Disorders of neurotransmitter systems

Classical neuromediators - criteria

- Produced in the presynaptic neuron.
- Stored in the presynaptic terminal and released from here in amount sufficient to induce its specific effect on the postsynaptic neuron or effector.
- Exogenous administration of the substance induces identical response as its endogenous release.
- There is a specific mechanism for elimination of the substance from the place of effect (synaptic cleft).

Neuromodulators

- Many other substances that influence signal transmission. They can change sensitivity of the postsynaptic element to the main mediator.
- After release, they can disperse into the surrounding interstitial space and influence cells (paracrine secretion).
- Examples: endorphins, enkephalins, prostaglandins, NO, CO, hydrogen sulphide, VIP, NPY, gastrin, bombesin…

Classification of neuromediators: Structure

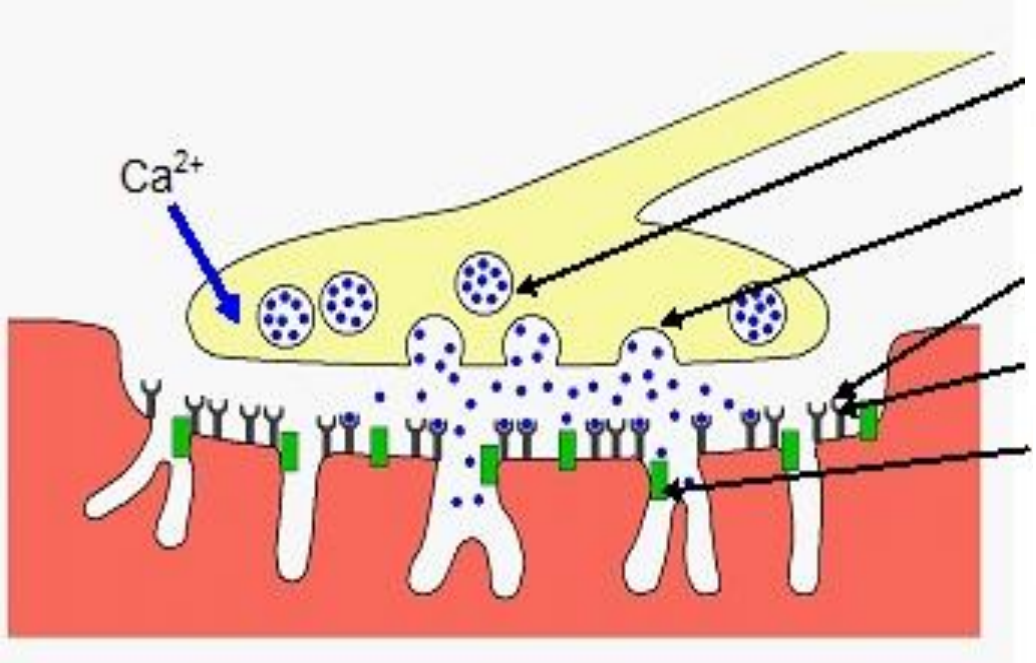
Small molecules:

- Aminoacids: glutamate, aspartate, glycine
- Aminoacid derivates: GABA, serotonin, catecholamines
- Acetylcholine
- Others: purines (ATP, ADP, adenosine), gases…

Large molecules:

- Peptides: endorphins, enkephalins, substance P, NPY…
- Endogenous cannabinoids

Disorders of synaptic transmission



Glutamate – the main excitatory neurotransmitter

- Present in the whole CNS, important for synaptic plasticity.
- Synthesis and inactivation in interaction neuron – astrocyte.
- Receptors: - ionotropic (kainate, AMPA, NMDA)
  - metabotropic (AP4, ACPD)
- Relation to **epilepsy**, exogenic administration of glutamate or NMDA agonists can induce seizures.
- **Glutamate excitotoxicity** (ictus, Alzheimer, ALS, epilepsy)
- Origin of **schizophrenia** hypothesis – defective function of NMDA receptor-gated channel (ketamine – reduction of channel conductance).
- Excess of NMDA receptors and high sensitivity in the childhood - **glutamate in food - ADHD risk**

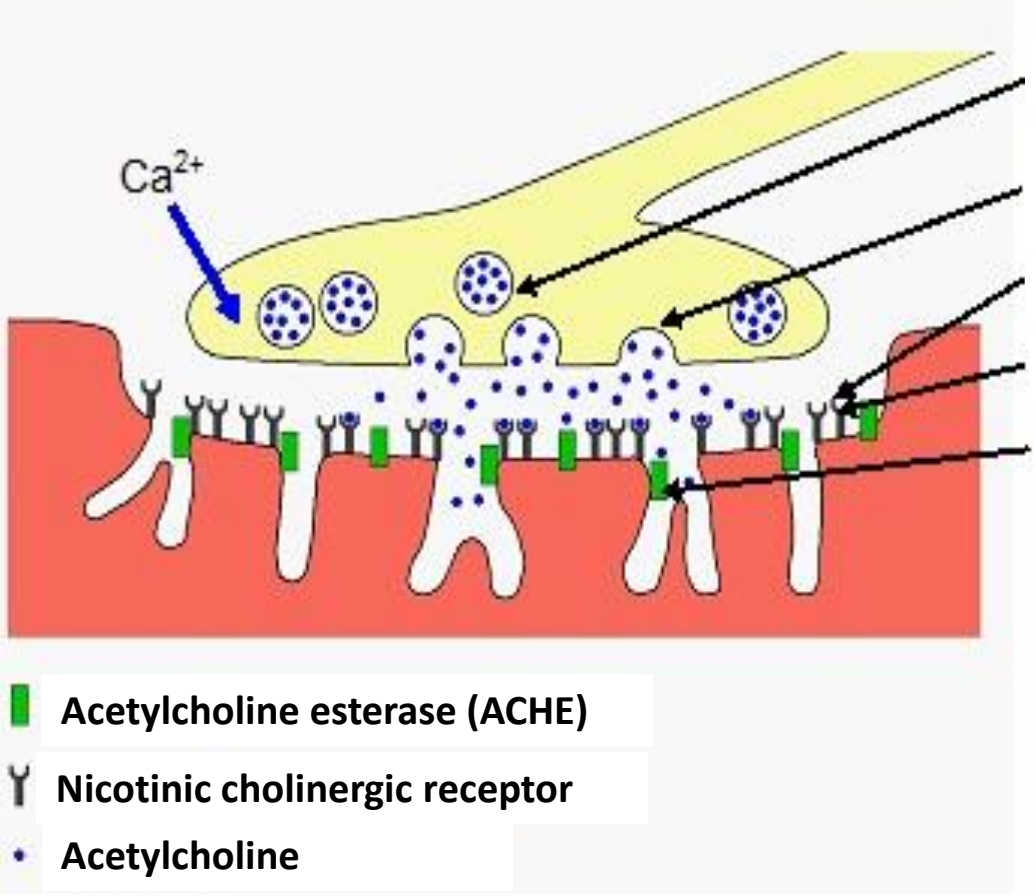
GABA – the main inhibitory neurotransmitter

- Decarboxylation of glutamate, cooperation of neurons and astrocytes
- Receptors: $GABA_A$, $GABA_B$, $GABA_C$
- $GABA_A$ - ionotropic receptor gating the chloride channel (IPSP)
- Reduction of GABAergic transmission is involved in epilepsy pathogenesis
- Binding site for **ethanol, barbiturates, benzodiazepines** – increase conductivity od the chloride channel – inhibition, decrease of overall activity, reduction of memory capacity
- $GABA_A$ receptor antagonists – provocation of epileptic seizures (**penicillin, bicuculine, picrotoxin**)

Acetylcholine

- CNS, neuromuscular plate, preganglionic neurons of the autonomic nervous system, postganglionic neurons of the parasympathetic system
- Processes of learning and memory, modulation of sleep-waking cycle, movement modulation (striatum)
- Muscarinic and nicotinic receptors
- Extinction of cholinergic neurons: Alzheimer's disease (M1 rec.), Huntington's chorea
- Disorders of the neuromuscular plate: botulotoxin, organophosphates, myasthenia gravis, curare…

Disorders of the neuromuscular plate



Dopamine

- Catecholamine, synthetized from tyrosine
- Receptors D1-5, coupled with G-proteins
- Projection:

- nigrostriatal (Parkinson‘s disease)
- mesolimbic – **central reward system – ventral tegmental area** (neurons mesencephalic RF - amygdale, hippocampus, nucleus accumbens, connection with the prefrontal cortex, motivation, reward, punishment, **addiction**), D2 rec. hyperactivity in the schizophrenia – positive symptoms (hallucinations), antipsychotics blocking D2 rec.
- mesocortical (RF – prefrontal cortex, attention and mood modulation)
- tuberoinfundibular (dopamine from hypothalamus inhibits secretion of prolactin in the adenohypophysis), interruption of the hypothalamus-hypophysis communication leads to hypopituitarism, but prolactin secretion increases!

Serotonin

- Synthetized form tryptophan
- Reuptake and inactivation by MAO → 5-hydroxyindolacetic acid
- Modulates activity of other neurotransmitter systems
- Nuclei raphe
- Ascendant projection into the limbic system, basal ggl., hypothalamus, thalamus (emotions, mood, sleep-waking cycle, visceral functions)
- Descendent projections: to the brain stem, spinal cord, cerebellum, modulation of nociception – analgesic system
- 7 receptor subtypes - excitatory or inhibitory
- Antidepressants: increase concentration of serotonin in the synaptic cleft.

Noradrenaline (norepinephrine)

- Modulator of other neurotransmitter systems (activator or inhibitor)
- NA neurons in the brain stem – **locus coeruleus**
- Projection into almost all parts of the CNS (modulation of emotions, attention, vigilance, sleep and waking, memory trace consolidation)
- Regulates response to acute stressors!
- Insufficient function of the adrenergic system together with dopaminergic system is involved in **ADHD syndrome** (attention-deficit hyperactivity disorder) pathogenesis
- Depression – reduced brain NA hypothesis (inhibition of NA reuptake = therapy)
- Mania – functional excess of catecholamines in the brain

Nitric oxide - NO

- Mediator acting in the immune system, vasomotorics and neurotransmission (in the CNS recognized in 1988)
- Ability to diffuses freely across the membranes, acts without respecting anatomical connection
- Biological halftime: several seconds
- Expected role of NO in the CNS: activation of the guanylat cyclase – cGMP synthesis, modulation of ion channels, modulation of neuromediator release from presynaptic terminals, interaction with e.g. NMDA glutamate receptor, synaptic plasticity…
- NO-synthase: neuronal, endothelial, inducible (iNOS)
- Neurotoxicity mediated by excess of NO – demyelination (sclerosis multiplex)