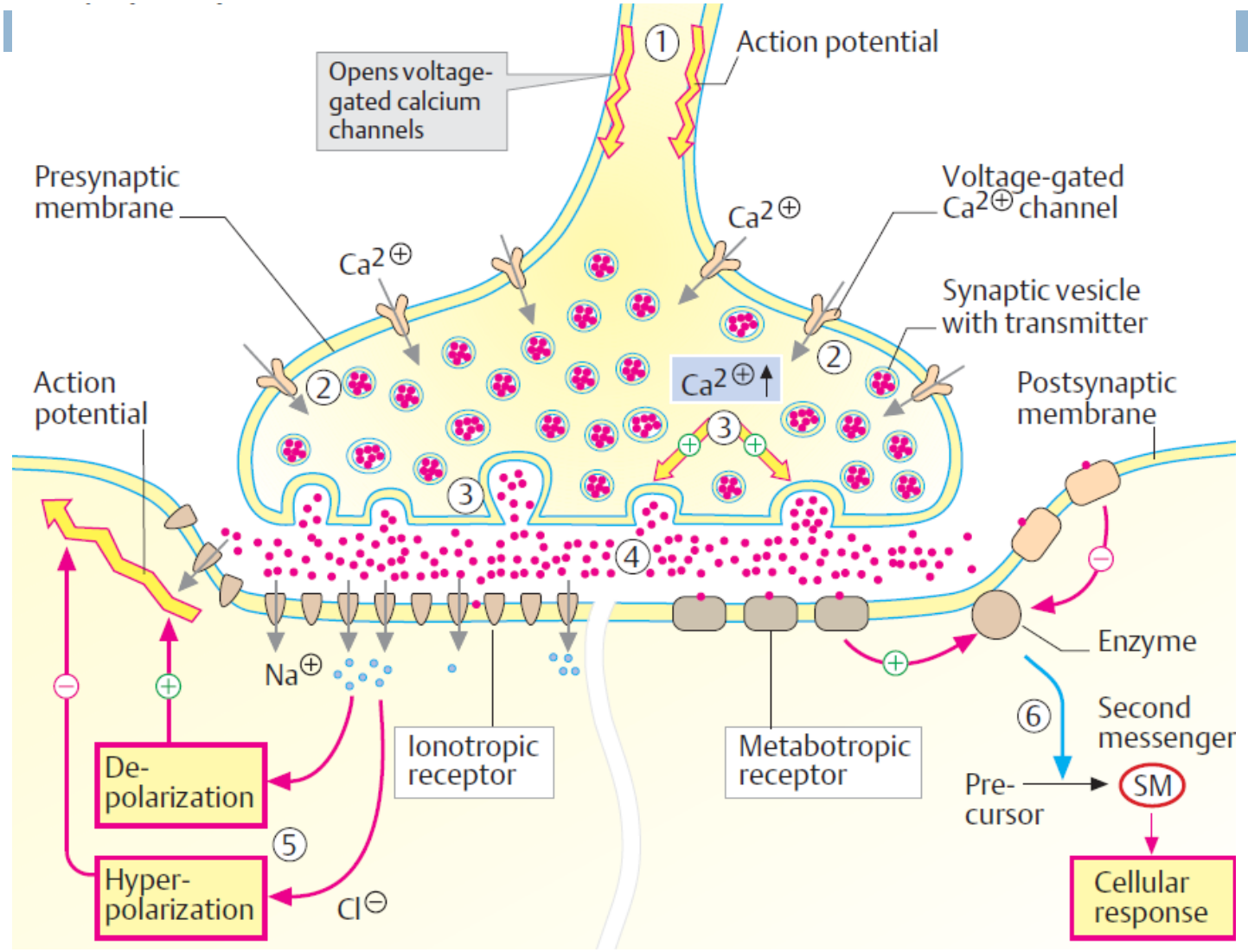
Biochemistry of nervous system, vision and sense. Metabolism of the eye. Mitochondrial disease.

Jana Švarcová

Synapse – passing the signal

① action potential reaches presynaptic membrane
② opening of the voltage gated Ca^{2+}-channels
③ released Ca^{2+} ions induce exocytosis of the neurotransmitter
④ exocytosis of the neurotransmitter
! each neuron releases only one **NT**
⑤ depolarization of the membrane → initiation of the action potential on post-synaptic memb.
⑥ different action of metabotropic receptors – interaction with G-proteins



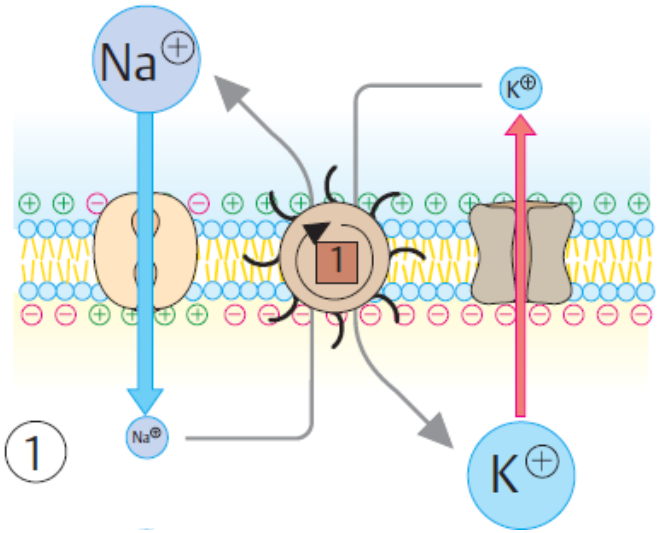
Passing the signal

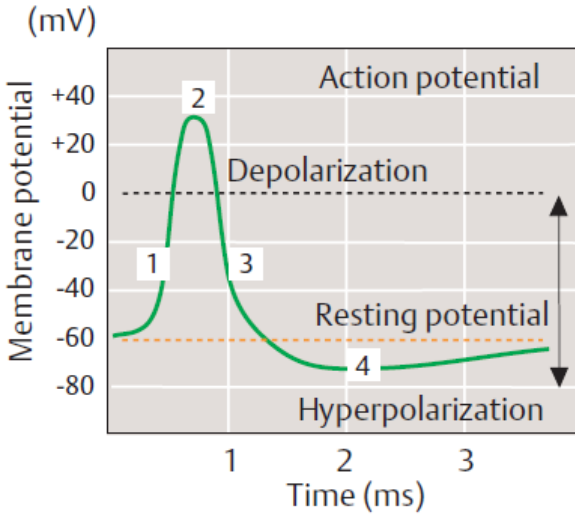
- **3 types of neurons** according to the function:
  - Afferent neurons - transport impulses from periphery to CNS (sensory)
  - Efferent neurons - transport impulses from CNS to muscles and glands (motoric)
  - Interneurons – mainly in CNS, interconnect neurons

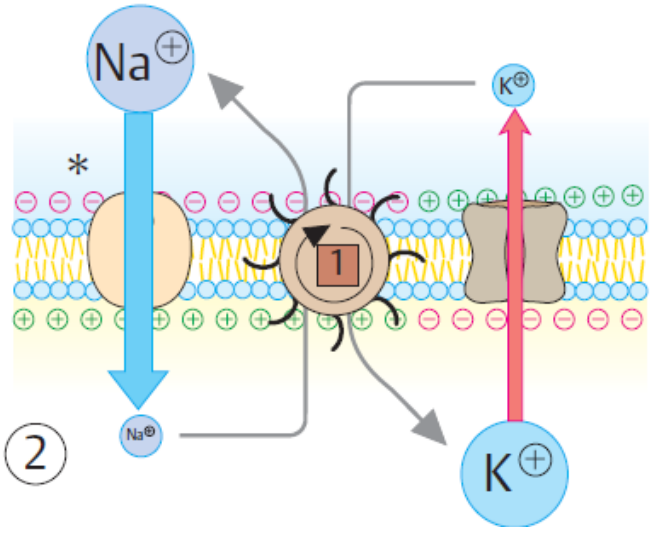
Action potential

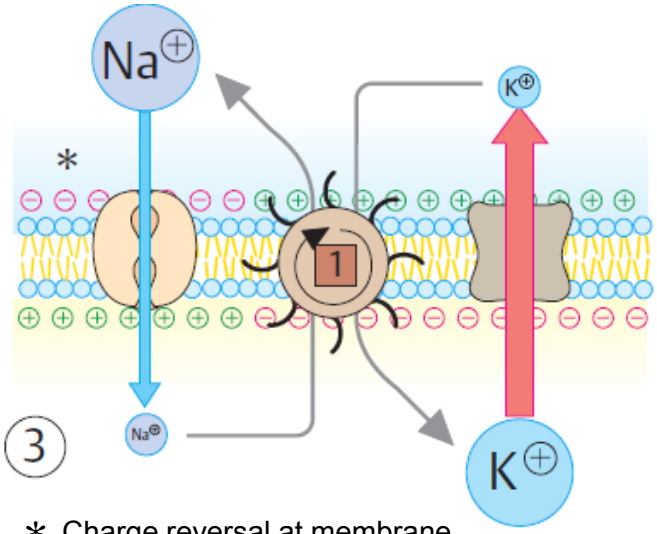
- = initiation and transfer of the neuron signal
- neuron signal – electric signal, created by ion flux across plasma membrane of the neuron
- membrane potential
  - intracellular – high conc. of K^+ (low Na^+)
- Na^+/K^+-ATPase – so called sodium pump requiring ATP
  - Initiation of the signal – important role – passive transport of K^+ across plasma membrane

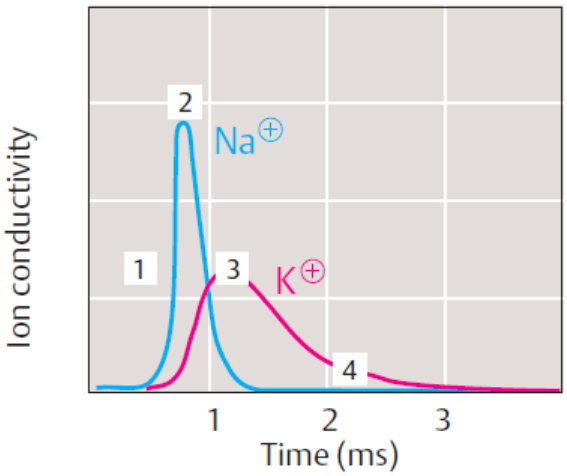
Action potential

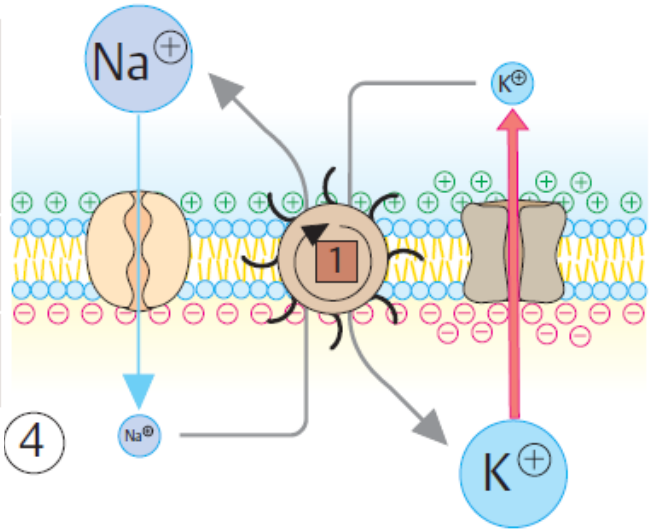












* Charge reversal at membrane

Neurotransmitters

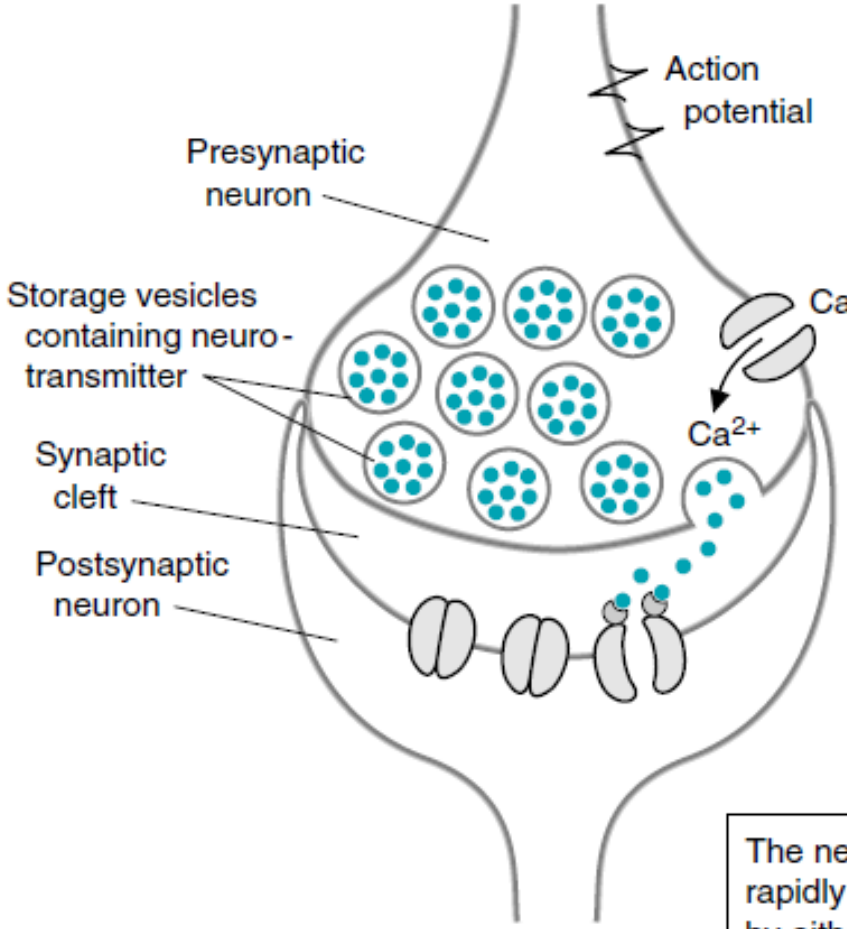
„small nitrogen-containing molecules“

- glutamate
- GABA
- glycine
- acetylcholine
- dopamine
- noradrenalin
- serotonin
- histamine
- adrenalin
- aspartate

Neuropeptides

- Small peptides synthesized in CNS
  - endorfines
  - Growth hormone and TSH („thyroid-stimulating hormone“)

Neurotransmitters



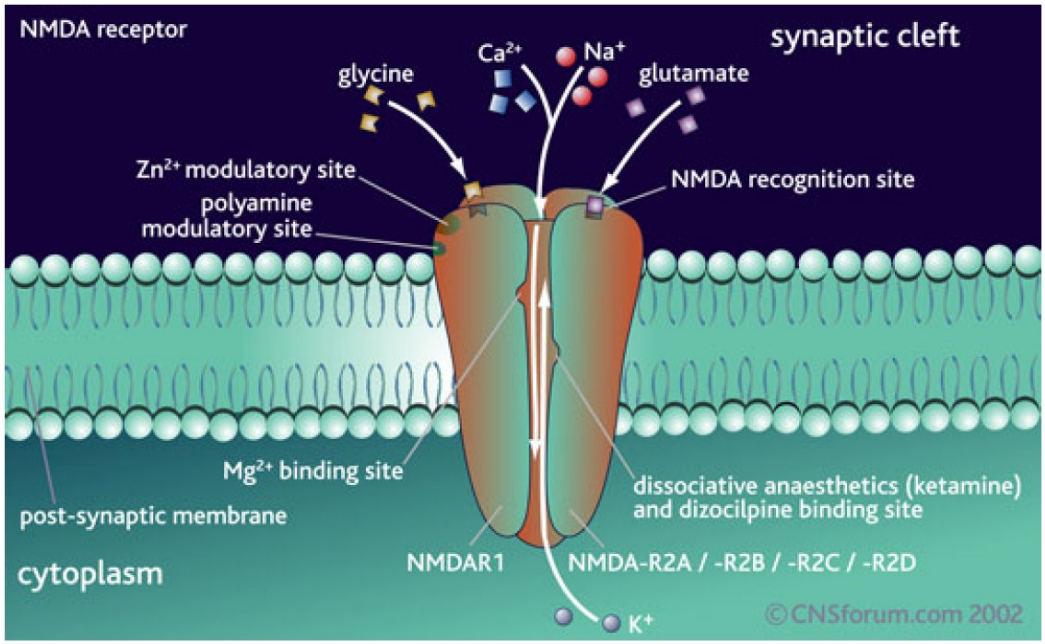
An action potential in the presynaptic neuron allows Ca^{2+} to enter and stimulate exocytosis of the neurotransmitter

The neurotransmitter binds to proteins in the membrane of the postsynaptic neuron, causing channels to open that allow the nerve impulse to be propagated

The neurotransmitter is then rapidly degraded, or internalized by either the pre-synaptic cell or glial cells (reuptake)

Excitation AA

- receptors for excitation AA:
  - **ionotropic** – subtypes according to the selecktive agonists:
    - **NMDA** – (N-metyl-D-aspartic acid)
    - **AMPA** – (amino-3-hydroxy-5-metyl-4-izoxazolpropionic acid)
    - **KA receptory** – (kainate receptors, kainic acid)
  - **metabotropic**
    - Stimulation of phospholipase C
    - inhibition of adenylatecyclase and regulation of specific Ca^{2+} and K^{+} channels

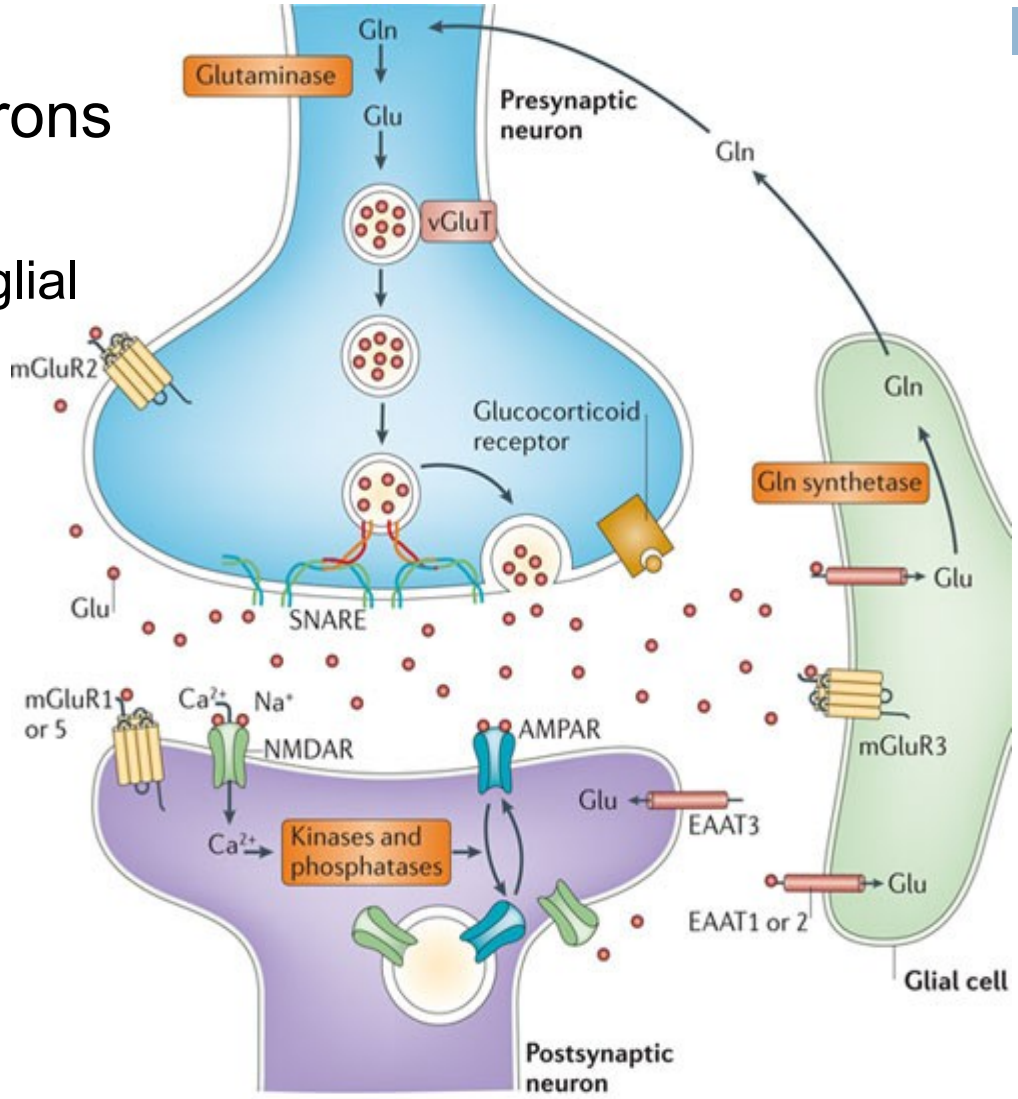


Glutamate synapse

- glutamate – excitation NT
- synthesized directly in neurons from precursor molecules
  - glutamine – synthesized by glial cells

↓

Resorbed by neurons and changed to glutamate
~ 80 % of glutamate
(alternative – synthesis from Glc or 2-oxoglutarate)
storage – vesicles
elimination – high affinity transporters for excitation
AA – presynaptic membrane and membranes of surrounding glial cells
= glutamate-glutamine cycle



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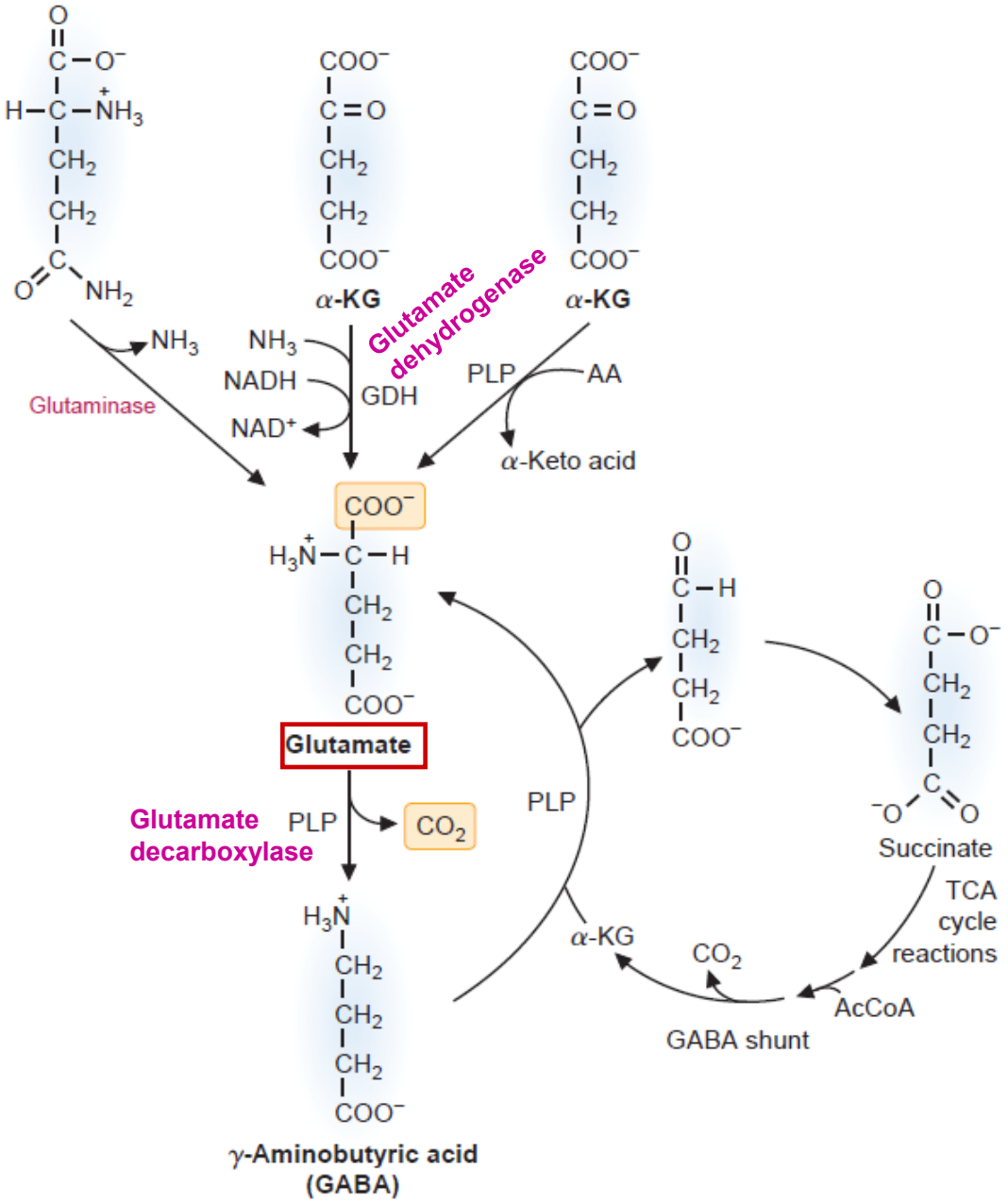
Inhibitory AA

- GABA – major inhibitory NT
- GABA synthesis – from glutamate (precursor Glc, Pyr)

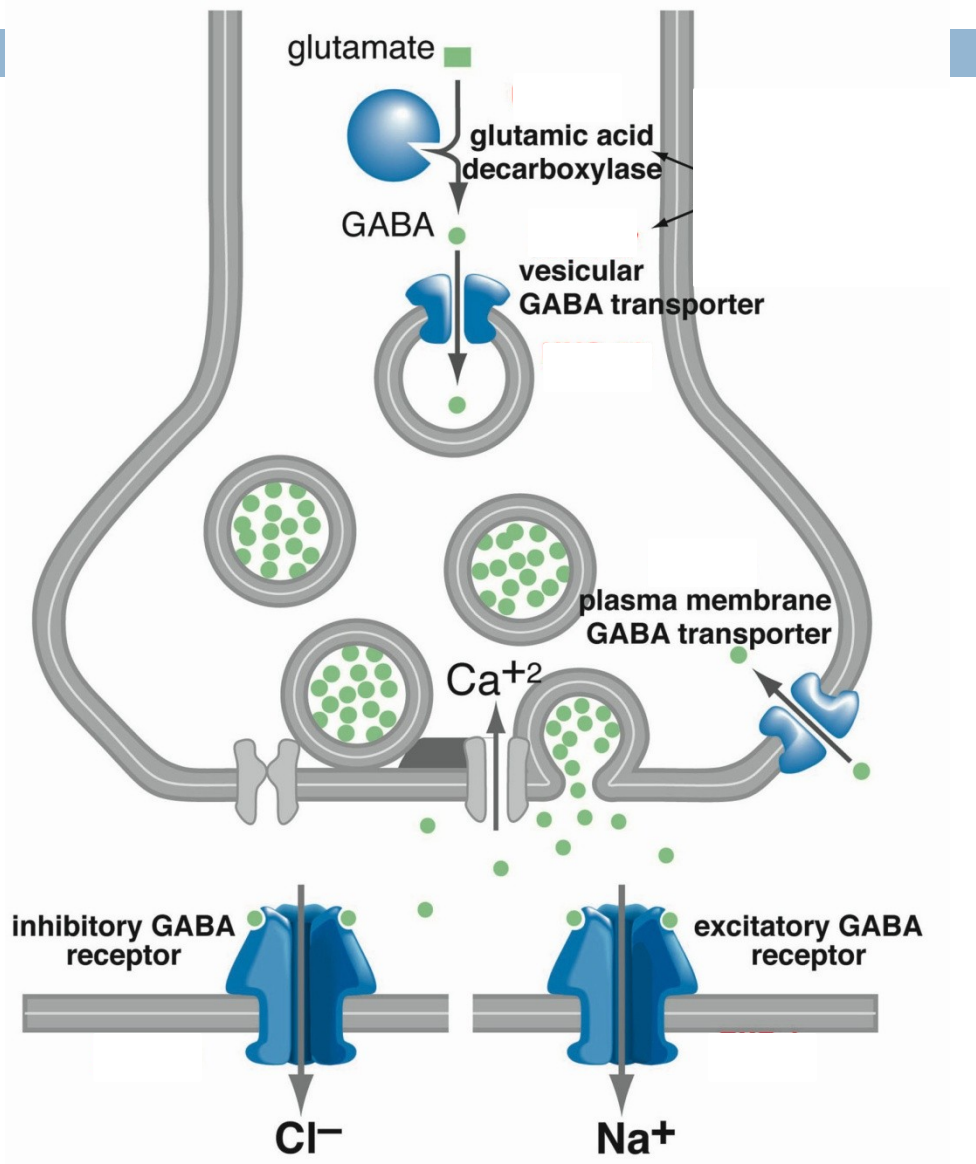
  cofactor – PLP (from vit. B_6) → vit. B_6 insufficiency– decreased concentration of GABA in brain → loss of synaptic inhibition

- ! Inhibitory effect of GABA – synthesised from compound with excitation effect



GABA-ergic synapse

- synthesized GABA – encapsulated into vesicles by GABA vesicular transporter
- After excretion – GABA resorbed from synaptic cleft (neurons or surrounding glial cells); transport requires presence of extracellular Na^+ and Cl^-



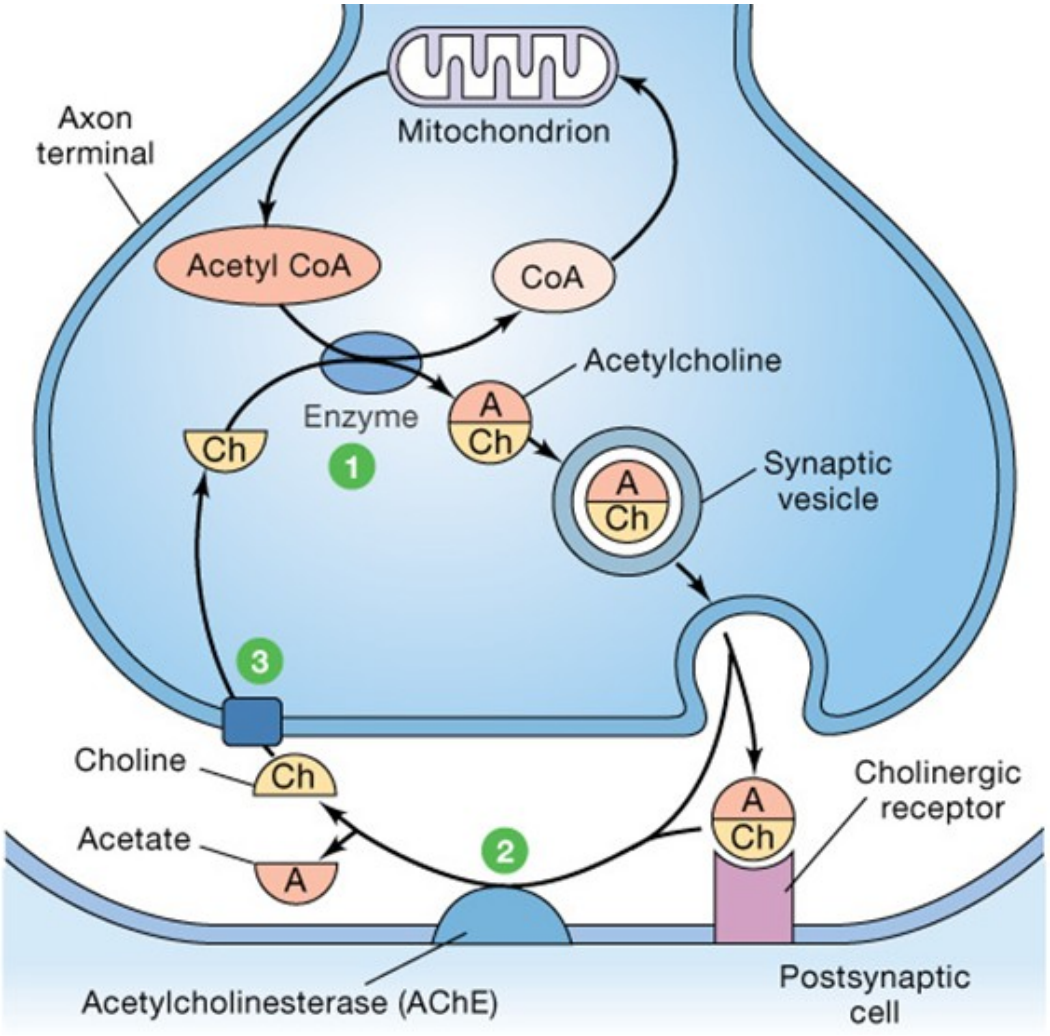
Acetylcholine

- The first discovered NT
- Synthesized from acetylCoA and choline in presynaptic part (cytosolar *E*-cholinacetyl transferase)
- choline – from plasma; transport dependent on Na^+. Required acetylCoA - from pyruvate, directly in neuron (glycolysis)

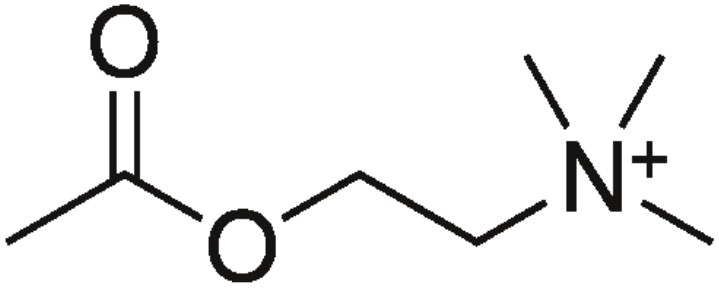
  storage – synthesized acetylcholine – in vesicles

  excreted – fast decomposition to inactive metabolites (acetate and choline;

  E-acetylcholinesterase). Choline is transported back to presynaptic part



Acetylcholine



- neurodegenerative changes of cholinergic neurons – serious pathological disorders
- cholinergic pathways – mainly modulation entry to cortical and hippocampus neurons
- → drugs blocking acetylcholinesterase improve memory and learning performance and can partly reduce the consequences of lesions in cortex
- **Alzheimer disease** – degeneration of cholinergic neurons in area of basal forebrain (= progressive loss of intellectual abilities)

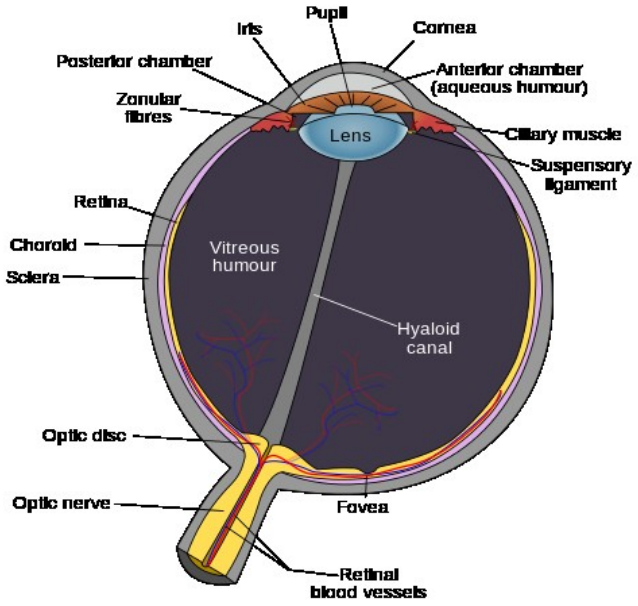
Nicotin type acetylcholin receptors

- Neuromuscular junctions, autonomous ganglia, adrenal medulla and CNS
- ligand gated voltage channels – activation leads to influx of Na^+ and Ca^{2+} $\rightarrow$ cell depolarization
- typical characteristics – desensitisation (independent to other proteins; e.g. arestin)
  - Rate of desensitisation – regulated by phosphorylation of receptor subunit by proteinkinase A and C (or long term exposition of ligand)

Biochemistry of the eye, vision and senses.

Vision

- perception of light (~400-750 nm) and its colours → resolution of contrast (black and white/colour) and thus the contours; using the eye movement + shape of the eye



- Outer parts of eye – cornea and sclera

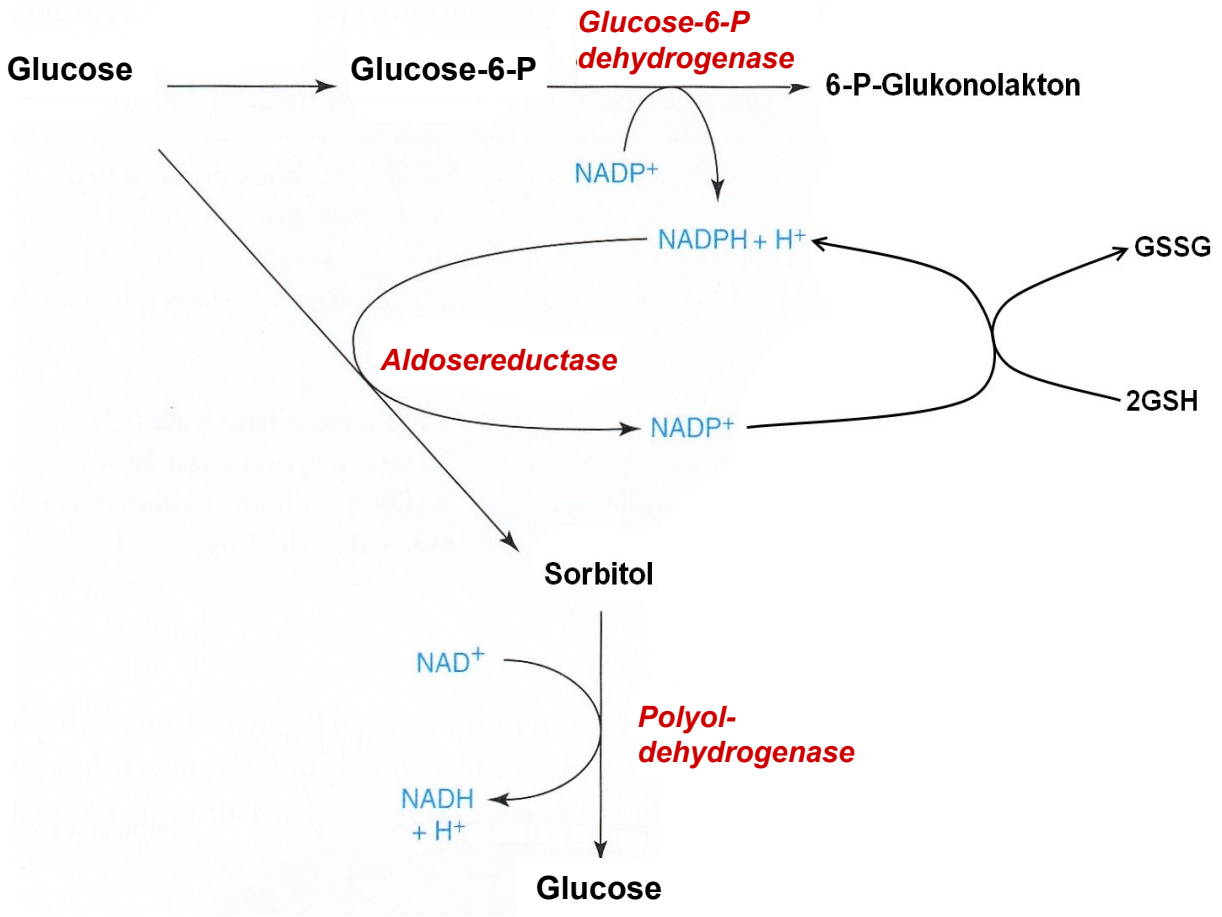
  cornea – veinless , colourless, hydrated, and formed by collagen, needed continuous moisturizing

  tears – nourishing covering cells of cornea and defense
- **iris** – regulating of light entering the eye
- **lens** – high protein content (α-, β-, γ-crystallins and theirs insoluble aggregates)
- **retina** – the light detecting layer of the eye containing photoreceptor cells
  - **rods** – black and white (low light intensity)
  - **cones** – colour vision

Cornea

- energy required for the integrity of cornea – dependent on the glucose metabolism
  - High percentage of ATP – aerobic glycolysis (more than 70 % of Glc – pentose shunt) ⇒ thus, the oxygen supply is limiting for normal cornea metabolism. The usage of atmospheric oxygen had been observed in 1930 (Fischer)
  - hypoxia – oxygen is supplied by tears; metabolism of cornea - anaerobic → production and accumulation of lactate. Synthesis of glycogen is inhibited and glycogen supplies in epithelium decrease (example: contact lenses)

Cornea

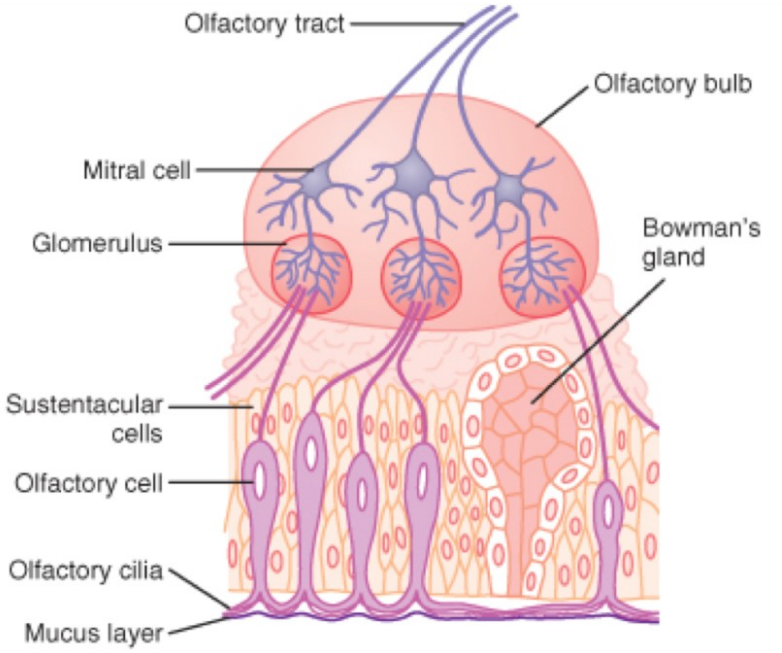


- **diabetic cataract** – increase of Glc → increase of sorbitol (↑activity of aldosereductase)

  Accumulation of sorbitol = increase of the lens osmolality → structural changes of the crystallins (aggregation/denaturation)

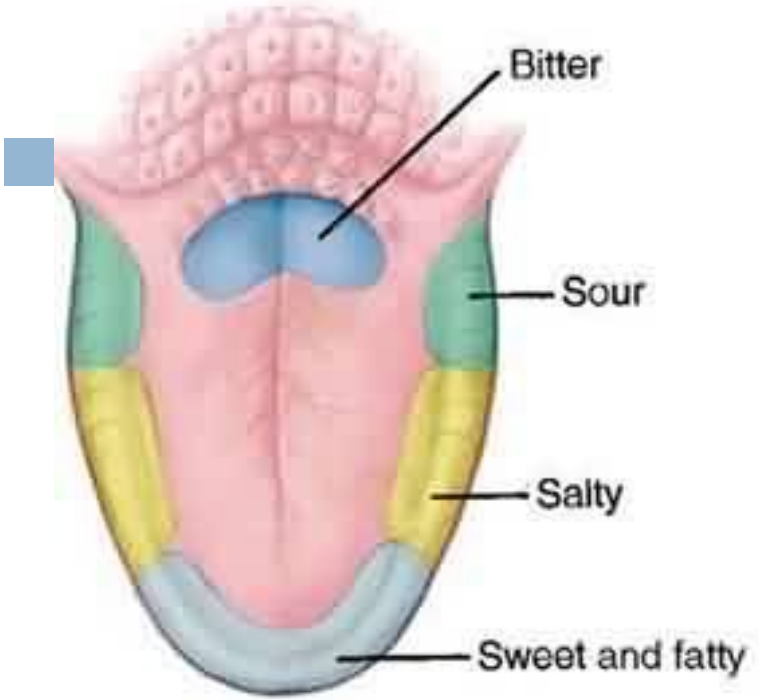
Olfaction

- olfactory receptors – several hundreds of different homologous olfactory receptors (vision – based on 4 different types of photoreceptor (3 cones and 1 rod) only
- olfactory epithelial receptor has only one specific receptor and reacts to only one or small number of similar smells
- odorants; reaching the cilia of receptors through mucilage layer, where they bind to Odorant binding proteins (OBP), and become water soluble



- Transport rate – size of the complex odorant-OBP, mucilage viscosity and mechanical obstacles (tangled cilia) → olfactory signal is therefore amplified in the beginning phase
- Transduction – interaction of odorant with specific receptor in cilial membrane of olfactory cell → activation of G_{olf}-protein, stimulating adenylatecyclase and production of cAMP. cAMP activates protein kinase, which phosphorylates polypeptides of Na^+-channel, opening.
  Opening of Na^+-channel depolarizes cell membrane → generation of electric signal to the brain .
- olfactory receptor cells can regenerate – difference from other sensing cells

Taste



- Taste receptor – located on taste buds
- Taste perception – only water soluble compound
- 4 basic tastes
- **Saltiness** and **Sourness** – change of membrane depolarization in receptors – ions influx across plasma membrane
- **bitterness** and **sweetness.** – sensing connected to activation of G-proteins
- **Umami –** the fifth taste. Name coming from japanese (*umai* = *tasty*, *delikate*). Specific taste receptor - **umami taste-mGluR4** (discovered in 2000). → sensing of glutamate acid(glutamates)
- **sourness** – concentration of H^+ ions, blocking outflux of K^+ *via* voltage channel
- **saltiness** = higher Na^+ concentration- passive influx of these ions to cell, pumped out by ATPase
- **sweetness** = sugars – activate membrane receptor → adenylatecyclase activation → formed cAMP blocks K^+ channel → membrane depolarization
- **bitterness**– specific protein gustducin (G_{gust}), which α subunit activates cAMP-phosphodiesterase→ decreased level of cGMP → closure of Na^+-channel and hyperpolarisation

Mitochondrial diseases

Characteristics of the diseases

- In general - mitochondria are energetic centres and mutation of Mt chromosomes cause defects in these energetic cycles ⇒ diseases manifest in organs and organ systems with high energy demand
  - for instance CNS consumes up to 20 % of all ATP produced by the body; this is the reason why CNS is the mostly affects organ. The others are muscles, heart liver and kidneys
- mitochondrial dysfunctions play important role in more serious cell damage
- some pathological states – important increase and decrease of the Mt volume ant their count (+ / -)
- So called megamitochondria – found in case of alcohol liver disease or some nutrient deficiencies

Characteristics of the diseases

- genetic information in Mt – prone to mutations (in similar way as nucleolar DNA)
- Mt genome exposure to the mutagens → changes in DNA
- Frequency of the mutation occurrence – in mtDNA in average 10 × higher than in nDNA

  reason of higher frequency of mutation:
  - in Mt less correcting mechanism
  - Main task of Mt - oxidative phosphorylation, causing increased concentration of oxygen radicals; BUT: mtDNA is not shielded by histons
  - mtDNA replication is more frequent , *P* of error↑

Characteristics of the diseases

- mitochondria – only maternal inheritance; (all children, no sex difference). Father suffering Mt disorder will not transfer this to his offsprings.
- Predictability of Mt disease is low (during youth the energetic effectivity is sufficient)
- ⇒ important ratio affected to "healthy" Mt (determined by Mt genotype)
  - heteroplazia × homoplazia (mutation of all mtDNA)
  - example. 20 year old – 85 % affected mtDNA ⇒ healthy appearance

    × close relative – affected 96% of Mt → the most serious symptoms

Characteristics of the diseases

Manifestation of hereditary Mt defects

- Deletion or point mutation of mtDNA – usually manifested by **mitochondrial encephalomyopathy**
- Clinically heterogeneous group of diseases *(*but there are common morphologic abnormities in Mt causing different disorders in Mt metabolism:
  - transport of the substrate from cytosol to mitochondria
  - utilization of the substrate
  - enzymes of citrate cycle
  - coupling of phosphorylation with electron transport
  - enzymes of electron transport chain
- clinical manifestation - not thriving, psychomotoric retardation, symptoms of encephalopathy, myopathy, hepatopathy, hypertrophic cardiomyopathy, atrophy of nervus opticus
- laboratory report – often lactate acidosis in case of defects in enzyme activity of respiratory chain complex, pyruvatedehydrogenase and ATP-synthase

Mt diseases - overview

- Leber's hereditary optic neuropathy (LHON)
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Maternally inherited myopathy and cardiomyopathy
- and others

Leber's hereditary optic neuropathy(LHON)

- One of the most common mitochondrial diseases caused by point mutation in v mtDNA
- Incidence is low , usually teenagers; prevalence cca 1 : 25 000
- Symptoms and manifestation of the disease- eye damage with gradual blinding. Beginning – temporary visual losses (loss of central vision and colour vision); severe optic atrophy and permanent decrease of visual acuity
- Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes (NADH dehydrogenase).
  - Mutations in any of the genes disrupt this process to cause a variety of syndromes depending on the type of mutation and other factors. It remains unclear how these genetic changes cause the death of cells in the optic nerve and lead to the specific features of Leber hereditary optic neuropathy.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

- At present the most common disorder with encephalomyopathy symptoms
- Appears in childhood
- Manifestation – low height, recurrent headaches, loss of appetite, vomiting, and seizures with lactate acidosis. Later spasms, brain damage caused by calcification of CNS, ischemias. Repeated stroke-like episodes.
- Affected neural tissue – occurrence of lesions, visible by magnetic resonance
- Other symptoms - in 1.5 % of the cases the diabetes mellitus is cased
  - probably – Langerhans islets are loosing the source of energy and subsequently stop insulin synthesis