action – the obligatory energy expenditure that occurs during its assimilation into the body)
3. Muscular activity: a) Shivering – simultaneous contractions flexors and extensors muscles, heat production.
Shivering pathways – hypothalamus – tr.cerebrospinalis and reticulospinalis
b) Voluntary skeletal activity

Ad B)
1. Vasoconstriction in the skin – alpha adrenergic sympathetic nerves – the decrease in heat loss

Lewis´ reaction – during long-term cold application – vasodilatation – red color of the skin – warming up - protective function

2.Position with the smallest body surface – quasi spheric shape

Hormonal changes:

The thyroid gland – in long-lasting stay in cold – calorigenic effect
The adrenal medulla- noradrenalin – vasoconstriction
Hypothalamus – the posterior pituitary – vasopressin – vasoconstriction and water retention

Reactions of the adult humans in hot environment

A) The decrease heat production and B) The increase heat loss
Ad A) 1. The decrease in metabolic rate – T = 25 – 30 ˚C
(higher temperature – a rise of the metabolic rate)
2. Reduction of the muscular activity

Ad B)
1. Vasodilation in the skin (BF through a-v anastomosis) via the decrease of the sympathetic tone
2. Sweating – vaporizaton – 1 l of sweat→ 500 kcal. Maximal volume of the sweat = 3 l/h → 1500 kcal/h
3. Panting – dogs.

Heat dissipation and loss in newborns

- by peripheral vasodilation – the increase of cutaneous BF
- sweating – evaporative loss – in newborns less effective than adults.

Capacity of the sweat glands = only about 1/3 of adult values.

In preterm infants, the maximal rate of sweating is less, and it is minimal or nonexistent in infants of less than 30 week´s gestation – inadequate development of these glands.

Prevention of cold stress and hypothermic for neonatal care –
- clinical implications:

Exposure to cool environment – cold stress often result in pathophysiological changes.
Lowered body temperatures are inversely correlated with survival.

Neutral Thermal Environment = a range of ambient temperatures within which the metabolic rate is minimal and thermoregulation is achieved by basal physical processes alone.
In adults 25 – 30 ˚C – in newborns at higher temperature.
Prevention of heat loss – incubators ...

Physiology of the fever

Fever = only the increase in body temperature (BT) - hyperthermia?
Hyperthermia can exist when heat production exceeds heat dissipation = disequilibrium
Variety of reasons: An increase in metabolic heat production, an impairment of heat dissipating mechanisms, a decrease in the heat –absorbing capacity of the environment due to high ambient temparture

Exogenous hyperthermia, enormous physical effort...evoke the BT increase – is not fever!

Fever = the increase of the BT due to immunologic reactions, by the increase of the set point of the central thermostat with defensive role.

Mechanisms of the fever:

PYROGENS = SUBSTANCES INITIATING FEVER

Microorganisms – viruses – protozoas

Pyrogens exogenous:

Toxins from bacteria, necrotic cells, viruses,
Cancer cells ... – exotoxins – exoproducts →
Monocytes, macrophages, lymphocytes – production of
Pyrogens endogenous:interleukin-1 (IL-1); IL 2; IL 6; TNF alpha, beta; CSFs
PGE_2 – a direct action on the hypothalamus -adjustation of a new set point for temperature.

Effects of the pyrogens

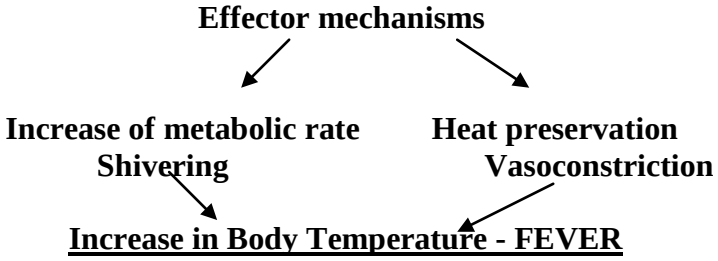
Haematologic – immunologic effects:

- CSFs - lekocytosis
- Stimulation of the lymphocytes activities (LyT,B,NK)
- Increase in phagocytic activity

Metabolic effects:

- negative N_2 balance
- catabolism of muscles
- increase in metabolic rate
- decrease in iron and zinc concentration level in plasma

- **Increase of set-point of the central thermostat**



Role of the fever

Defensive mechanism – Hipocrates (400 BC.) – „fever is a helpful mechanism in the fight against toxins in a body“

Activation of the immune system: phagocytosis, T and B lymphocytes,

- stimulation of the antibodies production
- inhibition of the growth of some microorganisms (due to the decrease of the iron and zinc in plasma)
- slowing the growth of some tumors
- unspecific discomfort

Positive efects up to BT 40º C
Hyperthermic devices

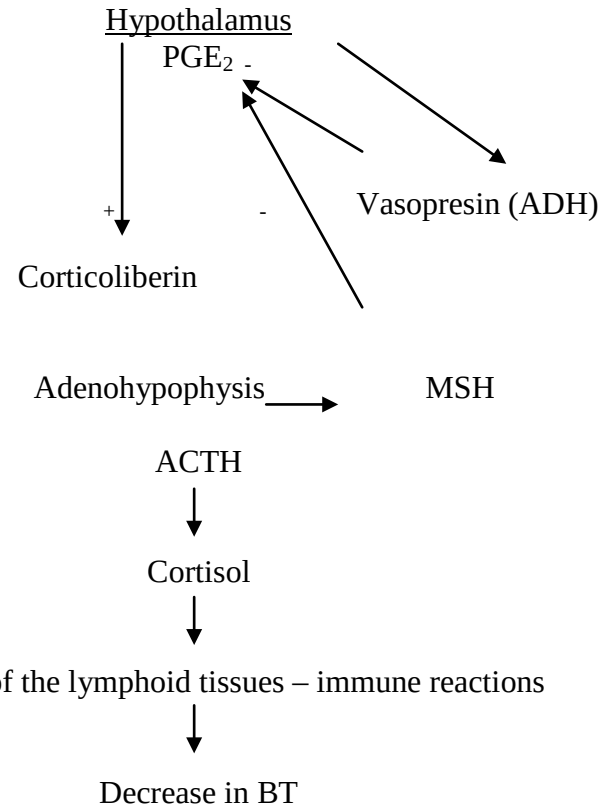
Negative effects of the fever

- Increase in metabolic rate, sweating, loss of minerals, dehydration
- Load of the cardiovascular system (mainly in elderly)
- Musle´s catabolism, hyperglycemia, metabolic acidosis
- Headache, pain in joints, musles – hyperalgesia (PGE – vs endorphins)
- Somnolence, apathy – substance „S“ produced in the brain by the pyrogen´s effect
- Decrease of the diuresis
- Decrease of the gastrointestinal functions
- BT higher than 41 C – decrease in immonologic reactions- possible damage of some central proteins – neurons in CNS

-

Physiological Antipyretic Mechanisms

Fever



EXERCISE PHYSIOLOGY

investigation of the effects and their mechanisms of:
- physical exercise on systems, organs
- training
- relaxation after exercise

Quantification of exercise intensity

Energy consumption:
Mild exercise: 120-450 kcal/hod, heavy: 450-600, super heavy 600 and more kcal/hod.

Oxygen consumption:
O_2consumption at rest approx 250 ml/min, max. up 3 000 ml/min

O_2consumption maximum = VO_2 max.
Mild exercise – VO_2 max. to 33%
Moderate = VO_2 max. approx. 50%
Heavy = VO_2 max. approx. 70%
Super heavy – VO_2 max. 70 – 100 %

PULSE OXYGEN (PO) = volume of the oxygen transported by 1 pulse (SV)

Consumption/intake of O_2 (at rest) = 250 ml/min
Heart rate (at rest) = 70/min
PO = 250:70 = 3,5 ml /pulse
During exercise up 20 ml O_2/pulse

Regulation of physiological function in exercise

Neural regulation:
Autonomic nervous system (ANS)
Changes in ANS before exercise – start
1st phase: Parasympathetics – reduction in tone (tachycardia)
2nd phase and endurance exercise: Sympathetics – activation in co-operation with endocrine system.

Humoral regulation in exercise

Adrenal medulla: Catecholamines: Adrenaline – positive effects on heart and liver (mobilisation of glycogen and free fatty acids).

Hypophysis (anterior pituitary):
Increase (20- to 40 – fold after 20 min of exercise) in growth hormone secretion . Stimulation of anabolism – strengthening muscle ligaments and tendons, increasing bone thickness.
ACTH –glucocorticoids – cortisol (rises in heavy and prolonged exercise)– hyperglycemia, it mobilizes both fat and proteins.
Prolactin – increased blood levels following exercise –mobilizes fat + antidiuretic effect upon kidneys
Endorphins: similarity to the opiates. Increased secretion by endurance exercise.
Psychological effects – depression of sensation of fatigue, euphoria. Together with prolactin can be factor responsible for exercise-induced amenorrhoea.

Pancreas:
Insulinemia drops by about 50% during and immediately after exercise. (A decrease in insuline secretion + increased uptake of the hormone by muscles.) Hypoglycemic effect combined with higher consumption of glucose.
Glucagon level rises – mobilization of hepatic glycogen.

EXERCISE AND CARDIOVASCULAR SYSTEM

Heart rate:
- Mild exercise: rapid-onset increase of heart rate by a reduction of vagal tone.After exercise recovery in 3-5 min.
- Heavy exercise: tachycardia by the reduction of vagal tone + activation of the sympathetics and adrenal medulla (catecholamines). Higher values of HR, recovery time up hours.

Limit for the sympathetics activation is individual – on average in exercise with 50 – 60 % of maximal oxygen consumption.

Calculating Heart Rate Training Zones: There are a number of ways to estimate maximum heart rate. Realize that we are estimating maximum heart rate not measuring it so it is not an exact science.
Two methods of Estimating Maximum Heart Rate

1. **220 - Age = Maximum Heart Rate**
Example: 40 year old 220 - 40 = 180 beats per minute (bpm) Max Heart Rate
2. **217 - (0.85 x Age) = Maximum Heart Rate**
Example: 40 year old 217 - (0.85 x 40) = 217 - 34 = 183 bpm Max Heart Rate

Recommended HR according to age for long-lasting exercise (LLE) and maximal HR for short-lasting exercise (SLE)

HR changes in recovery phase (after exercise)

1st min: An imediate exponential decrease in HR. 2nd min continuation + exponential drop of noradrenaline plasmatic level. Reactivation of vagal nerves + progressive reduction of the sympathetic and hormonal activities.
HR changes in recovery phase – used in performance testing (Ruffier´s test, Flack´s test)

Stroke volume and cardiac output:

Increase by 20-30% (from 80 to about 110 ml at 40-50% of maximum oxygen intake) - followed by steady state - constant. SV and CO reflects HR up to some limit. Exceeding of the limit (critical HR value) - accompanied by a drop in the cardiac pumping efficiency.
Tachycardia - shortening of the diastole (ratio St:Dt at rest = 1:2, in maximal tachycardia up 1:1) = a decrease in diastolic refilling of the ventricles.
The increase in stroke volume with exercise is accomodated by both – an increase of EDV and an increase of ejection fraction (normally 55-60%). The Starling relation curve is shifted to the left and up (effect of sympathetic stimulation, catecholamines).

Cardiac Output

The product of HR x SV. CO at rest = 3-3.5l/min/m^2 = 5l/min. Maximum CO = 19 l in young woman and 25 l in man. Endurance athletes up to 35 l/min.

Blood Pressure

Systemic: - syst: rises sharply during isometric and sustained rhythmic exercise. Function of the stroke volume. 200-220 mmHg.
- diast.: +/- influenced mainly by peripheral vascular resistance – *vasodilation in skeletal muscles circulation*
Pulmonary: +/- During isometric exercise (stretching)- impairment of the venous return = pooling of venous blood – an increase in venous pressure.

Distribution of Blood Flow

Muscle Blood Flow:At rest-open 200 capillaries/ mm^2, in working muscle 10-15x more. BF 2-5ml/ min/100g in comparison to 120.
Neural regulation through noradrenergic system (reduction of activity) and specific cholinergic sympathetic vasodilatory system.
Humoral regulation (a decrease in pO_2, adenosine, increased content of potassium, hyperosmolarity, NO, histamine + metabolites).
Different BF during static (isometric) and dynamic work, contraction/relaxation.

Blood Flow to Other Organs

Splanchnic circulation: A decrease in BF through splanchnic organs - redistribution of the blood to skeletal muscles. Visceral BF drops to only 25-30% of the resting value.**Brain:**

Cerebral BF remains constant during exercise. However, BF is redirected from one part of the brain to another – motoric zone, visual etc.
Bone: BF to bone can be increased up to 40% in response to mechanical loading.

BLOOD

During exercise - increased hematocrit, viscosity due to higher exsudation (filtration) of plasma in capillaries of skeletal muscles + higher production of erythrocytes.
Leucocytosis – through demargination. Mainly neutrophils and lymphocytes – defensive role.

Plasma

Glycemia: Short-lasting exercise – an increase up + 60%, long-lasting – endurance training – a drop
Lactate: after 15 min lasting exercise up 15-fold rise (from 1 to 15 mmol/l)
FFAs: heavy exercise – an increase 4x

Ventilation and Metabolism:

Ventilation: an increase by rising of V_T and respiratory rate. During mild exercise – proportionally to the oxygen intake – consumption.During heavy exercise – the ventilation is „overproportional" – additive stimulus - metabolic acidosis (lactic acid) via central chemoreceptors.. *Ventilation is not limiting factor for maximum effort. Ventilation at 80% of MMV covers needs of the maximum effort.*

Oxygen consumption: At rest 250 ml/min,during maximum efforts up 3000 ml/min.Individual limit value. An increase to steady state in 3-5 min.

Maximum aerobic capacity

Increasing of a loading – a linear rise of oxygen consumption to a individual maximum – further increasing – disproportion between requirements and intake = exhaustion - fatigue.
Plateau = maximum oxygen intake/consumption = maximum aerobic capacity.

Oxygen Debt

Aerobic resynthesis of ATP in working muscles cannot keep pace with their utilization. The anaerobic pathway is limiting – during a work – oxygen debt comes. After a period of exertion is over, extra O2 is consumed to remove the excess of lactate, replenish ATP and CP, and replace O2 that have come from myoglobin. The amount of extra O2 consumed is proportionate to the extent to which the energy demands during exercise exceeded the capacity for the aerobic synthesis of energy stores.
The O_2 debt is measured by determining O_2 consumption after exercise until a constant, basal consumption of O_2 is reached.
After mild exercise the debt is about 4, after heavy 20 l of O_2.

Blood gases

- mild exercise – unchanged
- heavy – a decrease in paO_2 (approx. by 8%). Enhancement of a-v difference $O_2$from 5% to 15%.

A drop in $paCO_2$ (approx. By 10%) due to hyperventilation

Acid-base balance: -heavy exercise: metaboli acidosis partially compensated by hypocapnia (tendency to the respiratory alkalosis).

Metabolism of the skeletal muscle cell

- Very short-lasting performances (to 20 second): utilization of the intracelular ATP a CP stores. *(In some seconds are exhausted ATP stores.)*

-Exercise duration to 6 min: In the 1st min – anaerobic glycolysis, lactat accumulation. Anaerobic glycolysis -maximum in 45 seconds. Aerobic metabolism starts again after 2 minutes.

- Endurance performances: Aerobic metabolism – glycogen stores + O_2. Time of the exercise is limited mainly by exhausting glycogen stores.

Termoregulation

Muscular work – increase in heat production - central temperature.
Sweating rate up 1 l / hod. Throgh sweat - excretion of lactic acid.
Long lasting sweating – fatigue of sweating glands – arrest of sweat production/evaporation – hyperthermia.

If exercise/heavy muscular work is performed in hot environment – redistribution of blood to skin circulation – limited skeletal muscles perfusion and physical output.

Effects of training on physiological parameters

Training = regular exercise, repetition of sport activities

	Without training	After training
Blood volume (l)	5,6	5,9
HRrest/min	80	40
HR max	180	180
SVrest (ml)	70	140
SV max	100	190
COrest (l/min)	5,6	5,6
CO maxim.	18	35
Heart weight (g)	300	500
Ventilation max (l/min)	100	200
O_2 consumpt max (l/min)	2,8	5,2

Bradycardia in subjects under endurance training:

Mechanisms:
Predominancy of vagal central tone – dynamic balance of the ANS shifted toward PS – enhanced RSA - Reduction of intrinsic heart rate of the sinoatrial (SA) node (rate of the spont diastolic depolarization). - Reduction of beta-adrenergic receptors in the right atrium - Changes in compliance of the heart – morphological adaptation

Morphological adaptation of the heart

Physiological hypertrophy of myocardium and dilation of the heart cavities. Hypertrophy of left ventricle, less of the right ventricle, atria and of pulmonary veins.
Reflection in ECG curves – mainly over LV (V_3-V_5).
Adaptation hypotony – tracking" to elderly.

Effects of training to the respiratory system

Increase in volumes/capacities (VC, FVC) – by 20-30%
Ventilatory reserve – rise from 1:5-7 to 1:9-15
Longer voluntary apnoic pauses
Increase in max. O_2 intake/consumption (from 3 to 7 l/min)

Bone system

Load – remodelation
Activation of the osteoclasts and osteoblasts.

Fatigue

Limitation of the performances

1)Peripheral, physiological (in muscles): Exhaustion of metabolic reserves,accumulation of metabolites.

2)Psychological (central): CNS – protective mechanism, a subjective feeling, deceleration of the signal transmission, inhibition of thinking and decision processes, sensoric function, anxiety, emotional lability.

1)Physiological: Tachycardia, tachypnoe...
2)Pathological: + spasms of musculature, tremor, hyperemic skin (+ white spots), nausea, headache, hypotension, cyanosis, dyspnoe...shock.

Reactions to non-physical forms of loading

Psychological and emotional load
Reactions similar to physical exercise effects: Tachycardia, hyperventilation, sweating, cutaneous hyperperfusion, sympathoadrenal system activation, increasing of energetic substances concentration in plasma – without increased consumption....
Stress – alarm reaction. Civilisation - psychosomatic diseases.

PHYSIOLOGY OF MUSCLES

1) Skeletal
2) Cardiac
3) Smooth

1) Skeletal Muscle

Anatomy and Histology

Muscle fibers (10-80 microns in diameter) = extrafusal fibres – surrounded by the sarcolemma. Each fiber contains several hundred – thousand myofibrils. Each myofibril has about 1500 myosin filaments and 300 actin filaments.

The filaments are in a matrix – sarcoplasm, in the sarcoplasm
- sarcoplasmatic reticulum.

The T-system – is continuous with the sarcolemma = the transverse tubules – run transverse to the myofibrils, branch among themselves.

Striations:
Bands „I" – light bands contain only actin filaments – isotropis
Bands „A" - dark bands – myosin + actin filaments – anisotropic
Zone „H" – lighter band in the bands „A"
Line „Z" – dark – in the bands „I"

The area between 2 „Z lines" = sarcomere

Biochemical characteristics

The myosin filament – multiple myosin molecules–each m.w. 460 000
1 molecule = six polypeptide chains – 2 heavy chains
- 4 light chains

The actin filament – complex of 3 different protein components: -
- actin,
- tropomyosin,
- troponin

Hexagonal arrangement of actin and myosin filaments =
1 myosin surrounded by 6 actin filaments.

Mechanisms of excitation and contraction of skeletal muscle

1) Mechanisms of excitation

The skeletal muscle fibres are innervated by alpha – motoneurons (myelinated) – from the anterior horns of the spinal cord.
Neuromuscular junction – the „motor end – plate"

Neurotransmitter - Acetylcholine – synthesized in the cytoplasm of the terminal of an end – plate. Enzyme acetylcholinesterase – for destruction of Ach.

Action: When the action potential spreads over the terminal, the voltage – gated calcium channels open and large quantities of Ca++ diffuse to the interior.

The calcium ions exert an attractive influence on the Ach vesicles and these vesicles empty their Ach into the synapsis – by exocytosis.

Ach – opens Acetylcholine – gated ion channels – it allow to large amount of Na+ ions to pour to the inside – carrying large numbers of positive charges = local end-plate potential 50-75 mV – which initiates an action potential.

Action potential of the skeletal muscle

Resting membrane potential = - 80 mV to - 90 mV
Duration of action potential = 1-5 ms (five times as long as in large myelinated nerves)
Velocity of conduction = 3-5 metres/s

Depolarization is a manifestation of Na+ influx, repolarization of K+ efflux – like in nerves.

Transmission of the action potentials along transverse tubules. It causes the release of Ca^{+2} ions form the sarcoplasmatic reticulum – calcium ions cause contraction.

This overall process is called excitation – contraction coupling

Ca++ initiates contraction by binding to troponin C - the binding of troponin I to actin is weakened, tropomyosin moves laterally and uncovers binding sites for the myosin heads.

When the head attaches to an active site, this attachment causes changes in the intramolecular forces between the head and arm.

The head is tilting toward the arm and the actin filament is moved along with it.

After tilting, the head automatically breaks away from the attach site. The head returns to its normal direction. The head combines with a new active site ...next step- **„walk – along“** theory of contraction or **„sliding“** mechanism of contraction.

Sequence of events in contraction and relaxation of skeletal muscle.

Steps in contraction:

1) Discharge of motor neuron.
2) Release of transmitter (acetylcholine) at motor end-plate.
3) Binding of acetylcholine to nicotinic acetylcholine receptors.
4) Increased Na+ and K+ conductance in end-plate membrane.
5) Generation of end-plate potential.
6) Generation of action potential in muscle fibers.
7) Inward spread of depolarization along T tubules.
8) Release of Ca^{2+} from terminal cisterns of sarcoplasmatic reticulum and diffusion to thick and thin filaments.

9) Binding of Ca^{2+} to troponin C, uncovering myosin binding sites on actin.
10) Formation of cross-linkages between actin and myosin and sliding of thin on thick filaments, producing shortening.

Steps in relaxation:

1) Ca^{2+} pumped back into sarcoplasmic reticulum.
2) Release of Ca^{2+} from troponin.
3) Cessation of interaction between actin and myosin.

Manifestations of the skeletal muscle activity

1) **Electrical** - polarisation, depolarisation, repolarisation

Recording of the electrical activity = electromyography.
Surface EMG – by using metal disks
Deep EMG – needle electrodes in a single muscle

2) **Chemical** - three pH changes:
- a decrease – dephosphorylation of ATP
- an increase - - " - of phosphorylcreatin –
- formation of basic creatine
- a decrease – acumulation of the lactic acid

3) **Mechanical**
Record = myographic curve

Latency time for transmission of the action potential through motoneuron, end – plate (2-2 ms), T – tubules – EC coupling

Types of contraction:
- isometric (same length)
- isotonic (same tone)

Mechanisms of excitation and contraction of smooth muscle

Regulation:
Autoregulation – myogenic – pacemaker cells
Humoral - catecholamines, estrogens, oxytocin ...
only unvoluntary control

Neuromuscular junctions of smooth muscle:
Autonomic nerve fibres – diffuse junctions – secretion of a transmitter substance into the interstitial fluid – diffusion to the muscle cells.

Terminal axons have varicosities are vesicles containing transmitter substance – Ach/NA.

The most SM cells are innervated by parasympathetic + sympathetic

nerves.
Exceptions: *m. arectores pilorum – only sympathetic*
m. ciliaris - only parasympathetic nerves

Summation of contractions
All /or none law – valid only for 1 fibril but not for whole skeletal muscle. Muscle as a whole has not a refractory period. Repeated stimulation – summation of contractions – tetanic contraction.

Tetanic contractions: - complete tetanus
- incomplete tetanus

Mechanisms of gradation of muscle response:
– the increase of discharge frequency in individual motor nerve.
The stimulation frequency for complete tetanus (summation of contractions) - in cold-blooded e.g. frogs = 20 Hz
- in mammals + humans = 50-100 Hz
– the recruitment of motor units (MU) = more MU are activated
e.g. with increasing voluntary effort.

Receptor of the skeletal muscle

Muscle spindles – consists of 2-10 muscle fibres = extrafusal fibres + endings (primary, secondary)

Innervation (motor) of the skeletal muscle
- alpha motoneurones – extrafusal fibers
- gamma motoneurons – intrafusal fibers
Both from spinal cord.

The motor unit (MU) = all muscle fibers supplied by a single motor neuron (3-6 muscle fibers/motoneuron – in muscles for precise movement – hand, eye ..., 100-500 in the leg, back ...)

Skeletal muscle blood flow

2000 – 2500 capillaries/mm^2 area
In resting muscle – open only 100/mm^2. BF of resting skeletal muscle 2-4 ml/100 g/min
During contractions BF is stopped – between contractions is increased as much as 30-fold – 50-100 ml/100 g/min
Rhytmic exercise.

Physical manifestations of the skeletal muscle activity

1) The strength (force) = maximal weight held against the gravity (maximal contraction against a maximal load):
- in cold-blooded animals 3-4 kg/cm2
- in humans 3-10 kg/cm2

Dynamometers.

2) The work – a) positive – during isotonic contraction – against gravity (force/weight/times distance)
b) negative – when weight is lowered – the muscle actively resists the descent of the object – but weight x distance (negative) is done
c) static – during isometric contraction – a muscle generates force but cannot shorten or lengthen

The overall mechanical efficiency of skeletal muscle (work done/total energy consumption) = 0% during isometric contraction up to 35% (isotonic contraction)

3) Heat production
- Resting heat – at rest – in basal metabolic processes
- Initial heat - 1) activation heat – also without contraction
  2) shortening heat – only in isotonic
- Recovery heat – for restoration to muscle´s precontractory state
- Relaxation heat - after isotonic contraction for return of the muscle to its previous length.

Changes in temperature 10^{-3} to 10^{-4} ^oC

Energy sources for skeletal muscle contraction

ATP – for transport Ca^{++} and „head" myosin movements
Resynthesis of ATP – from phosphorylcreatin
Resynthesis of phosphorylcreatin – from glycogen ← phosphorylases a,b

Another sources – free fatty acids, acetoacetate acid, amino acids
FFA – the major substrates for muscle at rest

Cori cycle

muscle	**Blood**	
	glucose	
↓	←	↑
glycogen		glycogen
↓		↑
lactic acid	→	liver

Muscle fatigue

Prolonged and strong contractioins - depletion of glycogen
- exhaustion of metabolic sources

- accumulation of metabolites

Neuromuscular junction – muscle – nerve
Central fatigue – synapses of motor area – protective effect
Orbelli effect – sympathetic and/or catecholamines – put off fatigue

Contracture:
- long-lasting contraction – if transport of Ca^{2+} into the reticulum is inhibited – a relaxation does not occur.

ATP is necessary for re-transport of Ca^{2+} - lack of ATP

Rigor mortis:
After death – complete depletion of ATP and phosphorylcreatine **–** accumulation of lactic acid – a decrease of pH – katabolic without anabolic processes.
The myosin heads attach to actin in fixed way.

Nysten law – in order:
heart (1-2 hours), skeletal musculature (3-6 hours):
diaphragm – head – neck – trunk – arms – hands – legs.

The relaxation in the same time order – after 1-5 days.
Proteolytic enzymes.

SMOOTH MUSCLE

– cca 3% of b.w.
Morphology
SM lacks visible striations – only „A" substance – anisotropic.
Thin membrane, central localized nucleus, fibres 120-380/2-10 microns.
Poorly developed a sarcoplasmatic reticulum, a few of mitochondria.
Actin, myosin, tropomyosin – but without troponin

Types:

1) Visceral – syncytial smooth muscle – because of its interconnections among fibres. In the walls of most hollow viscera: the gut, the bile ducts, the ureters, the uterus, the bronchi, the bladders, the blood vessels ... (= single – unit-SM)

Control of visceral SM by humoral – non-nervous + nervous signals.

2) Multi-unit – each fibre operates independently of the others – is often innervated by a single nerve ending. Their control is exerted mainly by nerve signals. Like skeletal – but without voluntary control.

M. arectores pilorum, m. ciliaris.

Physiological properties of the smooth muscle

1) Plasticity – adaptation to volume – without the increase of the tone (e.g. receptive relaxation)

2) Electrical activity – in the resting state the membrane potential about -50 to –60 mV (less than in skeletal muscle). Unstable potential – changes in potential itself without an extrinsic stimuli.

Often associated with a basic slow-wave rhythm.

Spike potential – in single-unit SM (10-15 ms)

Action potential with plateau – onset – similar but repolarization is delayed for several hundred to several thousand ms - prolonged periods of contraction (the uterus, the vascular smooth muscle ...)

3) Excitability – high – labile. SM cells react to different stimuli: mechanical, humoral, temperature changes

4) Contractility – long latency, the prolonged periods of contraction. Slowness of onset of contraction and relaxation. Often rhythmic contractions. Smooth muscle fatigue – relaxation – no contracture.

4) Excitation – contraction coupling – slow process. Long latency –
- 50-100 ms after excitation – full contraction about ½ s latter. Smooth muscle does not contain troponoin - but another regulatory protein – calmodulin.

Sequence of events in contraction and relaxation of the smooth muscle.

1) Ca^{2+} ions come from the membrane
2) Ca^{2+} bind with calmodulin and activate myosin kinase – a phosphorylating enzyme
3) Myosin kinase phosphorylates one of the light chains of myosin head (regulatory chain) – head achieves the capability of binding with the actin filament.

Differences between skeletal and smooth muscles

Morphology	**Skeletal**	**Smooth**

- fibres	long	short
- nuclei	many	1
- sarcomere	+	-
- syncytium	-	+
- sarcoplasmatic reticulum	good developed	poor developed
- ATP-ase	many	a few
- the motor end - plate	+	-
- innervation	motoneurons	autonomic nerves
- distensibility	limited	high – plasticity

Function

- pacemaker cells	-	+
- resting potential	stable	unstable
- action potential	uniforme (like nerve)	low amplitude with superpone spikes, plateau
- mechanisms of contraction	Ca^{+2}, troponic C,	Ca^{+2}, calmodulin
- sensitivity to humoral substances	low	high
- duration of contraction	short	long-lasting up to permanent

RENAL PHYSIOLOGY

Organs with excretory function: kidneys, lungs, liver, GIT, skin
Renal functions: 1) Excretory
2) Control of the concentrations of the body fluids
3)Endocrine
Physiological anatomy and histolog ofthe kidney
Nephron = functional unit
One kidney contains about 1 million nephrons, (2 millions together).
Basic anatomy of the nephron:
Glomerulus afferent arteriole, capillaries, efferent arteriole,
Bowman´s capsule
Proximal tubule – in cortex
Loop of Henle – descending limb - thick and thin segments

- ascending limb (in medulla)

Distal tubule – in renal cortex

Collecting duct – cortical

- medullary

Large collecting ducts (250), each transmits the urine from about 400 nephrons

The sum of the inner surfaces – total excretion and resorption surface = 5-7 m^2.

Renal calyces, renal pelvis, ureters, urinary bladder.

The glomerular filtration

Glomerular filter:

Glomerular membrane – 3 major layers:

1) Capillary endothelial layer
2) Basement membrane
3) Layer of epithelial cells

Permeability of the glomerular filter

- Capillary endothelial layer – fenestrae – 100 nm in diameter
- Basement membrane – meshwork of collagen and proteoglycans fibrilae
- Epithelial cells – podocytes with pseudopodia – filtration slits – 25 nm wide

The glomerular filter permits the free passage of substances to 4 (40 angstroms) nm in diameter, 4-8 nm – selectively, > 8 nm totally excludes.

Molecular weight: substances < 70 000 D – pass through GF

> 90 000 D – do not pass

70 – 90 000 – by the molecules shape

The plasma protein albumin molecule is only about 6 nm and it does not pass ← the basement membrane with a complex of proteoglycans has very strong negative electrical changes – like plasma proteins = electrostatic repulsion of the molecules.

Summary: 2 basic regulatory limitations for filtration:

1) The sizes of the pores in the membrane
2) Its negative electrical charge

Glomerular filtration (GF) – due to a work of heart – energy of cardiac systole – also energy for GF

Filtration pressure (FP) = BP – ($P_{oncotic}$ + $P_{hydrostatic}$) = 60 – (25 + 15) = pribl. 20 mmHg – but only at the afferent end of the glomerular capilaries. Fluid leaves the plasma, oncotic pressure rises, FP decreases to zero → GF only in the beginning of the glomerular capillaries.

Regulation of GF = Regulation of the RBF

Changes in GF:

- In newborns – 20 % GF/100 g in comparison with adults
- Decrease inthe night, during sleep by 30 %
- Decrease in orthostasis, excessive physical effort

- Stop if BP will decrease under 40 mmHg

The glomerular filtration rate (GFR)

= quantity of glomerular filtrate formed each minute in both kidneys
= 120-125 ml/min in men
= 110 ml/min in women
The toal quantity per day = 180 l (over 99 % of the filtrate is reabsorbed)
The filtration fraction (FF) = the fraction of the renal plasma flow that becomes glomerular filtrate.
The normal plasma flow through kidneys = 650 ml/min, normal GFR = 125 ml/min = > FF = 16-20 % (0.16 – 0.20)

Composition of the glomerular filtrate
Glomerular filtrate is the same as plasma, except that it has no significant amounts of proteins (0.03 %).

In increased glomerular permeability (e.g. nephrotic sy.)
- loss of plasma proteins into the urine

Renal circulation

Renal BF = 1300 ml/min = 20-25 % of CO = renal fraction of the CO
(400 ml/min/100 g)

Renal artery – small arteries – afferent arterioles – glomerular capillaries –
- efferent arterioles – peritubular capillary system – venules – veins – renal vein
Two cappillary beds
Pressures in the renal circulation:
High capillary pressure in glomerulus

Regulation of the renal blood flow

Autoregulation
– **myogenic** (Bayliss, l902) – the ability of organs to regulate their own BF. Intrinsic contractile response of smooth muscle to stretch. The increase intramural P → distention of the smooth muscle → depolarization of the muscle cells → contraction.
The wall tension is proportionate to the distending pressure times the radius of the vessel.

- metabolic – through vasodilator substance.
When BF increases → vasodil. substances are washed away → vasoconstriction; vice versa.
- tissue pressure hypothesis of autoregulation:
When BF increases the accumulation of interstitial fluid → compression of the capillaries and venules.

Neural: sympathetic nerves ($Th_6 – L_3$) – vasoconstrictioin, only during orthostasis, physical effort, stress. The resting tone does not exist.
Humoral:
- catecholamines – vasoconstriction
- renin-angiotensin aldosterone system – vasoconstriction
- system kallikreins – bradykinin

- kalidin

Hageman f.

↓

Prekallikreins → *Kallikreins (glycoproteins – liver, kidneys)*

Kininogens → *kalidin + bradykinin* - *vasodilatation,*
(alpha$_2$ plasma proteins) ↓ *PVR,* ↑ *diuresis,*
natriuresis

- prostaglandins – PGE – vasodilatation,↓ PVR

System kallikreins, prostaglandins = counterbalance to the RAA system

- Adenosine – ATP → AMP → adenosine → vasoconstriction in afferent arterioles → ↓ GF
- Bacterial pyrogens – vasodilatation
- Drugs – hydralazines, coffein etc. – vasodilatation
- Hypoxia – under 50% sat. O_2 – vasoconstriction

The Renin – Angiotensin – Aldosteron System (RAR)

Tigerstadt l898 – kidney extract ——— hypertension
The substance – renin
Renin – product of the granula – juxtaglomerular (JG) cells - synthetized and stored in an inactive form – prorenin.
Stimuli – intrinsic reaction – prorenin molecules are converted by tissue kallikrein – renin.

Renin = a proteolytic enzyme. 90 % in kidneys,
10 % brain, heart ...

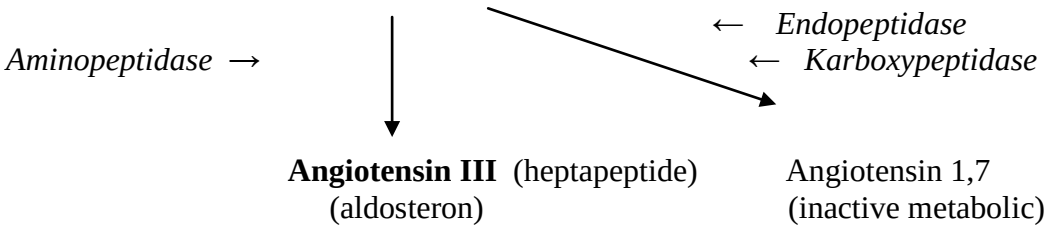
Angiotensinogen
(tetradekapeptide – liver, plasma)

Kallikrein + *Heparin* -
↓
Prorenin → *Renin* →

Angiotensin I (dekapeptide)

Captopril -
Angiotensin converting enzyme →
(ACE) lungs

Angiotensin II (oktapeptide)



Stimuli that increase renin secretion.
Sodium depletion, diuretics, hypotension, hemorrhage, upright posture, dehydration, constriction of renal artery or aorta, cardiac failure, cirrhosis, various psychological stimuli.
Hypotension, hypovolemia, hyponatremia

Actions of RAA system
1) **Vasoconstriction** – mainly in vasa efferens – increase in BP in glomerular capillaries and GF
Effect – direct/ indirect – through catecholamines (NA)
2) **Positive inotropic effect**
3) **Facilitation of the release** of – noradrenaline
- vasopressin
- ACTH
- aldosterone
4) **Dipsogenic effect** – through subfornical organ –
- increase in water intake

During hypotension and/or hypovolemia and/or hyponatremia:
1) Vasoconstriction and improvement in cardiac function
2) Sodium and water retention
3) Increase in water intake

Regulation of Renin Secretion

1) **Autonomic nervous system** – beta sympathetic + through beta 1 and cAMP
- alpha - " –
Inhibition of renin secretion by beta adrenergic blocking agents (propranolol)
2) **Baroreceptors** in vasa afferens – decreased afferent arteriol pressure → stimulation of renin secretion
3) **Chemoreceptors** in the macula densa. Renin secretion is inversely proportionate to the rate of transport of Na^+, Cl^- to the distal tubules → increased renin secretion
4) **Humoral factors** – Prostaglandins stimulate renin secretion
- Catecholamines stimulate renin secretion
- Vasopressin inhibits - " -
- ACTH
5) **Negative feedback** – increase concentration of angiotensin II – inhibits renin secretion

Tubular Functions

The glomerular filtrate = 170-180 l/day – definitive urine = 1 – 1.5 l
Modifications of the volume and composition of the filtrate in the tubules.

The glomerular filtrate flows through:

1) the proximal tubule
2) the loop of Henle
3) the distal tubule
4) the cortical collecting duct
5) the collecting ducts

The tubules may a) remove some substances from the filtrate = reabsorption
b) add some substances to the filtrate = secretion/excretion
c) both actions

Functions of the Proximal Tubule

Reabsorption – passive absorption – water – 60-80 % = obligatory absorption
- active transport – glucose + Na^+ co-transport
- Na^+, K^+, AA, acetoacetate ions, vitamins

Active transport – limited – by the ability of the energy and transports = transport maximum
of the absorption (T_m). After exceeding of T_m – the transport mechanism is saturated and the substance occurs in the urine.

Glycosuria – in hyperglycemia > 10 mmol/l = renal threshold for glucose
T_mG in men = approx. 375 mg/min
in women = approx. 300 mg/min

Secretion – when the concentration of the substance is higher in the loops of Henle than in glomerular filtrate. Mostly – active:
- heterogenous substances – penicilin, phenol red and sulphonphtalein dyes, sulphonamides, PAH – exogenous

Functions of the Distal Tubules

Length cca 17 mm – 40 l of fluid/day comes to the tubules
Absorption of the water (about 5 – 15 %), Na^+ (regulated by aldosterone).

Functions of the Collecting Ducts

Changes in osmolarity and volume mainly by means of the countercurrent multiplication system:

Fig.
Two tubes separated by semipermeable membrane – with ability to transport molecules of a substance in one-way. If the tubes are fulfilled with a stationary fluid – the activity of the membrane increases the concentration of the substance in tube A. When the fluid flows – the mostly concentrated fluid will be accumulated at the beginning of the tube B.

After connection of the next tube C – separated from the tube B by a membrane permeable for water – the solution flowing in C will become gradually more concentrated by the osmotic forces acting between B-C.

Application of the countercurrent system in kidneys

- Descending limb of the Henle´s loop is permeable for water and Na^+
- The ascending limb of the loop is relatively impermeable to water and permeable to Na^+, Cl^-,
  urea. Accumulation of the solutes → hypertonicity of the interstitium.
- The collecting duct is relatively impermeable to urea but permeable to water (in the presence of
  vasopressin). Interstitial hypertonicity is supported also by active resorption of Na form the duct to the interstitium.

Efect: the absorption of water = concentration of urine.

The role of vasa recta = additional countercurrent exchanger.
Descending vasa penetrate to the hypertonic portion – there water diffuses out of the vessels – and in the hypotonic portion – water diffuses into the vessels. The way of the solutes is in opposite direction. Recirculation of the water and the solutes from and into vasa recta helps to maintain hypertonicity.

URINE

Volume:1000 - 1500 ml/24 hours - in adult
Vary with fluid intake and withfluid output form other routes - skin, lungs, gut.
(Volume reduced during sleep and muscular exercise).

Specific gravity: 1010-1035 kg/m^3. (Specific gravity greater on protein diet.)

Reaction: Usually slightly acid- pH 4.5-8 – average 6.0
(Varies with diet- acid on ordinary mixed diet, alkaline on vegetarian diet.)

Colour:
Yellow due to urochrome pigment –probably from destruction of tissue proteins.Concentrated and darker in early morning –less water excreted at night but unchanged amounts of urinary solids.

Odour: Aromatic when fresh → ammoniacal on standing due to bacterial decomposition of urea to ammonia.

COMPOSITION of the urine:

Water - - - - - 1000-1500 ml/24 h

Inorganic	**substances**	millimols excreted in 24 h
	Sodium - - -	200
	Chloride- - -	200
	Calcium - - - -	5

Potassium - - - 50
Phosphates - - -25
Sulphates - - - 50

Organic substances
Urea - derived from breakdown of protein – therefore varies with protein in diet.
Uric Acid - comes from purine of food and body tissues.
Creatinine - from breakdown of body tissues; uninfluenced by amount of dietary protein.
Ammonia - formed in kidney from glutamine brought to it by blood stream;

*[In the **newborn,** volume and specific gravity are low and composition varies.]*

PHYSIOLOGY OF THE URETERS AND URINARY BLADDER

URETERS convey urine from kidneys to bladder: Long, narrow muscular tubes. Smooth muscle coats with outer fibrous tissue coat and inner mucous membrane.
Slow waves of contraction (every 10 seconds)propel urine along ureter. 1-5 small ´spurts´ enter bladder per minute.

URINARY BLADDER acts as reservoir for urine: Hollow muscular organ. (Size and position vary with amount of urine - stored (120-320 cc).
Smooth muscle coats –distend as urine collects: contract periodically to expel urine to urethra.
Smooth muscle of bladder wall runs down into urethra.
Internal shincter.
External sphincter.
Circular striated muscle (under voluntary control – CNS).

STORAGE AND EXPULSION OF URINE

Urine is formed continuously by the kidneys. It collects, drop by drop, in the urinary bladder which expands to hold approx. 300 ml. When the bladder is full the desire to void urine is experienced.

When bladder is empty and beginning to fill –

- inhibition of parasympathetic
- activation of sympathetic → Relaxation of bladder wall.

MICTURITION

= stretch reflex – carried out through centres in spinal cord. In older children and adults – reflex can be controlled and inhibited **voluntarily**.

Stimulus: Distension of the **receptors** in smooth muscle
When empty, pressure in bladder is zero.When 50 ml urine collect→pressure ↑ to 10 cm H_2O up to 300 or 400 ml → little increase in pressure.
(As bladder distends, walls of ureter are pressed together preventing regurgitation of urine.)

Afferent pathways to the higher centres through pons and midbrain. Sensations to consciousness

Micturition center: Parasympathetic $S_2 – S_4$
Sympathetic efferents L_{1-3} - inhibits ganglia

Efferent pathways: Impulses in parasympathetic nerves (pelvici)and in somatic nerves (pudendal).

Effectors: Smooth muscle in BLADDER WALL - contraction, sphincters smooth muscle – internal + striated muscle external -relaxation

Effect = Urination – micturition

PHYSIOLOGY OF THE NERVOUS SYSTEM

RECEPTORS

Specialized structures (free nerve endings, special cells) for detection of stimuli and their transformation into generator and action potential

- "sensors" – transforming stimuli into signal

Receptors + auxiliary structures = sense organ (eye ...)

Receptors (sense organ) + afferent pathway + relevant portion of CNS = analyser

Classification of receptors:

A) Based on stimulus:

1. Mechanoreceptors: pressure, vibration, movement (cutaneous, hearing, statokinetic r., proprioceptors)
2. Radioreceptors: thermoreceptors - infrared radiation
   photoreceptors - light
3. Chemoreceptors: a change in the chemical composition of the environment (ext. + int.), contact – taste, telereceptors - smell

B) Based on localization:

1) **Exteroreceptors** - *telereceptors* (vision,auditory and olfactory senses)
   - *contact r.* (sense of taste, tactile s.)

2) Interoreceptors - baroreceptors, chemoreceptors, cells for osmotic pressure and a.-v. difference of blood glucose (hypothalamus) = visceroreceptors

3) Proprioreceptors – in muscles, tendons, joints

4) Nociceptors – pain

C) <u>Based on velocity of adaptation:</u>

1. Rapidly adapting = phasic, gradually $\downarrow f_{AP} =$ ADAPTATION
2. Slowly adapting = tonic - stable intensity of stimulus

STIMULI

specific form of energy – able to stimulate receptor

Differential sensitivity: each kind of receptors - specific energy - the most sensitive to this kind of the stimulus = <u>adequate stimulus</u> - the lowest threshold for response

Non-specific energy – <u>inadequate stimulus</u> – higher threshold

Principles of receptors function:

- Stimulus - membrane permeability changes (influx of Na^+ - change in membrane potential) $\Rightarrow$ generator potential as a local response of excitable membrane
- it spreads out with decrement to initial segment of axon
- amplitude proportional to stimulus quantity
- reaching the threshold **action potential**
- ↑generator potential $\Rightarrow$ ↑ frequency of action potentials

Characteristics of the receptor potential:

1) <u>Gradation</u> by the strength of the stimulus: the number of channels opened and depolarization is proportional to the intensity of the stimulus

2) <u>Propagation</u> – no propagation, the receptor potential is localized in the receptor –local potential

3) <u>Timing</u> – long latency, long response (rapid/slow adaptation)

4) <u>Ability to evoke AP</u> – when the receptor potential rises above the threshold level. The more the receptor potential rises, the greater becomes the AP frequency.

- Frequency coding

<u>Signal conduction</u> 0,5-120 m/s

Nervous fibres: classified according to myelinisation and velocity of conduction

Aα, Aβ, Aγ, Aδ, C, Convergence vs. Divergence

Sensoric information coding

AP in nerve fibre - uniform and potentials are similar in all nerves.

Differentiation of stimulus intensity:

1) by differences in action potentials firing rate

2) by differences in the number of activated receptors

Intensive stimuli – activation other receptors and sensory units = recruitment of sensory units.

SENSORY UNIT

- is one afferent axon and all peripheral branches with receptors
- At low intensity only receptors with lower threshold are activated, at max.intensity – all receptors
- Intensive stimuli – activation of further receptors and sensory units = recruitment of sensory units.

PAIN

„Unpleasant sensory and emotional experience associated with tissue damage"

-**protective mechanism:** draws attention to risk of damage, removes the cause of damage

Pain receptors = nociceptors (algoceptors) = free nerve endings, 50-100/cm^2, in tissues

= slow adaptation

- mechanical, thermal, chemical (bradykinin, serotonin,histamine, K+, acids ...)

Pathways: 2 fibre systems:

1) Aδ fibres – 2-5 μm (6-30 m/s) – fast+sharp pain – mainly for mechanical and thermal pain

2) C fibres – 0.4 – 1.2 μm (0.2 – 2 m/s) –slow, dull, diffuse pain.

Fibres – to spinal cord – through dorsal spinal roots.

Spinothalamic tract

1) Neospinothalamic – fast pain – Aδ fibres – the tract passes upward to the brain in the anterolateral columns – to the thalamus.

2) Paleospinothalamic – for slow – chronic pain – C fibres – substantia gelatinosa – anterolateral pathways.

Then to somatosensory cortex in gyrus postcentralis

The role of CNS in pain perception:

Reticular formation = arousal, concentration

Thalamus and limbic system = emotional component

Hypothalamus = concomitant autonomic reactions - *sympathetic activation*

Cortex = perception of pain

Pain classification based on:

Function: physiological vs. pathological

Duration: acute vs. chronic

Type:

- **rapid**: after 0.1 s, sharp, localized, *stimuli:* mechanical, thermal, *conduction:* Aδ-fibres
- **slow**: after >1 s, diffuse, dull, imprecise localization

Phantome pain

- pain in non-existing part of body; *mechanism:* based on projection law
- increased activity in neurons of dorsal horns that have been a part of sensory pathways from removed limb

Classification of pain II.

1) **Superficial pain**: well located, sharp, acute
2) **Deep pain** – poorly localized, nauseating, changes in BP, sweating – autonomic reactions. From the bones, tendons, joints.
3) **Visceral pain** – from viscera – abdomen, chest. Localized stimulus does not cause pain. Diffuse stimulation of nerve endings – severe pain (ischemia, distention of gut...). Referred pain.

- *Pathways – via sensory fibres of the autonomic nervous system. Pain is difficult to localize.*

Referred pain:

When pain is referred – it is to a structure that is developed from the same embryonic segment (dermatome) as the structure in which the pain originates = **dermatomal rule**.

- E.g. the heart – the arm, the testis – the kidneys – ureters – medial parts of thigh

Mechanisms of referred pain:

1) Convergence theory: There are more sensory fibres in the peripheral nerves than axons in the spinothal. tract → there must be convergence.

- *Somatic and visceral afferents converge on the same spinothalamic neurons.*

2) Facilitation theory: Incoming impulses from visceral structures reduce the threshold of spinothalamic neurons receiving afferents from somatic areas – already minor activity in the pain pathways from the somatic areas passes on to the brain.

Changes in pain perception

1) Hyperalgesia

2) Hypoalgesia

- peripheral: stimulation of tactile and pressure receptors reduces pain perception (acupressure, acupuncture, massage)
- centraly: Psychogenic mechan.+ endogennous opioid system (enkephalins and endorphines)

3) Analgesia

Analgetic system of CNS

Three parts:

1) Periaquaeductal gray (mesenceph., pons) (enkefalins)

2) Nucleus raphe (pons, medulla) (Serotonin, "enkefalinergic" praesynapt. inhib.spinal neurons)

3) Hypoalgic system of dorsal horns (spinal cord)

- *Endogenous opioids in brain and spinal cord (endorphins enkephalins, dynorphins)*

Pain threshold

- lowest intensity of stimulus eliciting pain: low interindividual variability; intraindividual variability - according to state of consciousness and according to the stimuli from periphery (hunger-satiety, disease, fatigue)

Pain tolerance

- Maximal intensity and duration of pain that subject can withstand. Correlation with age. Influence of culture.

Physiological and pharmacological principles of the analgesia

treatment of pain

- Distracting techniques (controlled breathing, rhythmic tapping,..)
- Skin stimulation (cold compress, liniments, massage, acupuncture..)
- *Mechanism:* stimulation of tactile sensitivity Aβ-fibres – transmission inhibition

Gait control theory
Modification of inputs at the spinal level synapses in dorsal spinal horns –*"gates"* – opening/closing of action potentials transmission.
- Gates closes when:
- impulses through thick fibres
- influences from upper centres

Pain control
- **Analgetics** vs. placebo
- **cordotomy** – tract interruption at the level of spinal cord
- **rhizotomy** – interruption of dorsal spinal roots
- **neurotomy** – interruption of peripheral nerve

RETICULAR FORMATION, EEG, SLEEP

RETICULAR FORMATION

RF = reticular-diffuse connections of neurons, cells don't form obvious nuclei
- med. oblongata, pons Varoli, thalamus

→ **analyzer**
→ **integrator**
→ **„control" of CNS**

→ concentration of various information from CNS and receptors to small number of neurons - general system for controlling the level of activity of the brain and the spinal cord

Functions of RF:
- regulator of ANS (heart rate, breathing rate, GIT)
- sleep, fatigue, control of consciousness
- modulation of pain
- motivation to perform any activities
- control of walk, eating, urination, defecation, sexual activity...
- control of some forms of behavior
- predisposing factor for personality: introvert/extrovert ...

→ **coordination of somatic and autonomic ff.**
→ **coordinator of efferent info → organism as a whole**

RF:
ascendent neurons → cerebral cortex → RAS
descendent neurons → spinal medulla
- facilitation
- inhibition

Ascendent system:
- activates cortex, hypothalamus, limbic sy

↓

reticular activation system (RAS)

↓

RAS + thalamus (non-specific nuclei)

↓

keep consciousness

- el. stimulation of RAS: → *„arousal" reaction* on EEG

- non-specific system

- activation influence on RF:
important for entrance of info into consciousness, formation of temporary connections
→ higher forms of behavior (learning, memory...)

- RAS acts on the level of concentration on sth.
- modulation of afferent information from receptors (vision, hearing, proprio)
- stimulation of RAS:
- epinephrine
- mild hypoxia
- hypercarbia
- impulses from proprioreceptors and nociceptors

- destruction of RAS („*cerveau isolé*") → deep sleep, miosis, Ø response to stimulation

Descendent system:
- via tr. reticulospinalis → spinal interneurons
- effect on motoric function:

tone and movement

↓

control of voluntary and involuntary movement

- descendent neurons act:
a. on α and γ spinal motoneurons
b. on Renshaw interneurons

Activity of Reshaw cells:
Spinal motoneurons give off a recurrent collateral - synapse with an inhibitory motoneuron (Renshaw) - terminates on the cell body of the same spinal neuron or other SN - inhibitory synapse with mediator (glycine) → inhibition of discharge of the SN

→ desc. system of RF acts on **motoneurons of extensors**
(control by cerebellum and cerebral cortex)

- *decerebration rigidity*: transsection at the level of lamina quadrigemina → elimination of inhibitory influence from CNS – predominance of facilitation - ↑ tone, spasticity of extensors (opistotonus)

Descendent system of RF:

Facilitation area	**Inhibitory area**
dorsolateral – MO, PV, mesencephalon, diecephalon	ventromedial - MO
bigger area – small cells	smaller area – big cells
mostly crossed fibres	mostly uncrossed fibres
Activation:	**Activation:**
statokinetic receptor vestibular cerebellum collaterals of specific sensor pathways cerebral cortex	spinal cerebellum basal ganglia cerebral cortex
Function:	**Function:**
↑ excitability of spinal centers of somatic reflexes acts on reflex tone antigravitation muscles ↓ tone of flexors	↓ spinal reflexes (especially tone of extensors) ↓ voluntary movement
Importance:	
keeping posture and position of the body	

Gama system and RF: 2 types of pathways to γ neurons

1.homogenous fascicles of thicker fibers with rapid conduction of excitation
→ coordinate fast movement and setting the tone
2. disperse thin fibers with small speed of conductivity
→ set muscular tone of large areas

RF:
- regulates muscular tone and motility
- influences autonomic ff. (body temperature, sexual ff., water metabolism...)
- continuous activity (10-20 excitations/s)
- control of vigility and sleep – hypotonia, depressed motility

ELECTROENCEPHALOGRAPHY (EEG):
= recording of electrical activity of the brain

→ **EEG (electroencephalography)** – recording from surface of the skull
→ **ECoG (elektrocorticografia)** – recording from surface of the brain

- changes of summation potential of huge number of neurons (depolarization: deviation ↑, hyperpolarization: deviation ↓)

- electrodes (10-20): unipolar, bipolar (longit., transvers., circul. arrangement)
- change in potential → *wave:* frequency and amplitude

Rhythm:

alpha (Berger rhythm): 8-13 Hz, ampl. 30-50 μV

→ **rhythm at rest, vigility with closed eyes**

beta: 14-30 Hz, ampl. 5-10 μV

→ rhythm of activity

Desynchronization: transition of alpha into beta rhythm

→ opening the eyes, sensoric stimulus, mental activity

arousal response: RAS, non-specific nuclei of thalamus

theta: 4-7 Hz, 50 μV

→ **vigility in children**

→ **emotional stress in adults**

delta: 1-3.75 Hz, 100-150 μV

→ deep sleep

Clinical importance of EEG:

- neurology (pathological conditions, hematoma, epilepsy)
- psychiatry (depressive disorders)
- depth of anesthesia, determination of biological death, research (in space)...

EEG investigation:

- rest rhythm + activation methods to change the rhythm, resp. to provoke pathological discharge in the brain (opening the eyes, hyperventilation, photostimulation...)

Investigation of evoked potencials:

- EP = potencials evoked by a stimulus (light, sound...)

1. Primary EP:

- potential from specific cortical structures
- highly specific by its localization – recorded over endings of sensoric pathways

2. Secondary EP:

- without specific localization
- related to RAS and non-specific thalamic system

→ *functional neuronography*: maping of cortical areas according to the projection of individual receptor areas

Ontogenesis of EEG:

- newborn: delta 1-3/s, but with low ampl. (50 μV)
- in 2.-3. year: beginning of theta
- in 3.-4. year: beginning of alpha in occipit. leads
- after 10. year: well-formed alpha rhythm (delta-theta-alpha)
- after 60. year: less alpha, more theta (alpha-theta)

SLEEP:

Vigility:
= situation when organism dinamically and knowingly communicates with his environment

- role of RF:
→ afferent information from receptors
→ efferent impulses from cerebral cortex
→ influence on adrenal medulla

Sleep:
- unconsciousness from which the person can be aroused by sensory or other stimuli (compared to coma)

- sleep centers: hypothalamus
nuclei of thalamus
reticular formation
telencephalon

Hypotheses of sleep:
- ancient (Greece) – soul (consciousness) goes away from the body during sleep – Thanatos (God of death), Hypnos (God of sleep), Oneiros (God of dreams)
- circulatory hypothesis: ↓ blood flow in brain → sleep
- ↓ activity of RF (RAS) – non-specific thalamic nuclei (stereotypes to decrease activity of RAS)
- chemical hypothesis: hypnotoxines – DSIP (delta sleep inducing peptide), PG D2 ↑ sleep, PG E2 ↑ vigility
- humoral theory – serotonine ↑ sleep, noradrenaline ↑ vigility, fight or flight

A. Non-REM sleep: 4 stages
1.transition of vigility to snooze:
- muscle tone decreased, slower breathing
- EEG: waves with ↓ ampl. and ↑ frequency (beta)

2. snooze:
- relaxed position
- EEG: *sleep spindles* (similar to alpha rhythm, but RF not completely supressed), ampl. 50 μV, freq. 10-14/min.

3. light sleep:
- hypotonia of muscles
- EEG: ↑ ampl., ↓ freq.

4. deep (delta) sleep:
- slow breathing, ↓ heart rate, total regeneration, synchronization
- EEG: ↑ ampl., very low freq. (delta waves)

B. REM sleep:
= **paradoxical sleep**: originally depressed higher etages of CNS (areas of cortex) now active („watch points"), older parts inhibited
- characterized by dreams

- hypotonia of muscles
- rapid eye movements
- EEG: similar to vigility

Organization of sleep stages:
1. falling asleep
2. non-REM
3. REM

- non-REM and REM sleep (2. + 3.s.) repeat 4-6 x per night
- 1 period = 90-100 min.
- at the end of night ↓ 3. and 4. s. non-REM and ↑ REM
- REM is about 25 % of sleep – important for IQ (fixation of information in the memory)

→ sleep per day:
newborns 16-20 h.
adults 7-8 h.
older people 5-6 h.

Changes in sleep:
Non-REM sleep:
- predominancy of parasympathetic tone – predominant anabolic processes
- ↓ heart rate, f. of breathing and blood pressure
- ↓ metabolism
- ↓ excitability of nervous system
- release of gonadotropines and STH (growth)

REM sleep:
- improved blood flow in brain stem and hypothalamus
- ↑ local temperature and O2 consumption – ↑ brain metab.
- ↑ synthesis of RNA and proteins (wound healing)
- ↑ excitability of receptors
- ↑ heart rate and breathing – „guard of the organism“

THE AUTONOMIC NERVOUS SYSTEM (ANS)

autonomic“ – involuntary (independent on a human will)
- the portion of the nervous system that controls the visceral functions of the body helping to maintain a dynamic and static conditions in the internal enviroment
↓
- homeostasis

ANS reflex:
Receptors:
chemoreceptors, baroreceptors, mechanoreceptors....
Afferent pathway:
Sensitive fibers
Centers:
In spinal cord, medulla oblongata, hypothalamus...
Efferent pathway:

Interrupted in autonomic ganglion → preganglionic and
postganglionic neurons = two neuronal pathway
Effectors:
Visceral organs – heart, smooth muscles, glands

Efferent pathway of the ANS
- **preganglion neurons**:
  the cell bodies are located in the intermediolateral gray
  column or the motor nuclei of the cranial nerves
- the **axons** – preganglionic fibers (myelinated slow-conducting B fibers)
- **postganglion neurons**
- **the axons** – postganglionic fibers (mostly unmyelinated C fibers)
- visceral **effectors**

- each preganglionic axon diverges to an average of 8-9 postganglionic neurons → autonomic output is diffused → principle of divergency

Reflexes

	SOMATIC	**AUTONOMIC**
Receptors:	proprio-, exteroreceptors	special rp.
Afferen.	In sensoric nerves	in all types: symp.,pasy...
Centers	spinal cord	spinal cord, medulla oblongata, pons, hypothalamus
Efferent.	one-neuronal	two-neuronal
Effector	skeletal muscles	heart, smooth muscles, glands
Reflex time	short	longer (neurotransmitter sec.)
Effect duration	short	longer
Purpose	control of posture locomotion	control of autonomic functions

The transmisson at the synaptic junctions in the ANS
- ✓ autonomic synaptic junctions**:**
  - pre - and postggl. neurons
  - postggl. neurons and effectors

- chemically mediated by transmitter agents:
  principal transmitter agents: acetylcholine (Ach), noradrenaline (NA)
  - cholinergic fibers - Ach
  - noradrenergic (adrenergic) fibers – NA (A)
  - nonadrenergic noncholinergic system (dopamine, VIP...)

Cholinergic neurons:
- ✓ **all preganglionic neurons (sy + pasy !)**
- ✓ the anatomically postganglionic parasympathetic neurons

- ✓ the anatomically sympathetic postganglionic neurons which innervate sweat glands and which end on blood vessels in skeletal muscles **(sympathetic cholinergic vasodilator system)**

Noradrenergic (adrenergic) neurons:
- the remaining postganglionic sym. neurons
- the adrenal medulla – sympathetic ganglion

The transmitter agents:
I. Acetylcholine
- synthesis: cholin+acetylCo A *(acetyltransferase)*

- inactivation: *acetylcholinesterase:* cholin+acetate
Cholin – the uptake for the resynthesis Ach

very short effect duration

Receptors for Ach
- nicotinic (N) receptors
- in the synapses between the pre- and postganglionic neurons, in the neuromuscular junction

- muscarinic (M) receptors:
postggl. PS neurons
  - M1 – Gp protein
  - M2 – Gi protein

Parasympathomimetic drugs: Ach, methacholine...
Parasympatholytic drugs: atropin, scopolamin...

II. Noradrenaline (Norepinephrine)
- transmitter of postggll. sympathetic endings
- CNS
Phenylalanine→Tyrosine→DOPA→Dopamine→Noradrenaline→ Adrenaline

The terminations of the NA effects:
1. diffusion to the blood (capillaries)
2. active reuptake mechanism (taken up to the noradrenergic neuron up to 70%)
3. Inactivation of NA:
   - by COMT (catechol-O-methyltransferase) - normetanephrine, and conjugates
   - by MAO (monoamine oxidase) – 3methoxy-4-hydroxymandelic acid (VMA) and glycol

the effect duration is longer than Ach

Receptors of sympathetic nervous system:

- ❑ α – α1, α2

- β – β1(cardiac rp.), β2 (bronchial)

The influence:
α : vasoconstriction, intestinal relaxation....
β : ↑HR, ↑ contractility, vasodilatation, lipolysis...

Sympathomimetic drugs: NA, A, phenylephrine....
Sympatholytic drugs: phentolamine, propranolol

Physiological anatomy of the sympathetic nervous system

- **thoracolumbal division** of the ANS
  truncus sympaticus + sympathetic ggl
- pregg. fibers – short
- postggl. fibers – long

Physiological anatomy of the parasympathetic nervous system

- **craniosacral division**:
- cranial outflow: III., VII., IX., X. (75-80%)
- sacral outflow: S2-S4
- preggl. fibers – long
- postggl. fibers – short (located on or near the visceral struc.)

Function of ANS subsystems

SYMPATHETIC NERVOUS SYSTEM:

- emergency situations, predominant in conscious state
- stress
- increase of energy release – catabolic reactions
- positive trophic effects on the heart, hypertensive reaction
- bronchodilatation
- inhibition of GIT activity
- mydriasis
- glycogenolysis, ↑ glucose blood,, lipolysis
- ....

PARASYMPATHETIC NERVOUS SYSTEM

- recovery processes
- decrease of energy consumption – at rest, sleep...
- anabolic reactions
- negative trophic effects on the heart
- hypotension
- bronchoconstriction
- Increase of GIT activity
- miosis....

Autonomic tone and excitability

Tone – there are discharges in autonomic nerves at rest

- reflex: (stimulation of baro-, chemoreceptors)
- central (hypothalamus)

- sympathetic (e.g. smooth muscles in vessels)
- parasympathetic (e.g. heart)

Excitability: - the ability to change the autonomic tone

Autonomic reflexes

I. Classification by localization of receptors and effectors:

1. viscero-visceral
2. viscero-cutaneous
3. cutaneous-visceral
4. viscero-motoric

II.Classification by organs and systems

1.Cardiovascular – control of the HR, BP, barorp. reflexes....
2. Respiratory – (e.g. H-B reflex...)
3. Gastrointestinal: (e.g. defecation)
4. Urogenital system: (e.g. micturition)
5. others.... (e.g. eyes r.)

Regulation of the ANS

- spinal cord: (micturition, defecation....)
- medulla oblongata (more complicated rr. – cardiovascular, respiratory, salivation...)
- midbrain - eyes rr. - accomodation, pupillary
- **HYPOTHALAMUS** – center of the ANS
- - "head ganglion of the ANS" (Sherrington)
- CAN - central autonomic network

medial prefrontal cortex, insula, gyrus cinguli....

HYPOTHALAMUS

Connections:

- with the posterior pituitary by neural fibers – **hypothalamo-hypophyseal tract**

- with the anterior pituitary by blood vessels – **portal hypophyseal vessels (system)**

- many aff. and eff. connections among hypothalamus and other parts of CNS

Functions of hypothalamus

- integration with autonomic nervous system („center")

sympathetic – in dorsal (lateral) region
parasympathetic – in anterior region

- temperature regulation (cutaneous cold receptors, temperature sensitive cells in hypothalamus; anterior h.- heat; posterior h. - cold
- endocrine control
- water balance and food intake
- thirst (osmoreceptors, lateral superior hypothalamus)
- hunger: „glucostat" cells sensitive to rate of glucose utilization

ventromedial satiety center
lateral hunger center

- emotional (behavioral) and sexual functions
- biological rhythms (lesion of the suprachiasmatic nuclei disrupt the circadian rhythm)

Examination methods of the ANS

I. Cardiovascular system

- the variability of cardiovascular parameters
- short-term, long-term

Ewing battery of cardiovascular tests

- deep breathing
- orthostatic test
- Valsalva manoeuvre
- hand-grip test

o**ther cardiovascular tests**

- oculocardiac test, diving reflex, mental and physical load...
- pharmacological tests...
- **baroreflex sensitivity:** simultanous continual recording of heart rate and blood pressure
- electrodermal activity (skin sympathetic response)
- MSNA (muscle sympathetic nervous activity) – microneurographic m.

Other systems:

- GIT: (e.g. evoked oesophageal potentials...)
- eye reflex...

The cardiac activity – extreme sensitive to modulation of the ANS!

Psychosomatic relationships

- cerebral cortex – the influence on the respiratory, cardiovascular, immune, autonomic and other systems

- relationships - cortex - organs
  organs - cortex

- **efferent influences of the cerebral cortex:**

1. inducing - to provoke organ activity (e.g. cephalic influence of gastric secretion)
2. modulating - adjustment of the function (e.g. HR before work)

- **afferent impulses: from organs to the CNS**

- disturbance of visceral functions → disturbance of cerebral cortex function (pathological dominant) – nonadequate efferent impulses to the organs – circulum vitiosus

The principles of psychotherapy:

- the therapy of mental and physical disorders using psychological methods

(dialogue, communication, relaxation...)

relaxation method:

- autogenic training (Schultz, 1932)
- relaxation and concentration method
- the state of internal mental concentration and maximal somatic relaxation → conditioned reflex
- autosuggestion

m**ental concentration → somatic relaxation**

- ✓ *music therapy, meditation, yoga, hypnosis...*

The physiological effects of relaxation methods

- the principle: to restore the balance between the activity of the sympathetic (F/F) and parasympathetic (rest and digest) branches of the ANS

- CVS: ↓HR, ↓BP (ECG, FINAPRES)
- respiratory system: ↓respiratory rate, slow and deep breathing (Respitrace)
- cerebral activity: alpha rhythm (EEG)
- muscle activity: ↓muscle tone (EMG)
- lower oxygen consumption
- improvement of self-control, self-confidence....

Biofeedback

- continual monitoring of several physiological parameters (HR, BP, breathing, muscle tone, EEG...)
- voluntary influence on the followed parameters
- biofeedback + relaxation therapy

THE SENSES

THE SENSE OF VISION

Vision: an ability to receive, process and interpret an information in the form of visible light to perceive the form, color, size, movement, and distance of objects
-eye: optic system - creation of an image on retina
-receptors and visual pathways - analysis of an image

A: OPTIC SYSTEM

1. Lens system: 4 refractive interfaces:
air / cornea / aqueous humor / crystalline lens / vitreous humor

ACCOMODATION:
= the process by which the eye increases optical power to maintain a clear image on the retina (for far and near objects)

Mechanisms: contraction of ciliary muscle (pasy, n.III)→ relaxing of suspensory ligaments → convex lens with ↑curvature (elasticity) → higher refractive power (children: 20 → 34 D ..power of accomodation)

Presbyopia – in elderly people

Errors of refraction: - spherical (emmetropic, myopic, hyperopic eye)
- aspherical - astigmatism

2. Pupil:
- variable aperture system (1.5 – 8 mm)... miosis, mydriasis

Function: - to adapt the diameter of aperture to light conditions
- relation to depth of focus

B: RECEPTORS AND VISUAL PATHWAYS

1. Retina:
- light-sensitive portion of the eye, several layers

aa) Pigment layer (melanin prevention of reflection inside eyeball,
storage of vitamin A- exchange with outer segment of photoreceptors

a) rods and cones: real photoreceptors of an eye - in outer segment- photosensitive pigment (R: scotopsin, C: 3 types of photopsins I,II,III 30-300x less sensitive, differential spectral sensitivities)

Photochemistry of vision:
Rhodopsin (protein scotopsin + 11-cis retinal) light Reformation
trans-retinal scotopsin + el.changes
Retinal isomerase
cis-retinal
trans-retinol cis-retinol

Electrical changes: in conductance for Na+ and AP

- distribution of photoreceptors
- photopic and scotopic vision

Dark adaptation:
- biphasic time course: During the first phase, the light sensitivity threshold decreases sharply before stabilizing after a few minutes. This first phase represents the adaptation of cones.
- After about 5 minutes, sensitivity increases again and stabilizes once more after about 20 minutes. This second phase represents the adaptation of rods.
- mydriasis, ↑synthesis of photosensitive pigments

Visual acuity: sharpness of vision
- Best developed in central fovea region (35.000 C, slender body, max.visual acuity- 25-60")
- outside the foveal area - ↓density of receptors, ↑convergence)

Testing of visual acuity - optotypes

b) bipolar cells

- depolarizing/hyperpolarizing on receptors stimulation

c) horizontal cells

-lateral inhibition of bipolar cells – enhancing and detection of visual contrast

d) amacrine cells

- many types, various means of stimulation

e) ganglion cells -transmission of signal to CNS – AP

-convergence (R: 60:1, C: 2:1)
-3 types: W (40%)- from R, broad fields, directional movements X (55%)- from C, small receptive fields, color vision; Y (5%)- broad fields, to rapid changes of image

2. Visual pathways:

Collaterals of optic tract:
Hypothalamus (circadian rhythm)
Pretectal nuclei (accomodation, pupillary light reflex)
Superior colliculus (eye movements)

Field of vision:
-visual area seen at given moment
- monocular, binocular
- blind spot (15 deg. lateral to central point of vision)

Abnormalities:
-scotomata
-hemianopsia bitemporal (longitudinal lession of chiasm)
homonymous (lession of optic tract)

Entoptic phenomena:
- visual effects whose source is within the eye itself

1. Floaters (muscae volitantes)
-slowly drifting transparent blobs of varying size and shape
-particularly noticeable when lying on the ground
looking up at the sky
-caused by imperfections in the fluid of the eye

2. Scheerer`s phenomenon = blue field phenomenon
-noticeable when viewed against a field of pure blue light
- tiny bright dots moving rapidly along squiggly lines in the visual field
-caused by leucocytes moving in the capillaries in front of retina

3. Phosphenes
-perception of light without light actually entering the eye

-caused by mechanical, electrical, magnetic stimulation of retina

THE SENSE OF HEARING

The importance of hearing:

- orientation
- warning against danger
- at communication
- speech self-control

Anatomical notes:

1. **External ear** – the pinna (helps to direct sounds), the external auditory meatus, auditory Canal – transmits sound waves to the tympanic membrane
2. **Middle ear** – separated from extrenal ear by tympanic membrane (called eardrum), chain of ossicles – the malleus, the incus, and the stapes. They connects the TM to the oval window (an opening into the inner ear). Striated muscles: m.stapedius, m.tensor tympani. Eustachian tube – connects middle ear to the pharynx and equilizes pressure differences between external and mid.ear (flying, diving)
3. **Inner ear** – bony and membraneous labyrinth (cochlea and vestibular apparartus), receptors for two sensory functions. Cochlea – spiral-shaped organ, divided by basal and Reissneri membranes to three parts – scala tympani and scala vestibuli – by perilymph (helicotrema), between – scala media – by endolymph). On basal membrane – organ og Corti with receptors – hair cells

Adequate stimulus for auditory receptors – **sound**

- sound is produced by waves of compression and decompression transmitted in air (or other media such as water), propagation in the air – 335 m/s
- sound composed of many unrelated frequencies - noise

- frequency (nm.of waves per time) – gives height of the tone
- amplitude of the sound vawe – gives colour of the tone
- intensity of the sound in decibels (dB) – over 100 dB can damage organ of Corti, over 120 dB can cause pain

- normal human ear is sensitive to pure tones with frequencies between 16 Hz and 20 kHz
- less than 16 Hz – infrasound, over 20 kHz – ultrasound
- highest sensitivity of human ear – at 1-3 kHz
- speech – at frequencies 250 – 3000 Hz (about 65 dB)

the phenomenon of masking
– the presence of one sound decreases the ability to hear other sound
- absolute and relative refractery period of auditory receptors and nerve fibres beiing stimulated before
- sound background – increases hearing threshold

Sound transduction – the functions of external and middle ear

- the ear transformates sound vawes of external environment to the action potencials of auditory nerves

1. transmission of souns through the ossicular system

- vawes cause the tympanic membrane to oscillate. The ossicles are connected to the TM by handle of the malleus, which is taughtly bound to the other bones. The vibrations are transferred by the ossicular system through the oval window on the structures of inner ear (by the vawe movement of perilymph)
- stimulation of the organ of Corti – causes action potencials in nerve fibres

function of mm.stapedius and tensor tympani: when loud sounds are transmitted to the CNS through the ossicular system $\Rightarrow$ reflex contraction of both muscles occures **– attenuation reflex** – protect cochlea from damaging vibrations caused by excessively loud sounds

2. transmission of sound through the bone

- vibrations are transmitted by the bones of the skull on the fluid of inner ear
- because the cochlea is embedded into the bony cavity
- (tuning fork or very loud sounds, especially the mastoid precess)

3. transmission of the sound by the air

- through the TM, the air in the middle ear, oscillations of the round window membrane
- of a little importance, mostly under pathological conditions

Function of inner ear

Organ of Corti – the neural apparatus responsible for transduction of sound

- receptors in two lines – outer and inner hair cells, at the apex of the cells – stereocilia, touching the tectorial membrane
- at the base of the hair cells terminate the nerve fibres of neurons from ganglion spirale

Stimulation of auditory receptors

- movement of the stapes causes waves in perilymph of scala vestibuli

Basilar membrane serves as frequency analyser – it distributes the stimulus along the organ of Corti so, that different hair cells will respond to different frequencies of the sound – place theory of hearing

- waves at high tones (high frequency sounds) activate the basilar membr. near the base of the cochlea
- waves at low tones (low frequency sounds) – max. of the amplitude – at the top of cochlea

- the sound causes deformation of basal membrane, deformation of the hairs and occurence of receptor (generator) potencial. If the RP is of a high intensity, it excites the cochlear afferent n.fibres $\Rightarrow$ elicits action potencials

- frequency of AP in the auditory nerve is related to the sound volume

Central auditory mechanisms

1st neuron in ganglion spirale – axons of these bipolar afferent neurons form the auditory part of n.statoacusticus (n.VIII), they end in ncl.cochlearis dorsalis et ventralis between pons and MO

2nd neuron – in cochlear nuclei, through crossed and non-crossed pathways to the sub-cortical centers – colliculi inferiores (for acustic-motor reflexes)
some neurons – to the different nuclei in pons, FR, cerebellum

3rd neuron – in corpus geniculatum mediale – to the projection neocortical field in gyri of Heschl in temporal lobe, in Brodmanns area 41

- connection with other auditory cortical centers in temporal lobes – for further processing of auditory information (auditory memory, understanding of the speech, …)

- importance of fasciculus olivocochlearis – efferent fibres, to hair cells, decreases the response to the auditory stimuli - damping effect

Deafness – the loss of the ability to hear

Two most important types:
1. conduction loss (external and middle ear, foreign body in canal, infection)
2. sensorineural loss (damage of organ of Corti, nerv – drugs ATB, tumor,…)

- if the cochlea and nerve are still intact but the ossicular system has been destroyed, sound waves can still be conducted into the cochlea by means of bone conduction
- tuning forks – Weber and Rinne tests

The Chemical Senses

- the senses of gustation (**taste**) and olfaction (**smell**) depend on chemical stimuli
- they contribute considerably to the quality of life (in animals – have survival value)

OLFACTION (SMELL)

Nasal mucosa:
- olfactory receptors – chemoreceptors in olfactory mucosa (regio olfactoria) (area of 3-5 cm^2), in humans around 10^7 recep., replaced every 60 days
- other cells: free nerve endings of trigeminal nerve – responsible for nonspesific afferent inform. (pain), or for reflex responses – coughing, sneezing, + basal and supporting cells (mucus)

Olfactory receptor: bipolar cell, on its apical surface – cilia (10-20) detecting odorants dissolved in overlying mucus layer. They are unmyelinated, 2 μm long, called olfactory sticks. Axons penetrate the base of the skull through openings in the cribriform plate of the ethmoid bone as olfactory nerve filaments (fila olfactoria) to olfactory bulb.

Stimulation of the olfactory cells
- olfactory receptors – telereceptors
- they response to the odorant substance (gas) in inhaled air dissolved in the mucus

- chemical interaction with the membrane of the cilia
- they evoke receptor (generator) potencial by changing permeability of membrane for Na^+
- fast adaptation
- in humans – ability to distinguish between 2 – 4000 different odors
- the olfactory cells – the highest degree of chemical discrimination

Intensity of the stimulus – depends on concentration of the odor substance (the number of stimulated receptors and the number of moleculs reaching the cell)

Quality of perception depends on concentration: at low c.– pleasant, at high c. – unpleasant
Threshold of the smell – very small amount of stimulating agent is necessary to evoke smell sensation
- depends on interindividual and sexual differences, hunger, diseases (e.g isufficiency of suprarenal cortex – decreases the threshold)

anosmia – inability to smell
hypoosmia – decreased ability to smell
odor „blindness" – inability to detect special odor (deficiency of appropriate receptor protein in olfactory cells for that substance

Sniffing – half-reflex response provoked by presence of a new odor
- increases the ventilation of the upper part of nasal cavity
- contraction of lower parts of nostrils towards the septum followed by series of fast and shallow inspirations and expirations

Central olfactory pathway

1st neuron – cells in regio olfactoria
2nd neuron – mitral and tufted cells in olfactory bulb forming synapses (called olfactory glomeruli) with first neurons. Axons – tractus olfactorius

Tractus olfactorius:
1. stria olfactoria medialis – axons of tufted cells, passing middle line in commisura anterior and entering contralateral olfactory bulb. They connect both bulbs, gyri parahypocampales and corpora amygdaloidea
2. stria o.intermedia – terminates in substantia perforata anterior, responsible for olfactory reflexes – to limbic system and hypotalamus
3. stria o.lateralis – axons of mitral cells – to the nc.amygdalae, to prepyriform and pyriform cortex and the cortical portion of the amygdaloid nuclei ⇒ **the primary cortical center for olfaction. Secondary center –** area enthorinalis

Of an importance are : conections to the limbic system, to the hypothalamic autonomic centers, reflex centers in RF and thalamus

The function of the CNS in olfaction:
1. for perception of odor modalities as information to consiciousness and memory
2. affective quality of smell (pleasant or unpleasant feelings)

- resulting in autonomic responses: 1) „fight or flihgt" responses
  2) reflexes of food intake (salivation, gastric

juice secretion

e.g. vomiting – by central mechanisms due to unpleasant smell and taste stimuli

THE SENSE OF TASTE

- taste is a function of taste buds (9000) in oral cavity
- epiglotis, palate, pharynx and papillae circumvallatae et foliante
- in taste buds – receptor and supporting cells
- receptors are covered by unmyelinated endings of sensory nerves fibres
- fast adaptation

Taste stimuli
- substances dissolved in saliva and liquids
- 4 basic primary sensation of taste
- the tip of the tounge: **sweet** (sacharides, lead) and **salty** (anions of inorganic salts)
- two lateral sides: **sour** (high concentration of H^+)
- the root: **bitter** (heterogenous group of substances)

- sour and sweet – at the palate as well

Ability of different taste sensations: function of CNS
- combination of 4 primary taste sensations + smell sensation + temperature and composition of the food

ageusia – inability of taste sensations
hypogeusia – decreased ability of taste sensations
- for sweet and salt – damage of the tongue
- for bitter and sour e.g. prosthesis covering the palate

taste blindness – for certain substances

Central pathway of taste

- information from 2/3 of tounge – by sensory fibres of chorda tympani, from last third – with n. glossopharyngeus
- areas other than tongue - n.vagus

- the taste fibres form tractus solitarius

1st neuron – receptor cells – axons terminate in ncl.tr.solitarii (medulla oblongata), there is 2nd neuron – axons by tr. Solitario-thalamicus to the thalamus – there is 3rd neuron – and to the cortical taste center in gyrus postcentralis

The importance of CNS
1) perception - consiciousness and memory
2) affective evaluation
3) regulation of metabolism (after stress – increase in intake of sweet food
4) reflexes of food intake (salivation, swalloving, gastric juice secretion, defensive reflexes - vomiting)

Reflexes

„Reflex - a simple, involuntary, specific response of organism to a defined stimulus (stimulation of receptors) mediated by CNS"
Reflex arc

Classifications of reflexes:
A: *by receptor:* proprioceptive (myotatic)
exteroceptive
interoceptive

B: *by effector:* somatic (striated muscles) and autonomic (smooth muscle, gland)

C: *by ontogenesis:* inborn, innate = unconditioned
learned = conditioned

D: *by number of involved synapses:* monosynaptic and polysynaptic

Monosynaptic – myotatic reflexes:

Simple reflex arc: 2 neurons + 1 synapse
Receptor – muscle spindle
Afferent pathway
Centre in a spinal cord segment
Efferent pathway – to the striated muscle
Receptor and effector – in the same organ
Rapid response (50 ms)

Receptor: **muscle spindle** (5 mm);
- in parallel with extrafusal fibres innervated by A_{α} motoneurons ;

Inside the muscle spindles:
- Intrafusal muscle fibres - innervated by A_{gama} motoneurons = gamma motor system
- Receptors: 1) anulospiral endings (A_{alfa}) - to phasic changes = dynamic afferent
  2) flower spray endings (A_{alfa}) - to long lasting stretch = static afferent

Two ways of stimulation:
- Passive stretching of muscle
- Contraction of intrafusal muscle fibers through γ–motoneurons → subsequent activation of α–motoneuron.

Function of the muscle spindle
- Receptors - active at rest – stretching of the muscle activation of the anulospiral endings – higher frequency of the impulses –facilitation of the alfa motoneurons of the its own muscle.
- Response = reflex contraction of the muscle – slowing of the production of the muscle spindle discharges.

Function of the gamma-motoric system

- Two motoric descendent systems: alpha and gamma (both active)
  α – extrafusal fibres; γ intrafusal fibres
- influence of higher CNS levels
- Activity in α -motoneurons accompanied by an activity in γ -motoneurons ⇒ α - γ coactivation

Role of the gamma system

1) Simultaneously during muscle contraction (shortening of the extrafusal fibres) makes shortening of the intrafusal fibres of muscle spindles and preserves excitability of the muscle spindles receptors in a new initial length of the musle.
2) Elicits reflex muscle contraction to stimuli acting to γ motoneurons directly

<u>Golgi tendon organ</u>

- Between tendon´s fibres
- 1 receptor in series with 3-25 musc. fibers
- Affer. fibres type Aα- inhibitory neurons – inhibition of the agonist contraction (IPSP) or activation of antagonist contraction (EPSP). Stimulus – stretching of a tendon – by a passive stretching or by active musc. contraction

- Muscle relaxation – mediated by Golgi tendon receptors - as a response to strong stretching – **inverse stretching reflex**
- Reflex arc: Golgi r. – A alfa fiber – inhibitory interneuron – inhibition of the alfa-motoneuron to the agonist – relaxation (inhibition of the activity) of the muscle

Myotatic monosynaptic reflexes examination:
E.g.

- Bicipital (C5-C6)
- Tricipital (C6-C7)
- Patelar – knee-jark (L2-L4)
- Achiles tendon reflex (L5-S2)

Polysynaptic reflexes:

- More complicated reflex arc, interpoled neurons and synapses
- Receptors – in skin and mucosa (exteroreceptors)
- Receptor and effector in different organs
- Longer reaction time
- Smooth tetanic contraction

Groups:
Autonomic (see ANS)
Locomotive
Nutritional – suction reflex
Protective – cough, sneeze,...

- **Flexor reflex** (nociceptive – protective/defensive)

– flexors activated, extensors inhibited.

- **Crossed extensor response -**

strong stimulus – simultaneous activity of extensors on the opposite extremity

- **Extensor reflex** –
- touch receptors – increased tone of extensors - posture

- Extensor reflexes examination:
- Reflexes of the abdominal wall (Th7-9, Th9-10, Th10-12)
- Cremaster reflex (L1-2),
- Plantar reflex (L5-S2),...

Differences between proprio- and exteroceptive reflexes

Proprioceptive	Exteroceptive
• Receptors: in effectors	Out of effector
• Pathway : monosynaptic	Polysynaptic
• Reflex time: very short (cca 20 ms)	Long
• Dependence on the stimulus intensity:no	Yes
• Motoric action: one contraction (twitch)	Coordinated movement
• Summation - tetanus: no	Yes
• Fatigue: no	Yes
• Cortical influence: Weak	Strong

HIGHER NERVOUS FUNCTIONS, CONDITIONED REFLEX, MEMORY, LEARNING

HIGHER NERVOUS FUNCTIONS

Thalamus: system of nuclei in diencephalon
→ integration of sensoric, motoric and autonomic activity
- together with limbic sy and hypothalamus regulates autonomic ff. in emotions
  (pale face in shock, red face in happiness...)

= „gate to consciousness"
– all info from the peripheral receptors into the cortex cross the thalamus

Neocortex:
- exceptional role in regulation – integration of most motoric and sensoric functions of CNS
- determines the human being
- possibility to live without neocortex, but human loses his identity

Functional classification of neocortex:

1) Sensoric areas:
- somestetic analyzer
- analyzer of vision
- analyzer of hearing
- analyzer of smell
- analyzer of taste

2) Effector areas:
- primary motoric area
- premotoric and secondary motoric area

3) Association areas:
- multiple connections with sensoric and effector
areas of cortex and subcortical structures

a. prefrontal
- frontal pole of frontal lobe
- Brodman. area 8 a 9
- orbital area

- effer. pathways → into limb. sy, hypothalamus and mesencephalon
→ important for behavior
- destruction: hyperreactivity, disorders of behavior and intelect, disorder of personality

b. temporal areas:
- fronto-parietal
- fronto-temporal
- parieto-temporal
- parieto-occipital
- temporo-occipital

→ participate in **processes of learning and formation of memory traces**
→ temporal areas → important for development of ff. associated with the **speech**

Cortical structures determining speech:
Broca motoric centre od speech: – dorsal part of gyrus frontalis
Wernicke sensoric centre od speech: – between parietal and occipital lobe

Disorders:
- **sensoric agnosia:** = inability to distinguish subjects according to sensoric modalities (visual, auditive,...)
- **apraxia:** = inability of voluntary movement (in intact automatic movements and motoric innervation of muscles)
- **aphasia:** = disorder of speech functions (sensoric, motoric, conductive, sub-cortical, global)
- **agraphia**: = inability to write
- **alexia:** = inability to understand written text („word blindness, destruction of occip. lobe)
- **acalculia** = inability to count (destruction of gyrus angularis and marginalis)

LATERALITY OF HEMISPHERES:
Left hemisphere (causal):
→ speech ff.
→ reading, writing, arithmetic tasks...
→ control of voluntary movement
⇒ analytic gradual processing of information
- pathology: disorder of speech with intact emotional characteristics, problems with abstract thinking

Right hemisphere (intuitive):
→ other ff. than speech
→ complex processing of visual, auditive and other stimuli, space perception...
⇒ complex and simultaneous processing of information
- pathology: no disorder of speech ff., speech without intonation and emotions

sexual dimorphism:
= differences between genders in specific cognitive and motoric abilities and skills

Women:
- better verbal abilities (women more talkative)
  - spacial remembering the subjects
  - precise manual skills

Men:
- spacial tasks (rotation in the space)
- logic-mathematic tasks
- motoric tasks associated with spacial orientation

→ **women less lateralised than men**
- better connections between hemispheres
- testosterone stimulates predominantly development of the right hemisphere

SPEECH:
= verbal or written means of communication between people
- complex mechanism (prim.motor.cortex, thalamus)
- assoc.cortical areas allow the process of thinking
- ideas are transformed into sentences in gyrus front. inf. (Broca centre)

Components of speech:

1. sensoric:

- understanding of verbal and written speech
- intact auditive and visual sensoric organs
- transmission of info by affer. pathways into prim. cortical areas and to assoc. areas of cortex (gyrus temp. sup.)
- destruction of Wernicke's area ⇒ misunderstanding of heard or written speech;
  perception (sensoric) aphasia (fluent speech, but without sense)

2. motoric:

– intact association areas allowing the process of thinking - gyrus front.inf. - Broca's area
- destruction: → ***Broca expressive (motoric) aphasia*** (agrammatic speech)

conductive aphasia: dysfunction of the pathway connecting Broca's and Wernicke's areas (fasciculus arcuatus) without dysfunction of centers

global aphasia: dysfunction of both centers of speech (dysfunction of perception and production of speech)

Primary motoric cortex:

→ commands for activation of articulation muscles

- time dependance, changes in intonation and sound → cooperation with cerebellum, basal ganglia and sensoric cortex

Thalamus:

→ assurance of cooperation of physiological processes associated with speech (breathing, articul.muscles, ...)
- dysfunction of subcortical structures (thalamus) → disturbed continuity of speech

INNATE MECHANISMS OF ASSOCIATIVE AND INTEGRATIVE FUNCTION OF CNS

UNCONDITIONED REFLEXES:

= innate reflexes with structural basis caused by action of adequate stimuli on specific receptor area (I.P.Pavlov)
- originated during development

= mechanisms for assurance of ability to survive and live

classification:

- apetitive
- protective
- orientation
- sexual

Innate mechanisms:

1. Simple unconditioned reflexes:

- somatic and autonomic – salivatory r., spinal r.)

2. Drive:
- processes which represent an immediate response to fundamental necessities of the body
- they force the human to fill the needs
- after filling the needs - antidrive

3. Emotions
4. Instincts:
- complex of motoric activity and complicated forms of behavior typical for any species (instincts of birds)
- requires the same order of actions
- supply the existence of species, make easier orientation in space, teritorial instincts, social instincts
→ hierarchic relationships (relationships between individuals), sexual (supplies next generation)

MECHANISMS OF COMPLEX AND INTEGRATIVE FUNCTION OF CNS

CONDITIONED REFLEX:
- acquired response to originally indifferent stimulus, which was repetitively combined with natural stimulus leading to this response
- elementary physiological mechanism of higher functions of CNS (formation of temporary connections)
- as basis for these reflexes: unconditioned reflexes and keeping activation of neocortex

Origin:
- conditioned stimulus: biologically indifferent stimulus (ringing bell) → goes before unconditioned stimulus (food)
- conditioned reflex: repetitive connection of conditioned and unconditioned stimulus

Conditioning:
- formation of temporary connection
- complex of biochemical, neurophysiological and ultrastructural changes in the brain
→ in neocortex and in subcortical structures (RF, limb. sy)

Conditioning:
a. classical (Pavlov) (dog, food and light/ringing bell)
b. operational (Skinner)

e.g. rat in new box with small lever
conditioned stimulus (CS) = pressing the lever
unconditioned stimulus (US) – food ⇒ if hungry, press the lever

c. discrimination conditioning:
testing of discrimination abilities of animals
CS: metronom sound with rate 120/min
US: painful stimulus, dog takes away the leg

conditioning – changing the rate of metronom: 60/min without painful stimulus – in changing of these two rates – taking the leg away just in rate of 120/min ⇒ **differenciation inhibition**

Central inhibition and excitation:
- active processes in CNS

- depolarization of postsynaptic membrane → **excitation**
- hyperpolarization → **inhibition**

Dynamic stereotype:
- DS is a temporary unchanged complex of conditioned and unconditioned reflexes originated on the basis of stereotypes of repeating activities

Formation of DS:
- precise and unchanged order of repeating stimuli
- requires unchanged quality and quantity of stimuli
- constant and unchanging intervals between the stimuli

Advantages of DS:
- automatization of nervous activity, more effective
- lower consumption of oxygen
- without voluntary effort

Disadvantages of DS:
- inertion of processes – neurons may react non-adequately, they don't accept changed conditions of environment (car drivers)
- possibility of in-built mistake – its elimination then complicated (in children)

TYPES OF HIGHER NERVOUS ACTIVITY:
HNA = complex of acquired reflex mechanisms (conditioned reflexes), which dynamically change under the influence of various relationships

Classical classification of people according their temperament:
Hippocrates, Galenos:
melancholic, phlegmatic,
sangvinic, choleric

Pavlov: suggested physiological typology of individuals according to 3 basic properties of excitation and suppression
1) strength = intensity of response to stimulation
2) balance between excitation and suppression
3) functional mobility – dynamics of alternation (change) of excitation and suppression

- melancholic - weak type
- phlegmatic - strong, balanced type with low mobility
- sangvinic - strong, balanced, mobile type
- choleric - strong, non-balanced, mobile type

MEMORY:
= ability of CNS to code, to store and to evoke information in the form of memory traces
- engrams - and their use in the process of learning and formation of temporary connections

- human uses just about 4-5 % of the memory capacity

Memory:
- according to time of storing information:

- ultra-short (immediate) → fractions of s.
- uhort-term → s. - min.
- intermediary (medium) → min. - hours
- long-term → months - years

- according to emotional and rational form of knowledge:
- sensoric – imagine, experience, shape ...
- symbolic – terms, words, numbers ...

- according to the process of memory formation:
- primary
- secondary
- terciary

Processes of memory:

1.Encoding of information:

- storing the sensory and other experience

→ RF: selection of info and concentration of attention
(*orientation reflex*)
→ talamus: *„gate to consciousness"*
→ limbic sy: emotions, motivation
→ sensoric-association areas of neocortex:
- lateral cortex – analysis and differenciation of info
- temporal lobe – storing and connection of info - *„key"*

→ hippocampus:
- transmission of info from short-term to long-term memory → *„index of space and time"*

2. Storing of encoded information

– biochemical, biophysical and electrophysiological processes

3. Reccurent evokation of information in case of need

Short-term memory:

→ transition of excitation via circuit of
reverberating neurons between cortex and thalamus
(1 circuit = 1 wave α on EEG)
→ spreading the impulses into neo- and paleocortex
↓
after entrance into hippocampus the impuls (perceived phenomenon) circulates in Papez circuit

→ during the circuit of info we realise the phenomenon and place it into the memory (fixation of impulses)
- space and time summation of stimuli
- conditions which block elec. activity of brain (el.shock, coma, anesthesia) erose this memory = ***retrograde amnesia***

Intermediary (medium) memory:

thalamo-cortical reverberation leads to production of other structure of RNA in several neurons of neo- and paleocortex (during non-REM sleep)

↓

changes on synapses of neurons
(change in shape, size, number of synapses, perforations)

- about 15 % plastic synapses in the brain, the rest is built-in in circuits

Long-term memory:
changed proteosynthesis on the basis of changed RNA (in interaction with intermediary memory)

↓

synthesis of specific and non-specific proteins
(protein S-100, scotophobine....)

- hippocampus – deposition of engrams into the long-term memory

Role of sleep:
- **REM sleep:**proteosynthesis and fixation of engrams → change of medium to long-term memory
- **non-REM sleep:** synthesis of RNA

- selection, elimination and abstraction of information
- drugs suppressing REM sleep reduce also memory (barbiturates) and vice versa
- organization of sleep in children – prognosis of intelligence of the child (↑ REM - ↑ IQ)

Relationship between memory, EEG and sleep:
EEG rhythm alpha – theta:
- first stages of formation of temporary connections in the process of learning (hippocampus, RF)
- manifestation of reverberation processes between cortex and sub-cortical structures (thalamo-cortical reverberation)

Ontogenesis of memory:
- fetus *in utero* (voice, music, languages)
- perinatally – *imprinting* (first percept after labour)
- childhood – great development of memory
- adulthood – well-balanced memory
- old age – predominance of engrams from the youth

LEARNING:
- ability to remember new information and its storing (formation of engrams and their fixation)

→ repetition of information
→ motivation

- elicitation of engrams from memory**:** U shape
(the best immediately after entrance of information and then 24 hours later)
- process of fixation – biochemical transcription in 30-60 min.

In process of learning – 4 integrated circuits:
1.specific senso-motoric areas of cortex:
→ analysis and differenciation of stimuli

2. non-specific sub-cortical system (RF):

→ keeps consciousness

- new stimulus → *orientation reflex* (*„arousal phenomenon"* on EEG) – concentration of attention to the stimulus, via RF suppressed realisation of other stimuli
but: repetition of the same stimuli → weaker OR → stimulus must contain *„new component"*

3. limbic system:

- emotions (positive stimuli – stronger trace, negative stimuli – weaker trace)
- motivation (positive motivation more effective)

4. temporal lobe:

→ deposition of information (traces) and their connections with already encoded information stored in the memory – function of *„key"*
- according to the similarity, ability to „un-lock" engrams stored in other areas of the brain

Forgetting:

- negative phenomenon with positive importance
- ability to remember important information
- speed of forgetting – highest in the first 2 days, then slower
- residuum: depending on the repetition (cca 25 %)

PHYSIOLOGY OF THE E N D O C R I N E SYSTEM

Regulation of functions: - neural
- hormonal (endocrine) – via chemical messengers - hormones

Hormone = substance produced by specialized cells, mediated via circulating blood to target cells (organs) to affect (control) their activity

Bayliss, Starling (1902)

History:

Prehistory: - 3000 (B.C.) – China – eating of sea-weed against a goiter
- 400 (B.C.) - India - eating of animal testes against impotency
- Castration of animals and men (eunuchism)

Modern history:1775 – De Bordeau: „testes produce not only ejaculate but also some substances to the blood..."
1849 – Berthold – castration of the cocks and transplantation of testes back (evaluation of effects by size of their crests)
1902 – Bayliss, Starling – secretin
1919 – thyroxin
1920 – insulin (Banting, Best, McLeod)
1930-40 – steroid hormones
1944 – GH

1979 – DeBold – ANH

Mechanisms of hormonal action

Hormones → hormone receptors on the membrane surface of the cells or inside the cells → cascade of reactions in the cell.

Hormone receptors = very large proteins. Each receptor is highly specific for a single hormone

Principal mechanisms:

1) Confirmational changes of the receptor – alter the membrane permeability to ions.
2) Increase transcription of selected mRNA.
3) Activating the cAMP system (the second messenger) which activates other enzymes.
4) Activating the genes of the cell – the formation on intracellular proteins that initiate specific cellular functions.

Properties of the hormone effects:

1) Target effect – hormone acts on target cells – organ (estrogen – uterus, mammary gland etc.)

2) Specificity – effect of the hormone is specific – it is irreplaceable by other hormone

3) High effectiveness – small quantities of a hormone are effective.

THE PITUITARY GLAND
(Hypophysis)

Morphology small gland - d = less than 1 cm, weight = 0.5 – 1 g.
It lies in the sella turrica at the base of brain and is connected with hypothalamus by the pituitary (hypophyseal) stalk.

The anterior, intermediate and posterior lobes

Histology: on the bais of the staining reactions:

In the anterior pars:
- chromophobe cell (50%)
- chromophile cells (50%)
  - acidophils (40%) – eosin –
  - basophils (10%) – haematoxylin

In the intermediate pars: basophils

In the posterior pars: neural fibrea, neuroglia

Hypophysis = mixture of more or less separate endocrine organs

that contain 14 or more hormonally active substances

Hormones of anterior lobe

1) Growth hormone
2) Hormones stimulating „target glands“ (the thyroid, the adrenal cortex, the ovaries, the testicles, the mammary glands)

Growth hormone (GH)

- somatotropic h. – product of the acidophilic cells

Protein hormone: 191 AA in a single chain, two forms:

1) m.w.: 22000,
2) m.w.: 20000

– both active

The basal GH level in adults = in average less than 3 mg/ml, in the children about 5 mg/ml.

Pulsatile secretion of GH – in 3.5 hours intervals.
The half-life = 6-20 minutes

Diurnal rhythm – in NREM sleep – increase the GH level.

The increase during a physical effort, after stress.

Physiological functions of GH

1) Stimulation of cartilage and bone growth:

In young beings in which epiphyses have not yet fused to the long bones - growth is stimulated by GH.
GH does not have direct effect – but it acts indirectly by causing the liver to form small proteins = somatomedins.

GH → liver receptors → proteosynthesis →somatomedins A,C → cartilage, bone receptors → growth to the length

2) Metabolic effects of GH:

A) Effects on glucose metabolism

a) Decreased glucose utilization – antiinsulin effect mainly in muscle.
b) Enhancement of glycogen deposition – glucose is rapidly polymerized into glycogen and deposited (because of a.)
c) Diminished uptake of glucose by the cells and increased blood glucose concentration. The cells become saturated (because of b.)

GH = diabetogenic effects

2) Effects on <u>fat</u> metabolism
GH releases fatty acids from adipose tissue and increases the FA concentration in the body fluids = ***<u>ketogenic effect</u>***.
Fat is utilized for energy in preference to both – glucose and proteins under the influence of TH – a source of energy during fasting and stress.

GH → receptors of f. cells → cAMP → phosphorylation → lipolysis

3) Effects on <u>proteins</u>

Proteoanabolic effects – via:

a) Enhancement of AA transport through cell membranes – directly
b) - " - of protein synthesis by the direct effect of GH on ribosomes. Positive N_2 balance.
c) Increased quantities of RNA promotes protein synthesis
d) Decreased catabolism of protein and AAs. GH mobilizes FFA (2.) for supplying of the energy and by this effect acts as a „protein sparer".

<u>Control of TH secretion</u>

<u>Hypothalamus</u> → growth hormone – releasing hormone (GHRH)

→ - " - - inhibiting - " - (GHIH) = = somatostatin

<u>Feedback</u> control – GH increases circulating insulinlike growth factor (IGF-1 = somatomedin C) and IGF-1 inhibits secretion of GH and stimulates secretion of the somatostatin.

<u>Stimuli</u> affecting GH secretion: *Figure*

<u>Abnormalities of GH secretion</u>

1) <u>Deficiency</u> of GH effects during childhood results in <u>dwarfism:</u>

- with *deficient secretion* of GH
- with normal/hypersecretion of GH in order to *receptor deficiency*

2) <u>Hyperfunction:</u>

- in children → <u>gigantism</u> (giantism) – large quantities of GH are produced – symmetrical growth

- in adults → acromegaly – after the epiphyses of the long bones have fused with the shafts (diaphyses) – the person cannot grow taller, the bones and soft tissues can continue to grow in thickness
→ enlargement in the small bones (hands, cranium, nose, supraorbital ridges, jaw ...).

Thyroid-stimulating hormone (TSH, thyrotropin)

Glycoprotein hormone.

Effects:
TSH stimulates:
- thyroid secretion and growth of thyroid gland
- increases – uptake of iodide, synthesis of 3-Monoiodotyrozine (MIT)
- BF in thyroid gland

Whenever TSH stimulation is prolonge, the thyroid becomes enlarged = **goiter**

Adrenocorticotropic hormone (ACTH, corticotropin)

Polypeptide (39AAs).

Effect:
ACTH – stimulates: growth and function of adrenal cortex (mainly zona fasciculata and reticularis).

The effect - through cAMP: The increase in intracellular cAMP activates protein kinase A → stimulation of corticosteroids production.

Abnormalities of ACTH secretion:

Hypersecretion:
Hypersecretion of ACTH in adrenocortical insufficiency – *Addison´s disease* (by autoimmune disease or by desruction of the adrenal glands - tuberculosis, cancer).

Symptoms: Hyperglycemia (through) increased glucocorticoid activity), **negative nitrogene balance**, **fat infiltration** of the liver.
Hyperpigmentation (ACTH has MSH – melanocyte – stimulating hormone activity because of MSH is made up of AA residues of ACTH molecules).

Follicle – stimulating hormone (FSH

Glycoprotein hormone.
Before puberty only in small concentration – then it increases.
Without diurnal rhythm.

Effects:

FSH stimulates - in male: testicle growth and spermatogenesis

- in female: ovarian follicle growth, it controls secretion of estrogens from the follicles...

Luteinizing hormone (LH, ICSH)

Glycoprotein hormone
Effects:
LH stimulates - in male: growth of the interstitial cells of testicles, testosterone secretion
- in female: ovulation and luteinization of ovarian follicles

Prolactin (LTH – luteotropin)

Protein.
Basal level 1-20 mg/ml.
During gestation, progressive increasing of the level-- at he end – up 200 mg/ml.

Effects (three main):

1) Mammotrophic effect – development of the breasts at puberty

2) Luteotrophic effect – stimulation of the corpus luteum, stimulation of the progesteron secretion

3) Role in secretion of milk - producing effect.

Suckling stimulates prolactin secretion. In mothers who do not nurse their baby – a decrease in prolactin level to basal value in 2-3 weeks.

Prolactin and estrogen synergize in producing breast growth, but estrogen antagonizes the milk-producing effect of prolactin on the breast. Estrogens may be administered to stop lactation.

On the other side – prolactin inhibits GnRH secretion – the ovulation during lactation is inhibited – 50% nursing mothers do not ovulated.

Beta – lipotropin (beta – LPH)

Polypeptide. 13 AAs the same as in MSH.
Effect: Lipolysis

Control of anterior pituitary secretion

1) Feedback control – hormone of the peripheral gland (adrenal cortex, thyroidea ...)inhibits in the adenohypophysis secretion of the trophic hormone

2) Control by hypothalamus – through hypophyseotrophic hormones - stimulating - releasing hormone

- inhibiting hormones

GH ← GH – releasing (GHRH),
GH – inhibiting hormones (GHIH) = somatostatins

TSH ← thyrotropin – releasing hormone (TRH)

ACTH ← corticotropin – releasing hormone (CRH)

LH + FSH = gonadotropins ← gonadotropin – releasing hormone (GnRH)

PL ← prolactin – releasing (PRH),
prolactin inhibiting hormones (PIH)

HORMONES OF INTERMEDIATE LOBE

Gamma-lipotropin (gamma LPH)

Polypeptide – *like beta LPH.*
Effect: Lipolysis.

γ – LPH arises from β – LPH ← proopiomelanocortin (POMC)

POMC is synthesized in the hypothalamus, lungs, GIT, placenta.
It is hydrolyzed to ACTH, beta-LPH, beta-endorphin, and MSH.

Melanocyte – stimulating hormones (MSHs)

alpha, beta, delta ...

MSHs are made up of AA residues of the ACTH molecules –
- *(also ACTH has MSH activity)*

Action on - melanophophores in the skin of fish ...
- melanocytes in mammals.

Melanocytes synthesize melanins –transfer to keratocytes in skin – for pigmentation of hair and skin – darkening in 24 hours.

HORMONES OF THE POSTERIOR LOBE

Hypothalamo – hypophyseal system
Peptidic hormones: Arginine - Vasopressin (ADH= antidiuretic h.)
Oxytocin

Biosynthesis – in the supraoptic and periventricular nuclei (bilaterally) in hypothalamus. In different cells.

Transport - intraneural – in the axons of neurons to their endings

- in the posterior lobe. Velocity = 0.25 mm/hour

Secretion – from the posterior lobe in pulses

Metabolism: - Vasopressin – half-time cca 18 min in humans.
Destruction in the liver and kidneys.

Effects of Vasopressin (ADH)

1) Regulation of hydration - of body water
Regulation of vasopressin secretion through osmoreceptors – mainly in hypothalamus – vesicular cells – in ncl.supraopticus and through volume-receptors - low – pressure baroreceptors in RA.

Diminishing of the circulating volume by 6-10 % and more — stimulation of LP and HP baroreceptors. Vasopressin through V_2 receptors in the nephrons – in the thick ascending limb of Henle and the collecting duct – increases cAMP and the permeability of the membrane to water, urea, solutes – absorption – antidiuretic effect.

2) Regulation of systemic (peripheral) vascular resistance (SVR)
Vasopressin increases BP by an action on the smooth muscle of the arterioles – increase in SVR – through V_1 receptors.

Vasoconstriction in splanchnic, renal, coronary, cutaneous and uterine circulation.

Hemorrhage = a potent stimulus to vasopressin secretion.

3) Effect on memory

Vasopressin – neurotransmitter- facilitation of the memory.

Effects of oxytocin

1) Contraction of the smooth muscle of the uterus.
The sensitivity of the uterus to oxytocin increases during gestation. It is inhibited by progesteron. During labor – descent of the fetus down → impulses in the af. nerves to hypothalamus → secretion of oxytocin → contraction of uterus.

During coitus – contraction of uterus facilitates sperm. transport.

2) Contraction of the myoepithelial cells in the ducts of breast –
- during lactation – milk ejection.

The milk – ejection reflex = neuroendocrine reflex.
Receptors = touch r. around the nipple in the breast.

Impulses → hypothalamus → secretion of oxytocin →
→ contraction of the ducts.

3) Effects on the memory – negative.

THE THYROID GLAND

Morphology: 2 lobes + thyroid isthmus in front of the larynx.
Histology: The thyroid is made up of follicles. Single layer of cells – filled with colloid

Production of thyroid hormones:
- thyroxine (T4),
- triiodthyronine (T3)

Biosynthesis:

Processes: 1/Iodination, 2/ condensation of tyrosine molecules
3/ binding in peptide linkage in thyroglobulin 4/secretion

1/ Iodination – Iodide – trapping mechanism (iodide pump) – active transport against a concentration and electrical gradient. Iodide is oxidized to iodine.

2/ Synthesis = condensation – Iodine is bound to the 3rd position of thyrosine molecules - by enzyme „thyroid peroxidase". T4 and T3 are synthetized in the colloid.

MIT – DIT
2 x DIT = T4 + alanine
MIT + DIT = T3 + alanine

3/ Thyroglobulin = the biggest protein molecula in human body.
m.w. = 660 000 (2 subunits) – synthesized in the thyroid cells

4/ Secretion of the hormones: During secretion – colloid is ingested by the thyroid cells, the peptide bonds are hydrolyzed by peptidases – free T3 and T4 are secreted to the capillaries.

In normal human thyroid - 23% MIT, 33% DIT, 35% T4, 7% T3, traces rT3

Per day – T4 – 80 microgramms
T3 – 4(20) microgramms

Transport:
T4, T3 are bound to plasma proteins: - albumin
- prealbumin (TBPA)
- globulin (TBG)

99.98 % - of the T4 in plasma is bound – only 0.02 % - free T4
99.8 % - of the T3 - " - - 0.2 % - free T3

Latency and duration of action:
After injection of thyroxine – long latent period (2-3 days). Once activity does begin, it increases – maximum in 10-12 days.
Half-time – 15 days.
Some of the activity persists 6 weeks to 2 months.

Metabolism: Deiodination in the liver, the kidneys ...
T4 to T3 (up 33 % of T4) and to RT3 (45 %).

Enzymes: 5´ – deiodinase (T3), 5 – deiodinase (rT3), diiodothyronines

In the liver T4 and T3 – conjugation to sulfates, glucuronides → the bile → the intestine. Reabsorbtion/excretion. Stool, urine.

Effects of thyroid hormones

1) Effects on growth and development: General and specific effects.
Growth and differentiation of the tissues – proteosynthesis.

In cold-blooded animals – metamorphosis (tadpoles to frogs).

In mammals and humans– bone growth, maturation of CNS (synapses, myelination) and peripheral nervous system

(The reaction time of stretch reflexes – e.g. Achilles reflex).

2) Effects in adults:
a) Calorigenic action – increase in heat production.
Increase the O_2 consumption (exceptions: brain,testes, uterus, lymph nodes, spleen, anterior pituitry).
Effect lasts up to 6 days.

Metabolic effects:

- carbohydrates – increase of absorption from GIT,uptake of Co by the cells, enhanced glycolysis
- proteins – T4 and T3 - in small doses – proteoanabolic effect
- in higher doses – proteokatabolic effect
- fat – lipolysis, but a decrease in circulating cholesterol level. Loss of weight.

c) Effect on O_2 transport – thyroid hormones increase the dissociation of O_2 from Hb by increasing red cell 2,3-DPG

d) Effects on heart – th.h. increase the number and affinity of beta-Adrenergic receptors in the heart – they increase sensitivity of the heart to catecholamines. Increase in CO.

e) Different actions: - cutaneous vasodilatation – decrease in SVR
- hepatic conversion of carotene to vit. A

(in hypothyroidism – carotenemia)
- stimulation of milk secretion
- normal menstrual cycles and fertility
- mentation, irritability of CNS
- effect on catecholamines
- respiration – increase the rate and depth of respiration
- GIT – increase appetite and food intake, secretion juices, motility – diarrhea

Regulation of Thyroid Secretion

I. Pituitary TSH – its specific effects are:

1) increased size, number and secretory activity of the thyroid cells
2) increased activity of the iodide pump
3) increased iodination of tyrosine and coupling
4) increased proteolysis of the thyroglobulin in the follicles –
   - release of thyroid hormone into the blood

II. Feedback mechanisms through the hypothalamus and TSH

Hypothalamic hormone – thyrotropin releasing hormone (TRH) –
- direct effect on the secretion of TSH.

The negative feedback effect of thyroid hormones on TSH secretion – through hypophysis and also through hypothalamus.

Abnormalities in thyroid gland functions

Hyperthyroidism

Causes:
Thyreoidal: toxic adenoma, thyrotoxicosis, Graves´s Disease (autoimmune)solitary toxic adenoma,Toxic multimodular goiter, TSH-secreting pituitary tumor,thyroiditis, ektopic thyroid tissue
Extrathyroidal: Administration of T3 or T4 (iatrogenic hyperthyroidism)

Symptoms:
- intolerance to heat
- weight loss (hyperphagia)
- diarrhea
- nervousness
- psychic disorders yet inability to sleep, tremor of hands
- goiter
- exophtalmus (due to swelling of the retro-orbital tissues)
- sweating
- a warm, soft skin
- increased pulse pressure
- increased cardiac output
- tachycardia – thyrotoxic heart

- drop in SVR (cutaneous vasodilation)

Hypothyroidism

Causes:
Lack of iodine (endemic goiter), idiopathic nontoxic colloid goiter, goitrogenic substances in some foods (thiocyanotes in cabbage, turnips – Brassicacea family vegetables) – progoitrins –
- active antithyroid agents, secondary – hypothalamic hypothyroidism, pituitary hypothyroidism ...

Symptoms:
in infancy and childhood – cretenism – failure of growth
- mental retardation
- protruding tongues

in adults – goiter – endemic (lack of iodine – need 50 mg/day,iodized salt) – due to hyperproduction of TSH
- somnolence
- muscular and mental sluggishness
- bradycardia, decreased CO, blood volume
- increased weight
- constipation
- depressed growth of hair
- frog-like husky voice
- myxedema – edematous appearance the body

Hormone of the thyroid parafolllicular C - cells = Calcitonin

C-cells – 15-20 % of the thyroid gland volume – in the interstitium between the thyroid follicles.

Calcitonin – 32 AAs, m.w. 3500

Effects: Calcitonin – decreases blood calcium ion concentration
(in minutes after injection) by two ways:
- a decrease the absorptive activities of the osteoclasts (the immediate effect)
- a prevention of a formation of new osteoclasts (prolonged effect).

Mainly in children.
In adult only a weak effect.

Effects – exactly opposite that of parathyroid hormone.

Regulation – increase in plasmatic Ca++ causes an immediate increase in the rate of calcitonin secretion.

Therapeutic application – synthetic, human, salmonic – against osteoporosis.

The Parathyroid Glands

Morphology – 4 glands – located immediately behind the thyroid gland. Each 6 x 3 x 2 mm in adults.

Two types of cells: - chief cells – secrete parathyroid hormone
- oxyphill cells – unknown function

Parathyroid Hormone (PTH)

small protein – 84 AAs, m.w. 9500. Activity depends on the first 34 AAs.

The normal plasma level = 10-55 pg/ml. Half-time less than 20 minutes.

Effects:

In the bone - osteoklasts – bone destruction – absorption
- osteoblasts – bone deposition
- osteocytes – stabilization

PTH:
– in the bones: - stimulates osteoklasts – releases Ca++ from the bones = mobilization of the Ca++ → the increase to the plasma Ca++.

- in the kidneys: PTH – increases phosphate and decreases calcium excretion in the urine (increases reabsorption Ca++ in the distal tubules).

- in the GIT: PH increases Ca++ absorption from the intestine.

Regulation of PTH secretion

1) Decrease in Ca++ concentration in the extracellular fluid causes the increase in PTH secretion. Feedback – opposite effect – increase the Ca++ concentration — decreased activity of the parathyroid glands. E.g. – excess Ca++ or vit. D in the diet.

2) Increased plasma phosphate stimulates PTH secretion. Chemoreceptors – the secretion cells in parathyroid glands.

Abnormalities

PTH – essential for life.

Hypoparathyreoidism – after parathyreoidectomy – decrease in Ca++ plasma level – signs of neuromuscular hyperexcitability:

Hypocalcemic tetany:
Chvostek´s sign – contraction of facial muscles elicited by tapping over the facial nerve.

Trousseau´s´ sign – a spasm of the hand muscles by occluding the circulation.

Hyperparathyreoidism – Hypercalcemia. Renal stones.
If Ca++ more than 4 mmol/l – a danger of the calcium rigor of the heart.
Demineralization, osteoporosis, pathological fractures.
M. Recklinghausen.

Calcium Metabolism

Ca++ - in the human body about 1100 g – 99 % in skeleton

The plasma Ca++ - 2.25 – 2.75 mmol/l – partly bound to protein and partly free – ionized Ca++ (1.25 – 1.5 mmol/l).

Absorption – from the GIT
Mobilization and deposition – in the bones
Excretion – urine, stool, sweat

Roles of the hormones in the Ca++ homeostasis with action on: - GIT
- bones
- kidneys

Summarization:

1) Calcitonin - inhibition of osteoklasts – hypocalcemic effect
- inhibition of the renal resorption of Ca++
- inhibition of GIT activity

2) Parathyroid hormone – stimulation of osteoklasts – hypercalcemic effect
- inhibition of the Ca++ renal excretion
- stimulation of Ca++ resorption in the GIT

3) Hormone – vitamin D

Vitamin D

= group of sterols produced by the action of UV light on provitamins.

Vit. D3 (cholecalciferol) is produced in the skin from 7- dehydrocholesterol by sunlight.

It causes formation of a calcium binding protein in the intestinal epithelialcells = prolonged effect on calcium absorption - plays a role in promoting calcium absorption by the formation of a Ca++ - stimulated ATP-ase and by formation of an alkaline phosphatase in the epithelial cells.

Negative feedback control – Ca++ - vit. D.

The Adrenocortical Hormones

Morphology: Two adrenal glands.Weight (1): 3-7 grams.
Size: 4 x 2.5 x 0.5 cm

Histology: Two parts – two separate organs:
- the adrenal medulla
- the adrenal cortex

The adrenal cortex: - Zone glomerulosa:
Product: mineralocorticoids

- Zone fasciculata:
Product: glucocorticoids

- Zone reticularis –
Product:androgenic hormones

Hormones - steroids

A) Glucocorticoids:
Cortisol (hydrocortisone) and cortisterone
Prednisone (synthetic, 4x as potent as cortisol),
Dexamethasone (30 x)

Effects on:

Carbohydrate Metabolism:
1) Decreased glucose utilization by the cells

2) Stimulation of gluconeogenesis (formation of glucose from proteins and other substances). Mobilization of AAs from the extrahepatic tissues.

→ Elevated blood glucose concentration (50% and more above normal) - (adrenal diabetes)

Protein Metabolism

1) Reduction in cellular protein stores (except those of the liver) Increased catabolism of protein. Cortisol depresses the formation of RNA in tissues (including lymphoid tissue)

2) Increased blood amino acids and enhanced transport into hepatic cells — expanded utilization of AAs by liver; increased protein synthesis in the liver including plasma proteins, increased conversion of AAs to glucose (gluconeogenesis)

Fat Metabolism

1) Mobilization of fatty acids – from adipose tissue.
Increased FFA concentration in the plasma. Shift the metabolism from the utilization of glucose to FFA in starvation, stress.

Other Effects of Glucocorticoids

1) Antiinflammatory effect - stabilization of the intracellular lysosomal membranes and inhibition of lymphoid tissue.
2) Function in stress
3) Increased SVR, BP.

B) Mineralocorticoids – aldosterone (95% of all m. activity)

1) Renal effects:
Transport of Na^+, K^+ and H^+ through the renal tubular walls.

Aldosterone increases - absorption of Na^+ (and H_2O)
- excretion of K^+ (H^+)
in the distal tubule, collecting tubule and duct.

2) Circulatory effects:
Maintaining of extracellular fluid volume.

In the absence of aldosterone secretion – a decrease in EFV –
- *circulatory shock*

In the hypersecretion of aldosterone – an increase in EFV and CO.

C) Adrenal androgens and estrogens (dehydroepiandrosterone, testosterone...)
Androgens - masculinizing effects
- promoting protein anabolism, growth

Estrogens - converted from androgens in the circulation

Source of estrogens in men and postmenopausal women.

Regulation of adrenal cortex hormones secretion
Glucocorticoids + androgens:
Hypotalamus: corticotropin – releasing factor ∧ ACTH
in hypophysis∧ blood ∧ adrenal cortex.
Cortisol – direct negative feedback effects on:
1) hypothalamus
2) anterior pituitary gland

Mineralocorticoids

Stimuli:
1) Increased K^+ concentration increases secretion
2) Decreased Na^+ - " - - " -
3) Activation of RAA system - " -
4) ACTH

Abnormalities of adrenocortical secretion
Hypoadrenalism – Addison´s disease

(autoimmunity, tuberculosis, cancer, haemorrhage)
Signs and symptoms: Hypoglycemia, hypotension, weakness, hyperpigmentation (ACTH)
Substitution th.

Hyperadrenalism
Hypersecretion of cortisol = **Cushing´s disease** – motilization of fat from lower part of the body, with deposition of fat in the thoracic region, edematou face, hyperglycemia, (androgens – acne, hirsutism), osteoporosis, **supressed immune system – death of infection**

Hypersecretion of aldosterone = **Conn´s syndrome** – depletion of K^+, increase in blood volume, hypertension.
Muscular weakness, even paralysis caused by the hypokalemia.

Adrenal virilism – excess growth of facial hair, in women – men´s type of figure, muscles.
Hypoplastic uterus – female pseudohermaphroditism.
In boys before a puberty – precocious pseudopuberty

STRESS

H. Selye
Stress = complex of reactions to external or internal changes which disturbe normal action of the organism or threat its existence
= stimuli (stressors) which cause increase in ACTH level

Stress: - eustress - positive
- distress - negative

Stressors:
1) Intensive mental activity
2) Emotions
3) Physical – intense heat or cold, noise, vibration
4) Chemical – inflammation, burn, thirst, hunger
5) Exercise, effort
6) Immobilzation
7) Trauma, surgery
8) Infection, diseases

Function of adrenal cortex in stress
Selye: After stress – enlargement of adrenal cortex, hypertrophy of cortex, involutioin of lymphoid tissue, ulcerations in GIT – from the hyperproduction of adrenocortical hormones.

Almost any type of stress (physical or neurogenic), causes an immediate and marked increase in ACTH and cortisol.

Activation of the axe: Hypothalamus – hypophysis – adrenal glands.

Effects:
Rapid mobilization of AAs, FFA - energy
Maintaining of blood volume and BP.

At the beginning of stress:mobilization of glucose by catecholamines,
glucagone

Latter – mobilization of AAs, FFA, by glycocorticoids
Lipolysis – glycerol and FAs – main source of energy for muscles and liver in stress
Positive inotropic effect
Hyperreactivity of vessels
Analgetic effect

PANCREAS – ENDOCRINE FUNCTION

Pancreas - exocrine (pancreatic juice)
- endocrine

Endocrine – hormones

Cells – producers – in anatomic islets – 1-2% of the mass of pancreas (1-2 million islets)

Islets composed of A-cells - 25% (glucagon)
B-cells 60 - 75% (insulin)
D–cells (somatostatin)
PP (F) - cells (pancreatic polypeptide)

Secretion to pancreatic veins – portal vein (higher concentration of insulin in liver 2-10x higher than in the peripheral circulation)

INSULIN

Peptide m.w. 6000 – 2 chains of AAs - linked by disulfide bridges
Connecting peptide = C-peptide
Secretory granules contain insulin, C peptide, zinc (to join 6 insulin molecules into hexamers)
Secretion by exocytosis via contraction of microfilaments (myosin+actin) through microtubules and plasma membrane – equimolar amounts of insulin and C-peptide.

Regulation of secretion
The most important stimulator of insulin secretion = GLUCOSE (phosphorylated - by glucokinase).
Feedback relationship – the lower is glycemia – the lower is insulinemia.

Action of GIT hormones:
Stimulatory: GIP, gastrin, secretin, CCK-PZ and glucagon-like polypeptide from intestinal cells
AAs – stimulate

EFFECTS OF INSULIN

Anabolic hormone
The major sites of insulin actions: liver, muscle, adipose tissue
Result of insulin action – decreases the plasma concentrations of

- glucose
- free fatty acids
- ketoacids
- essential AAs (leucine, isoleucine, valine)

Carbohydrate metabolism

Insulin stimulates:

- the transport of glucose from the plasma, across the cell membrane to cytoplasm for rapid phosphorylation (hypoglycemic effect of insulin)
- glycogen formation from glucose-6-phosphate (muscle,liver)
- glycolysis and oxidation (less)
- production of alpha-glycerol phosphate – used to esterify FFA, thus storing them as triglycerides (in adipose tissue)

Effect of insulin – the main hormone enabling metabolism glucose in cells

Fat metabolism

Insulin

- facilitates transfer of circulating fat into the adipose cell in adipose tissue
- inhibits lipolysis of stored triglyceride – FFA releas is suppressed
- stimulates synthesis of cholesterol from acetyl CoA
- stimulates de novo synthesis of FFA

Effect of insulin – an increase the fat content of the liver

Protein metabolism

Insulin

- stimulates the transport of Aasfrom plasma, across the cell membrane into cytoplasm
- increases overall synthesis of proteins – anabolic effects
- anticatabolic effect – inhibition of the enzymes of proteolysis

Effect of insulin – important contributor to growth, the tissue regeneration, bone remodelling.

The key metabolic role of insulin means that its absence causes distortion of homeostasis. Plasma levels of glucose, FFA and ketoacids rise to extreme heights. Plasma pH and bicarbonate fall.Extreme loss of adipose mass and lean body mass occurs.

Insulin deficiency – diabetes mellitus

Insulin excess – hypoglycemia – convulsion, coma.
Without insulin replacement – death.

Insulin substitution – beef, pork, human insulin (recombinant technology).
Application – subcutaneous way – intensified therapy – simulated physiological secretion.
Insulin pumps.

GLUCAGON

Important regulator of intrahepatic glucose and FFA metabolism
Catabolic hormone
A-cells - single chain peptide m.w. 3500
Preproglucagon – proglucagon – glucagon

Regulation of secretion

In contrast to insulin – glucagon synthesis is inhibited by high glycemia and stimulated by low glucose level (2-4-fold
increase – from basal level of about 100 pg/ml).

Insulin directly inhibits glucagon secretion – paracrine action of islets
The major energy substrate (FFA) also suppresses glucagon release
A protein meal and AAs – substrates for glucose production stimulate glucagone secretion.
Prolonged fasting and exercise, stressful condition etc. – requiring glucose mobilization – increase glucagon secretion – through sympathetic (alpha receptors) nervous system.

Glucagon is extracted by the liver – short half-life.
As with insulin, glucagon is dewgraded in the kidney and liver

Effects of glucagon

Opposite to those of insulin:
Glucagon promotes mobilization of fuels – mainly of glucose
Hyperglycemic effect
Profound glycogenolytic effect – activation of glycogen phosphorylase and inhibition of glycogen synthase
Stimulation of gluconeogenesis
Glucagon actions on adipose tissue or musles – non significant

Glucagon deficiency - hypoglycemia
Glucagon excess – makes diabetes worse

INSULIN/GLUCAGON RATIO

The usual molar ratio in plasma I/G = 2.0

In circumstances that require mobilization and utilization of substrates – I/G = 0.5 and less (in fasting, prolonged exercise) due to a decrease in I and increase in G.

Conversely, in circumstances in which substrate storege is advantageous – after
a carbohydrate meal – I/G rises to 10 and more (I)

SOMATOSTATIN

Neuropeptide (hypothalamus)
D-cells - preprohormone – 2 somatostatin peptides 28 and 14 AAs.

Regulation of secretion
Stimulated by G, AAs, FFA, glucagone, CCK-PZ, VIP, mixed mealk.
Inhibited by insulin.

Effects of pancreatic somatostatin
A decrease the rate of digestion and absorption of nutrients from GIT and utilization:
Inhibition of GIT motility, secretion of juices and GIT hormones (gastrin, secretin)

Inhibition of the absorption of glucose and triglycerides across the intestinal mucosa.
Inhibition of insulin and glucagon secretion

Feedback regulation – entrance of food into GIT stimulates the release of the GIT hormones and actions – somatostatin – prevent rapid nutrient overload

Pancreatic somatostatin excess – hyperglycemia and other manifestations of diabetes.

THE GONADS

The male reproductive system

Morphology:
Testes – pair organ. 1 testis volume = 20-30 ml, weight 10-16 g
Scrotum – temperature about 32 ˚C. Regulation of T by contraction / relaxations of m. cremaster.

Histology:
- interstitial cells of Leydig (5% of V, 450 millions)
- Sertoli cells
- seminiferous tubules

Hormones of the testes

The principal hormone - testosterone – steroid
- dihydrotestosterone (DHT)

Producer: Leydig cells
Synthesis: from cholesterol (adrenal cortex 5%, testes 95%)
Secretion: 7 mg/day in normal adult males in pulses
Diurnal rhythm – highest concentration between 4 – 8 a.m.
Transport - free form – 2% (in puberty more)
- binding form – SHBG (sex hormone binding globulin)
Degradation – liver
Elimination – kidneys – urine

Regulation:
Hypothalamus (GnRH) ∧ hypophysis (LH – ICSH) ∧ testes

Effects of the testosterone:
Fetal period – responsible for development of the male type of gonads
Childhood - behaviour – more agressive play in boys
Puberty – growth and development of the primary and secondary sex characteristics: - gonads
- anabolic effects, hair growth (beard, pubic and axillar hair, enlargement of the larynx – voice becomes deeper, sebaceous thick secretion – acne)
Adulthood - maintaining of the sex characteristics
- stimulation of the erythropoeisis
- directly and indirectly through erythropoetin
- anabolic effects
- behaviour

Another hormones of testes
Sertoli cells – producers of: inhibins – (alpha ...)
effects: inhibition f the FSH

actins – stimulation of the FSH

Abnormalities of testicular function

Male hypogonadism in
- embryonic period – malformation of the gonads
- praepubertal – eunuchoidism – epiphyses remain open – tal stature, undeveloped musculature, voice high-pitched, pubic and axillary hair - normal (adrenal cortex androgens)
- postpubertal - regression of the sex characteristics
  - sterility
  - voice remains deep
  - loss, or declination of libido
  - ability to copulate persists longer

Male hypergonadism in
- praepubertal – pubertas praecox (precocious puberty)
- postpubertal – rare – androgen secreting tumors – Leydig cells tumors

Endocrine functions of the ovary

Hormones of the ovary - steroids
- non-steroids

Steroid hormones: - estrogens – secreted in follicular and luteal phase
- progesterone – in luteal phase

Non-steroid hormones: - inhibins – inhibition of the FSH

- activins – activation - " -
- relaxin

Transport - estrogens – 2% free form, 38% SHBG, 60% albumin
- progesterone – 2% free form, 18% CBG, 80% albumin
Degradation – liver
Elimination – kidneys (urine), liver (bile)

Regulation
Hypothalamus (GnRH) ∧ hypophysis (FSH – estrogens, LH – progesterone) ∧ ovary
Ovarian hormones – effects

Estrogens - growth and maintaining of the primary and secondary sex characteristics
- metabolism of Ca^{++} – antagonistic effect to PTH
- responsibility for prolipherative phase
- sexual behaviour – libido (with testosterone)

Progesterone - responsibility for secretory phase
- growth and differentiation of the mammary glands
- rise in body temperature
- natriuretic effect (antagonistic to aldosterone)

The ovarian cycle

Cyclic changes in ovary for ovulation
In the ovary at puberty 300 000 ova – in the course of a reproductive life only about 300 – 500 will maturate.

Phases: 1) Follicular phase – formation of an ovum – growth of the follicles – production of estrogens

2) 14th day – distended dominant follicle ruptures – ovum is extended – ovulation

3) Luteal phase – production of the estrogens and progesterone by corpus luteum.

Corpus luteum - corpus luteum graviditatis
- corpus albicans

The menstrual cycle
Cyclic changes of the uterine mucosa

- In follicular phase – maturation of the follicles – estrogens – increase in the endometrium thickness – proliferative phase

- After ovulation – in luteal phase – under the influence of estrogens and progesterone – uterine glands begin to secrete fluid – secretory

phase

- Regression of the corpus luteum – decrease of the progesterone secretion and local ischemia by PGF_{2alpha} – endometrial necrosis – bleeding - menstruation.

Loss of 50 – 80 ml – art. blood (75%), venous (25%).

Abnormalities of the endocrine ovarian functions

Fermale hypogonadism in
- childhood – sex characteristics undeveloped - late puberty – pubertas tarda - sexual infantilism
- adulthood - amenorrhea – absence of the menstruation
  - regression of the female sex characteristics
  - osteoporosis

Female hypergonadism in
- childhood – pubertas praecox
- adulthood – abnormalities in cycle, amenorrhea, menorrhagia, metrorrhagia.

PINEAL HORMONE – MELATONIN

The pineal – epiphysis – between 3rd ventricle – cerebellum
Neuroglia, parenchymal cells, highly fenestrated capillaries
Inervation: cervical ggl. superior, sympathetic nerves – beta receptors
Product – hormone: **Melatonin**
Biosynthesis: Tryptophan – serotonin – melatonin

Lynch et al. (1975): melatonin is secreted in humans at night (dark) in 10-40 times higher amounts than at mid – day.

Exposition to a permanent light – suppression of the melatonin production
Activation of the synthesis during the dark period – night

Light information (dark/light)→ retina → tr.retinohypothalamicus → hypothalamus → thoracic spinal cord → sympathetic nerves → cervical ggl. superior → postggl. sympathetic neurons → pineal → beta - adrenergic receptors → cAMP → N-acetyltranferase activity → **melatonin** (from serotonin)

Diurnal rhythm – night – stimulation of the synthesis and secretion
- daylight hours - inhibition

Effects

Amphibian – contraction of melanophores – melanin pigments – it lightens the skin (e.g. in tadpoles)
Mammals and humans
Synchronization of circadian rhytmicity:
- inducing effect on sleep

- induction of seasonal responses to changes in day length
- cyclic fluctuations of the awake/sleep states

Effects on reproducibility – gonads:
Inhibition / facilitation
Seasonal breeding animals - responding differently to the changes in day-length.
In rats/hamsters etc. – with a short duration of gravidity – activation of gonads in the spring
In animals with longer gravidity – (e.g. a doe – hind/ deer) – activation gonads in the automn (shortening of the day-lights hours).

Effects on immune processes – immunomodulatory role:
- Stimulatory effect on the processes and lymphoid cells, thymus, spleen
- Antioxidative effect – scavenger of some reactive forms of oxygene. The most effective lipophilic antioxidant.
- Oncostatic effect

Therapeutical use - treatment of:
- jet lag syndrome – circadian clock – hypothalamus – superchiasmatic ncl. Jet lag – from moving to a different time zone (W-E – shortens, E-W – lengthens day. The coordination of the biological clock – melatonin
- sleep-disorders – sleep promoting effect
- some types of depression – seasonal affective disorder
- imunomodulans/prevention. (Trials – treatment of malignancies and AIDS).

NATRIURETIC PEPTIDES

1956 - granular cells in atria
1981 – de Bold (Canada) extract from the atria (rats) – an increase of natriuresis and diuresis (30 x) – atrial natriuretic peptide ANP

Atriocytes → pre-pro-hormone ANP (149-153 AA) →
→ pro ANP (126 AA) → ANP (28 AA)

Half-time: 1-5 min
Rapid distribution and action
Elimination – endopeptidases – splitting

Stimulus: Distension of the atria – the right (klinostasis, volume -expansion – hypervolemia, failure of the right ventricle...)

Physiological effects of the ANP:

Regulation of the intravascular volume and of natremia

- Increase of natriuresis and diuresis – through an increase in perfusion and glomerular filtration
- Inhibition of the natrium reabsorption in collecting ducts
- Decrease in blood pressure through:
  - diminishing of the blood volume and cardiac output
  - vasodilation

- inhibition of secretion: aldosterone, vasopressin, catecholamines
- Enhancement of capillary permeability – peripheral edema

Neurotransmitter in CNS – in the nuclei for regulation of blood pressure and volume

Clinical aspects:

Hypertension – expected a decrease in ANP concentration – results of the studies: opposite findings – in hypertonics ussually hypersecretion of the ANP – compensatory changes

Congenital heart failure – increase in ANP level – indicator of the severity

Another natriuretic peptides:

Natriuretic peptide type B = BNP

Secretion in cardiomyocytes of the ventricles

Stimulus – pressure in the ventricle wall (hypertrophy of the left ventricle)

Half-time 20 min

Effects: Natriuresis, diuresis, vasodilation, inhibition of renin and aldosterone secretion

BNP – indicator of:
- the ventricles failure – correlation with ejection fraction of the LV
- LV hypertrophy

Natriuretic peptide C = CNP

Synthesis in the brain (cerebrospinal fluid) and in endothel

Autokrine/parakrine regulation in the brain/vessels

Inhibition of the smooth musculature of vessels – protective effect against hypertrophy (in hypertension)

Therapeutic application of the natriuretic peptides:
Indications: hypervolemic overloading of the heart, pulmonary edema, hypertension...
Apllication: isolated ANP and/or apllication of an inhibitor of the endopetidases

Effects: natriuresis, diuresis, vasodilation, a decrease of aldosterone level ....

PREGNANCY

Fertilization – of the ovum – in the uterine tube
Physiological functions of pregnant woman:

Endocrine changes:
Corpus luteum graviditatis – estrogens, progesterone, relaxin
Decline in function after 2 months of pregnancy

Placenta: – human chorionic gonadotropin (hCG) - luteinizing and luteotropic activity

Indicator of pregnancy - in blood (RIA) – 6th day
- in urine – after 14 days

- human chorionic somatomammotropin (hCS) – maternal growth hormone - positive N_2 balance, retention of Ca^{2+}

- relaxin – relaxation of pelvic ligaments

- beta – endorphins – unknown function (a change of behavior)

- prorenin

- inhibin, placentar GnRH – paracrine regulation of placentar hormonal activity

PHYSIOLOGICAL FUNCTIONS IN PREGNANT WOMAN

TBW – increase by 4-6 l (mainly in ECF compartment)

BLOOD

Blood volume: a rise from 4 up to 5.5 l
Plasma volume – an increase up by 1.2 l. Maximum in 34th gest. week
Plasma proteins – a decrease (from 70 to 60 g/l) – in particular albumins. Fibrinogen concentration rises.

Erythrocytes and haemoglobin concentration – a decrease
Htk – a decrease (from 0.44 to 0.33)
Viscocity – a decrease from 4.6 to 3.8
Leukocytes – leukocytosis – neutrophilia
Thrombocytosis
ESR – FW acceleration (fibrinogen, less ery)
Coagulation ability – an increase

CARDIOVASCULAR SYSTEM

Heart
- HR + by 15/min
- SV from 80 to 95 ml
- CO from 4.5 to 6 l/min

Blood pressure

- arterial BP syst. slight increase
- arterial BP diast. in pregnancy lower
- venous – depending on location – in upper part – unchanged, in lower parts increased

Blood flow – rise through kidneys, liver, skin

RESPIRATORY SYSTEM

Volumes and capacities
– rise in V_T by 40%
– decrease in VC and FRC (by 20-30%)

Ventilation – increase from 7 to 8 l/min
Increase in oxygen consumption
Hypokapnia

RENAL PHYSIOLOGY

Renal blood flow, filtration fraction, glomerular filtration - rise
Increased diuresis

GASTROINTESTINAL TRACT

Increase in food intake
Slowing of GIT motility, peristalsis (mainly gastric), obstipation, a decrease of the digestive juices secretion

Parturition - labor

Duration of pregnancy – 40 ± 2 lunar weeks (270 ± 14 days from fertilization)
During pregnancy – increasing in number of oxytocin receptors in the myometrium and the decidua (influence of estrogens and distension of uterus)
In early labor – uterus starts to react yet to normal concentration of oxytocin
Dilation of the cervix, mechanical stimulation by fetus – increase in oxytocin secretion.
Role of prostaglandins – evidence – prolongation of parturition after PG inhibitors.
Role of spinal reflexes and voluntary contractions of abdominal muscles.

PHYSIOLOGICAL FUNCTIONS IN NEWBORNS AND CHILDREN

Total body water (TBW) – increase – mainly ECF

Blood

Blood volume – increase
Plasma - relative hypervolemia
- plasma proteins – decrease – from 60-70 g/l, mainly albumin. Rise in fibrinogen level.

Red blood cells count - in newborns up 7.7 x 1012/l
- in suckling – lowest

Haemoglobin – (HbE), HbF, HbA (2,3 DPG)
Leukocytes – lymphocytosis in childhood
Blood groups - antigens – weaker activity
- aglutinins – absent

Platelets, clotting – without abnormalities

Cardiovascular System

FETAL CIRCULATION

Placenta - 1 umbilical vein (oxygenated blood - 80% O_2)
d.venosus -V.C.inf.+ blood from systemic arteries (70%)
RA + V.C.sup. (sat.30%) -
RV + through foramen ovale -LA -LV(sat.62%) -
upper extremities and head (brain)- V.C.sup.

RA- RV - PA - d.a.Botalli (sat. 52%) - descendent aorta -
abdominal organs,lower extremities
- 2 a.a.umbilicales - placenta
- V.C.inf.

First breath - start of breathing

Occlusion of umbil.cord – musculature:
circular - sensitive to oxygen increase
longitudinal - mechanical stretching
spiral - decrease in temperature

Stimuli initiating breathing after birth:

Hypoxia -hyperkapnia-acidosis - stop of the oxygen supply,
elimination of carbon dioxide,resp.-metabolic acidosis.
PO_2 decreases with rate 10 mmHg/min –stimulation:
- *peripheral chemoreceptors (aortal)*
- central - pH decrease.

Another stimuli:

- Cooling of the newborns body
- Tactile and pain stimuli
- Stimulation of proprioceptors
- Reflexes of airways and lungs
  Diving
  Hering-Breuer deflation reflex

Visual.acoustic,vestibular receptors
- Humoral effects -catecholamines

AERATION OF THE LUNGS

Lung fluid elimination

Lung fluid - during fetal life volume 30-35 ml/kg - the same like total lung volume in postnatal life

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Delivery - compression of the chest - 80-90 mmHg - 40 ml of the fluid
is squeezed out from the upper airways.
The first breath - strong negative pressure up - 75 mmHg - to overcome the resistance of the airways and viscosity of the lung fluid.
The first expirium - positive - a cry - pushes the fluid to alveolocapillary membrane - resorption.
Repetitive respiratory actions.

Elimination of the pulmonary fluid - 2 ways:

- resorption to lung capillaries blood (2/3)
- lymphatic vessels (1/3)

TRANSITORY CIRCULATION

Closure of the foramen ovale
Elimination of the inflow through v.umbilicalis
- venous return decreases, including BP in RA,RV,PA
- systemic circulation becomes shorter - BP rises
- BP in LA exceeds BP in RA -FO closes - functionally possibility of a reopening

Closure of the ductus venosus
Passive - reason - blood flow is stopped
Active - contraction of a smooth muscle sphincter

Closure of the ductus arteriosus
Diameter 0.5-0.6 cm length 1.25 cm - like aorta,PA

Factors for closure:
- The increase in PaO_2 - functional constriction
- Vasoactive substances
  - Vasoconstrictors : serotonin,NA,angiotensin
  - Vasodilators :Prostaglandins - PGE_2

During intrauterine life - balance between vasoconstrictors and vasodilators - after birth - placenta as a source of the PG production is eliminated - predominancy of the vasoconstrictors
Definitive closure up in 3rd month.

Clinical aplication : duct.art.apertus (open) - application of a cyxclooxygenase - PG blockers:

- aspirine - acetylosalicylic acid
- Indomethacine

Changes in pulmonary circulation

Fetal life - only 3 - 10% of the CO.After birth the pulmonary bed must be adaptade to capacity 100 % of the CO RV.

Vasodilation:

- Oxygen - an increase in satur.O_2 - vasodilation
- Substances - acetylcholine,bradykinin,PG
- Mechanical changes - aeration of the lungs
- Morphological changes - involution of the smooth musle layer in the vessels of the pulmonary bed

Changes in cardiac output

Existence of the 2 pumps in series - shunts are closed functionally - possibility of the reopening = transitory circulation

Consumption of the oxygen 2x higher than in adults = higher CO up 200 - 300 ml/min/kg

Heart rate

in newborns - mature - 110-130/min
premature - 120-140/min

Blood pressure in newborns

Methods for measurement of BP

- Invasive -catheterization
- Noninvasive - ultrasound tonometer
  -infrasound tonometer

Normal values of BP in newborns: mature - 90/60 mm Hg
premature - depending on gestation age
lowest 40/20 mmHg

Physiological changes of BP in newborns:

Cardiovascular reflexes - functioning:

- baroreflexes

- oculocardiac reflex
- Cushing reflex
- Cold reflex
- Kratschmer,diving reflexes
- ....

Diurnal rhythm - day-night fluctuations in BP
Crying - increase in BP by 30-40%
Food intake - increase in BP by 30%

Respiration

Respiratory muscles – lower tone, fatigue
Thorax – less mineralized, compliant
Airways – small diameter
Alveoli (size: d – only 20-50 μm, in adults up 300 μm)
Count: 20 millions versus 300 millions
Compliance – in absolute values low, specific the same
Resistance – up 10 x higher

Regulation of breathing - chemical – biphasic response to hypoxia
- neural – HB reflex well developed.

Gastrointestinal Physiology

Intrauterine nutrition:
- histotrophic
- haemotrophic

Postnatal nutrition:
- lactotrophic
- mixed

Existence of a special reflex – suckling reflex (non-conditioned, inborn, however unstable)
Salivation: low volume and a weak alpha-amylase activity in saliva
Swalowing – deglutition – well developed

Stomach:
- Volume: in newborns 5-10 ml, 1st year 250 – 300 ml
- Secretion: less HCl, higher pH (3-4)
  chymosin
  fetal pepsin (higher pH optimum)
  intrinsic factor – gradual increase in postnatal life
  (together with pH decrease)
- Motoric activities: lower, emptying of stomach in 2-3 hours

Small intestine:
- thinner muscular layer
- ability of the bigger molecules absorption, penetration of potential antigens

Colon: well developed functions, more frequent defecations

Liver

In fetal life – important function – condition for optimal development

Formation and storage of different nutrients – for immediate utilization after birth

Formation of plasma proteins, synthesis and excretion of the cholic acids, enterohepatic circulation – in utero

Conjugation and detoxification functions – active – relative insufficiency after birth – in early postnatal life – for detoxification and elimination of the great pool of bilirubin.

Low capacity of the oxidative metabolism in newborns

Gradual maturation after birth

Metabolism

BMR/kg increased in newborns (up 3x)

Predominancy of proteoanabolic processes

Metabolic pathways the same, immaturity of enzyme systems

The main source of energy – glucose and free fatty acids

Protein minimum in the 1st year up 2.5 g/kg (vs. 0.6 in adults)

Renal Physiology

Fetal period: Excretory organ – placenta
Formation of urine and micturition influence a composition of amniotic fluid

Newborns: Glomeruli size: smaller, less permeable (cubic epithelium)
Shorter proximal tubules
Longer Henle´s loops (relatively)

Decreased renal perfusion - lower BP.

Renal fraction 5-6% (in adults 20%)

Low sensitivity to ADH, decreased ability to concentrate urine – bigger diuresis for elimination of the metabolite pools.

Endocrine System

Fetal period:

Axis: Hypothalamus – adenohypophysis – target glands – in functions

Parathormone – secreted by fetus – however maternal parathyreoidea – the main source of the PTH

Thyreoidal hormones

Adrenal cortex hormones – predominancy of the sexual hormones – androgens

Pancreas – fetal insulin – important for keeping normoglycemia

Early postnatal period:

Thyreoidal hormones – necessary for physiological development of the nervous system – brain

Adrenal medulla – firstly predominancy of NA, latter of A

Nervous system

Metabolism: Ability of the anaerobic metabolism

Hematoencephalic barreer: Development after birth: Increased permeability in the early phases of postnatal life – penetration of different substances to the brain tissue (bilirubin – kernicterus)

Development of the movements:
Fetal period: since 6^{th} - 7^{th} gestatuional week
Postnatal period – phases:

- holokinetic – generalized movements
- monokinetic – from the end of the 2^{nd} month – movement by one extremity
- dromokinetic - from 5^{th} month – targetted movement
- kratikinetic – after the 1^{st} year – voluntary/involuntary movements

Developments of the dynamic stereotypes
Conditioned reflexes/learning/memory/speech
Ability of the memory formation – since intrauterine life.
Development of the speech – best from the end of the 2^{nd} year.

Thermoregulation

Fetal
The temperature of the fetus is approximately +0.5 ºC due to fetal metabolic activity.
Heat generated by fetal metabolism is dissipated by the amniotic fluid
or the placenta to maternal blood in the intervillous spaces.
Mother – fetal temperature gradient.

Newborns – heat losses are greater, more rapid and can easily exceed heat production. Because of the newborn´s larger surface area – to body mass ratio, decreased insulating subcutaneous fat, increased skin permeability to water.

After birth – transitional events:
The newborn losses heat rapidly after birth, especially through evaporative losses.
The newborn´s skin temperature (at T = 25 ºC in delivery room) decreases with the rate 0.3 ºC/min – central T – 0.1 ºC/min.
The infant´s T may fall 2 to 3 ºC after birth. In 6-12 hours – restoration of the temperature.

Consequences of the temperature change:
- Positive: - the initiation of the breathing
  - peripheral vasoconstriction – closing of the foramen ovale
  - stimulation of the thyroid gland

- Negative: The increase in oxygen consumption.

Heat production in newborns
Physical methods:
- Shivering – not important in the newborns
- Muscular activity – crying, restlessness

Chemical methods:
- Metabolic processes – the greatest amount of metabolic energy is produced by the brain, heart and liver.

- Special method of heat production in newborns = nonshivering thermogenesis – brown adipose tissue (BAT) metabolism.
In the term newborns BAT accounts for 2 to 7 % of the infant weight.
In the midscapular region, around the neck, under the clavicles, in the mediastinum, around the trachea, esophagus, heart, lungs, liver, kidneys, adrenal glands.

PHYSIOLOGY OF EMOTIONS

DEFINITION
- Strong urgent condition of the instinctive feeling related to the certain target activity.
- Emotions are demonstrated by
  - appetitive or
  - aversion behaviour

Apetitive behaviour

Physiological needs
Looking for pleasant sensoric experiences (taste, visual, acoustic), new positive stimuli, sport etc.

Psychic needs
Looking for social contacts, self – application and social social acknowledgments.

Looking for situations reinforcing self-esteem and self-respect.
Looking for sympathy, mutual understanding, love etc.

Aversion behaviour

Physiological needs
Avoidance of the hunger, thirst, pain, fatigue, too hot/cold environment...

Psychic needs
Avoidance of the social isolation, abortion, non-success, loss of social status, loss of self-esteem, etc.

Regarding to behaviour:

Emotions = affective component of interaction between important stimulus and the response
⇒ determinant of the behaviour of the individual

Components of the behaviour:
- cognitive – cortex
- **emotive** – affective - subcortical + cortical
- conations – cortical + subcortical - motion

Components of emotions
- psychic (fear, anger, sadness)
- autonomic (sweating, CVS, pale/reddish face)
- somatic (increase/decrease in muscle tone, body position, movements,...)

Regulation of emotions

- **Limbic system** (phylogen.oldest)
  amygdala
  hippocampus
  gyrus cinguli (limbic cortex)
  talamus

  Hypotalamus – reactions through ANS

  Cortex – mainly prefrontal.....

Emotions are not product of 1-2 CNS structures – they are result of coordinated activities of many of them.

Recently – very important structures: **prefrontal cortex** and **amygdala**

- **Prefrontal cortex** belongs to the places controlling emotions – mainly positive emotions – happiness, pleasure...

- **Amygdaloid ncl.** are responsible for anger, fear, sadness and other negative emotions

Amygdala

Temporal lobe
Corticomedial part – direct relation to autonomic functions and to smell
Basolateral – to cognitive activity – to frontal and temporal lobe

Afferent pathways
bulbus olfactorius....see Fig.

Efferent pathways
Reciprocal to afferents (see Fig.)

- hypothalamus
- thalamus- prefrontal cortex - cognitive emotional experiences
- hipocampus
- subst. grisea – brain stem, RF and parasympathet. nuclei – important for autonomic and somatic expressions of emotions and on emotions based behaviour.

Amygdala Functions

- Evaluation of information on emotional basis – using of memory – to positive/negative stimuli
- Key role in behaviour control (autonomic and motor reactions) – as response to emotions
- Role in development of memory traces – engrams – with emotional component - load, learning on the basis awarding/punishment

Role of amygdala in conditioned fear reactions:
Rats – dominant reaction - „freezing“ (passive avoidance).
Humans – sudden threat - „freezing“ – latter motoric activity (fight/flight) or continuation in immobility („freezing)

Stimulation of amygdala
In humans during operations of temporal lobe

- Fear with relevant ANS reactions
- Hallucination of the type „déja vue“

Destruction of amygdala
(experimental or by cancer process)

- Loss of the fear
- Loss of agressivity
- Reduction of emotional expressions
- Loss of facilitation of engrams production with emotional load
- Loss of effort for social communication (self – isolation)
- Hypersexuality

Limbic system

1) Weak influence of cortex on emotions (affective component and autonomic changes).
Only few connections to cerebral cortex

„It is easier to play than to mask emotions“

2) Inertia of emotions: firing from the neurons of the limbic system are present longer after stimulus (emotions „live“ longer than stimuli)

Role of the emotions

Physiological view: they help to survive to individuum / human (animal) kind

Personality view: they make life rich to positive/negative experiences – life fullness

Types of emotions – related to:
- Self-defense
- Nutrition
- Reproduction...

1. Emotions related to self-defence

- **fear** (passive defence - avoidance) – stimulation of hypothalamus and amygdala; mydriasis, sweating, postural changes, ...
- **agressivity** (active defence - avoidance);
- **placidity** (peacefullness) – contrary to agressivity

Regulation of the emotions related to the fear:
- amygdala responsible for balance between extreme emotions (agressivity/placidity)
- hypothalamus integration center for autonomic and somatic responses during defecnsive behaviour
- hormonal – testosterone increases agressivity (castration), estrogens - placidity

2.Emotions related to nutrition

Stimuli: **hunger, thirst** regulated by hypothalamus (hunger and satiety centers) as
- affective component – emotions - controlled by limbic system (and hypothalamus)
- $\Rightarrow$ nutritional behaviour (food search) – conation component

Other stimulus: **apetite** (strong cortical influence)

Physiological consequences: $\uparrow$ BP and splanchnic circulation, stronger peristaltics, decrease in skeletal muscles blood flow

3.Emotions related to reproductive activities

Determinants of:
- **sexual behaviour**
- **parental behaviour** (maternal and paternal)

Regulation of sexual behaviour
- neural: neocortex, amygdala, hypothalamus, limbic cortex
- hormonal: testosterone, estrogens

Emotional inteligency (EQ)

- ability to control individual´s own emotional status (and of other peole) and to use this information in relationships

- ☐ 5 components
1. self-consciousness (to understant internal feelings)
2. to control emotions
3. motivation (aimed to the target)
4. empathy
5. management of the social relationsips

HYPOTHALAMUS

Connections:
- with the pituitary gland , with the posterior lobe (neurohypophysis) by neural fibres – tr. hypothalamo – hypophyseus.
- with anterior lobe (adenohypophysis) by blood vessels (hypothalamic - hypophyseal portal system).
- many afferent and efferent connections between hypothalamus and other parts of CNS – mainly by limbic system, thalamus, midbrain, hippocampus and others.

Functions of hypothalamus
Regulation of the autonomic functions – control of organs through ANS. Integration of the somatic with autonomic nervous system „centers"

Regulations of the autonomic functions:

- Spinal cord (e.g. sacral) – regulation of defecation, micturition

- Medulla oblongata – more complex functions: cardiovascular, respiratory, salivation, vomiting, secretion of GIT juices…

- Middle brain – acomodation, pupillary reflexes (eye)

- **Hypotalamus = organ for integrative regulation**

1) Control of the cardiovascular system:
So-called neurogenic effects on heart rate and blood pressure
Stimulation:
- posterior and lateral region: sympathetic responses – tachycardia, hypertensive reaction, mydriasis...
- anterior – area preoptica: parasympathetic responses Reactions are modulated and transmitted through pons and medulla.

2) **Thermoregulation**
Hypothalamus anterior – monitoring of body temperature:
Central thermoreceptors – in area preoptica (2/3 for higher temperature, 1/3 for a decrease of BT – „cold")

Peripheral thermoreceptors – spinothalamic tracts, thalamus, collaterals to hypothalamus. In skin - periphery 10x more of the cold receptors than for hot environment.
Humoral signals – mediators (pyrogens) – transport through organum vasculosum laminae terminalis (OVLT) – the region non-protected by blood - brain barrier.
Changes of hypothalamic perfusion by vasoconstriction/ vasodilation of OVLT – influence on basal hypothalamic temperature – set of the set point for central BT.

Hypothalamus posterior – thermoregulatory center (area hypoth. posterior) – processing of information from area anterior and the periphery. Activation of effectors for thermoregulation.

3) **Regulation of hydratation and food intake**

Regulation of hydratation:

Regulation of water intake:
Centre for thirst in lateral hypothalamus
Information from:
Hypothalamus itself - osmoreceptors
Periphery – volumoreceptors, mouth, pharynx..

Regulation of fluid output (through kidneys):
Ncl. supraopticus - ADH (arginín – vazopresín = AVP)

Regulation of apetite:

lateral centre = **apetite** – dominant active
Ventromedial centre = **satiety** – after food intake – temporary inhibis the „feeding centre"
Corpus mamillare = coordinatio of the reflexes – movements of a tongue, chewing, deglutition, swalowing…

Information from:
Glucoreceptors – glucostats in the centre of satiety
Periphery

4. **Endocrine control**

Production of:
- *ADH(AVP)*
- *Oxytocine*
- *Hypothalamic neurohormons – regulation of adenohypophysis*

5. **Sexual functions**

- Regulation of gonads development, sexual cycles through *adenohypophysis.*
Control of sexual behavior: Activity of lateral regions of hypothalamus – stimulation of sexual behavior
Coordination of autonomic functions in erection, ejaculations in males.

6. **Behavioral responses associated with emotions**

Lateral hypothalamus – stimulation - hunger, thirst,activity and agressivity

Ventromedial hypothalamus – stimulation - subjective feeling of satiety, complacence, calmness, inactivity

Periventricular zone – near of the 3rd ventricle – stimulation – fear, aversion

7. **Sleep-wake patterns**

„Sleep centres", „wakefullness centre" – recently –only non-specific effects

Efects of hypothalamic lesions

Bilateral lesion of the lateral hypothalamus:
- a decrease of the food intake (anorexia)
- a decrease of the water intake
- passivity

Bilateral lesions of the ventromedial hypothalamic region:
- excessive food intake (hyperfagia)
- excessive fluid intake
- hyperactivity
- brutality
- expressions of anger - passion