Biochemistry of central nervous system (CNS)
Blood-brain barrier (BBB)

- Endothelial cells, feet of astrocytes
- Small concentration changes do not affect the composition of cerebrospinal fluid
- Macromolecules do not cross the BBB
- Amino acids have special transporters
- Glucose diffuses freely
Neurotransmission

- propagates nerve impulses from neuron to neuron or from neuron to effector cells

- Chemical synapses
  - neurotransmitters
  - depolarization => axon terminal releases neurotransmitters
  - postsynaptic receptors bind the neurotransmitters
  - neurotransmitters inhibit (IPSP) or activate (EPSP) postsynaptic cell
  - synaptic delay
    - one-way
    - inhibit or activate postsynaptic cell

- Electrical synapse (gap junction)
  - two-way, quick, always activator
  - heart muscle, glial cells, rarely neuron
Steps of neurotransmission

• SYNTHESIS – Cytosol of axon terminal – exceptions: peptid neurotransmitters, synthetized by ribosome in the body of the cell, and axonal transport transport them to axon terminal

• STORAGE – Synaptical vesicles – V-ATPase in the membrane of vesicles – maintain a H⁺ gradient – this H⁺ gradient drives the special neurotransmitter transporters
General characteristics

- Cns IS BUILT UP FROM $2 \times 10^{10}$ neurons and 3 times more glial cells
- The weigh of the human brain is about 2% of the total body weight, but glucose utilization reaches 66%
- The $O_2$ consumption is about 25% of the total
- The main energy source for the brain is ATP generated by oxidative phosphorylation
- creatine phosphate is able to store energy
- The CNS is protected from general metabolites of the blood plasma by the blood-brain-barrier
- Nervous tissue is rich in phospholipids, sphingolipids, which play an important role in cell membrane functions and myelin formation
- water content: Myelin 40%, white matter 70%, grey matter 80%
Carbohydrate metabolism

- The usual main energy source is glucose which is metabolized to pyruvate and lactate via glycolysis (90%)
- Hexokinase activity is about 20x as high as other tissues
- The drop of gluc concentration in CSF to 10-20% of the normal may cause come
- B vitamins are important in the function of pyruvate dehydrogenase complex (vitamin B₁, B₂, B₃, B₅)
- Lack of vitamin B₁ causes Wernike-Korsakoff syndrome

- TCA cycle is fully used
  - minimal amount lactate leave the brain
- Anoxia = lack of oxygen supply
- Low blood glucose level
- Risk the function of the brain
Carbohydrate metabolism

- Glucose is not only an energy source, but is also used for the synthesis of gangliosides, cerebrosides and various glycoprotein of the CNS
- Glycogen content is less than 0.1%
- In chronic hypoglycemia ketone bodies can be used as energy source
- GLUT transporters of the brain are insulin independent
- 3-5% of glucose is used in HMP shunt to produce NADPH for fatty acid and cholesterol synthesis and to produce ribose
ATP

• For maintaining the activity of ATP driven ion pumps

• For the fast turnover of RNA, proteins and transmitter substances

• For assembly of cytoskeletal system

• For motor proteins involved in axonal and vesicle transport processes

• To maintain the high activity of different kinases
Amino acid and protein metabolism

- There is an unequal distribution of amino acids between the CNS and the blood plasma.
- CNS contains in general 4 times more amino acids and about 400 times more glutamate and aspartate than other tissues.
- The high glutamate level is essential for the synthesis of both the main excitatory (glutamate) and inhibitory (GABA) amino acids of the brain.
- Another important role is to remove ammonia.
Lipid metabolism

• Fatty acids for cell membranes and myelin are synthesized within the CNS since they slowly pass the blood-brain-barrier
• thus the rate of their synthesis is high at early stages of the life
• CNS is rich in very long chain (C22-C24 atoms) fatty aids
• Due to a slow turnover, fatty acid synthesis decreases with age
• This is also true for cholesterol (about 25% of total chol. content of the body is found in the CNS)
Nucleic acid and nucleotides

- **Moto neurons** and large **pyramidal cells** contain the highest **RNA** concentration of the body.

- De novo synthesis of **pyrimidine** bases from CO₂ and glutamine as amino group donor does not take place due to the absence of **carbamoyl-phosphate synthetase**.

- Enzymes of **purine** synthesis are present but synthesis is slow.

- The lack of **hypoxanthine-guanine-phosphoribosyl transferase** may cause severe neurological disturbances (**Lesh-Nyhan syndrome**).
Neurotransmitters

A. Classic neurotransmitters: small molecules, synthetized in axon terminals, stored in vesicles
   1. acetylcholine
   2. biogen amines
      • Catecholamines: dopamine, norepinephrine, epinephrine
      • Serotonin
      • Histamine
   3. Amino acids
      • excitatory: Glutamate, aspartate
      • inhibitory: GABA, glycine
   4. Purinerg transmitters
      • ATP
      • adenosine

B. Gas neurotransmitters
   • NO, (CO, H$_2$S)

C. peptides
   • Vasopressin, Cholecystokinin, VIP, substance P
Glutamate

- Glutamate is the main excitatory neurotransmitter of the cerebral cortex
- Do not cross the blood-brain-barrier, it is synthesized within the axon terminals
- synthesis:
  - Transamination of $\alpha$-ketoglutarate
  - Deamination of glutamine
  - Glutamate dehydrogenase
Glutamate receptors

1. IONOTROPIC receptors
   - Ion channels
   - NMDA: N-methyl-D-aspartate
   - AMPA: α-amino-3-OH-5-metil-4-izoxazol-propionsav
     • They open sodium channels and cause depolarization resulting in an excitatory postsynaptic potential
   - Kainic

2. METABOTROPIC receptors
   - G protein-coupled receptors
   - Pre and postsynaptic receptors
   - Presynaptic receptors can inhibit or activate
   • Inactivating
     - Presynaptic reuptake
GABA

- This is the major inhibitory transmitter of the cerebral cortex.
- It is formed by the glutamate decarboxylase enzyme from glutamate.
GABA receptors

- GABA A receptor
  - Cl- channel
  - Several allosteric sites
  - Intracellular phosphorylation sites
  - Alcohol stimulate it (sedative effect)

- GABA B receptor
  - Metabotropic, G protein coupled

Long open period increase the possibility of opening
ACETYLCHOLINE

- Serine => ethanolamine => choline
- Nicotinic Ach receptors: ion channel
- Muscarinic Ach receptors: G protein coupled receptors, 7 transmembrane domain
- ACh-esterase inactivates it
nicotinic acetylcholine receptors

- nicotine activates it
- ionotrop receptors
- Nicotinic receptors are made up of five receptor subunits
- Opening of the channel allows positively charged ions, in particular, sodium and calcium, K, to enter the cell.
- can be blocked by curare
- Found in the neuromuscular junction

- CNS (2 types)
- positively charged ions
- depolarization
Muscarinic acetylcholine receptor

- **Muscarinic receptors** are those membrane-bound *acetylcholine receptors* that are more sensitive to *muscarine* than to *nicotine*.
- belong to a class of *metabotropic receptors* which use *G proteins* as their signaling mechanism.
- the signaling molecule (the *ligand*) binds to a *receptor* which has *seven transmembrane regions*, in this case the ligand is Ach.
- This receptor is bound to intracellular proteins, known as *G proteins*, which begin the information cascade within the cell.

*Amanita muscaria* from which muscarine was isolated.
## Muscarinic Acetylcholine Receptors

<table>
<thead>
<tr>
<th>Distribution</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex, hippocampus</td>
<td>Heart</td>
<td>Exocrine glands, GI tract</td>
<td>Neostriatum</td>
<td>Substantia nigra</td>
<td></td>
</tr>
<tr>
<td>G protein</td>
<td>Gaq</td>
<td>G αi</td>
<td>G αq</td>
<td>G αi</td>
<td>G αq</td>
</tr>
<tr>
<td>Intracellular response</td>
<td>Phospholipase C</td>
<td>Adenylyl cyclase inhibition</td>
<td>Phospholipase C</td>
<td>Adenylyl cyclase inhibition</td>
<td>Phospholipase C</td>
</tr>
</tbody>
</table>

Receptor blockers: atropin, scopolamine
Release of acetylcholine

• Inhibition (sympathetic effects)
• Botulinum toxin A (Clostridium species)
• It is sold commercially under the brand names **Botox** for this purpose.
• Botulinum toxin A:
  – it is used in minute doses both to treat painful muscle spasms, and as a cosmetic treatment
• Botulism: Double vision, drooping of both eyelids, loss of facial expression, swallowing problems, difficulty with talking, reduced movement of the muscles of respiration, dilated pupils, dry mouth and throat, constipation
• There are two primary Botulinum Antitoxins available for treatment of botulism

• Stimulation (parasympathetic effects)
• α-latrotoxin (widow spiders of the genus *Latrodectus*) (black widow, *Latrodectus mactans*); (redback spider, *Latrodectus hasseltii*);
• Piloerection, raised blood pressure, generalized muscle pain, abdominal cramps, extreme sweating,
• Antivenin
Cholinergic receptor inhibitors

- **Nicotinic receptor**
  - Tubocurarine (non-depolarizing neuromuscular-blocking drug)
  - Climbing vine (Chondrodendron tomentosum)
  - Skeletal muscle relaxation
- **Succinylcholine**
  - Depolarizing neuromuscular blocker (does not allow the muscle cell to repolarize)
  - First small, local, involuntary muscle contraction
  - Paralytic effect

- **Muscarinic receptor**
  - Muscarine, atropine, scopolamine
  - Heart: increased heart rate, contractility
  - Dilatation of pupil
  - Decrease of gastrointestinal functions (secretion, peristaltic)
Inhibitors of cholinesterase

- Reversible
  - Physostigmine, neostigmine
  - Intestinal atonia
  - Diagnosis and therapy of myasthenia gravis
  - Physostigmine is the antidote of atropin
  - glaucoma, Alzheimer's disease
  - parasympathomimetic alkaloids

- Irreversible
  - Alkylphosphates: DFP, malathione (insecticides)
  - tabun, sarin (chemical weapons)
  - runny nose, constriction of the pupils, difficulty breathing, nausea, victim vomits, defecates and urinates, coma, death
  - Ecothiopate (glaucoma treatment), cyclophosphamide (cytotoxic-cytostatic drug)
Catecholamines (dopamine, NA, A)

- The amino acid tyrosine is the starting material. It is taken up into catecholaminergic nerves by an active transport system.
- Inside the nerve, an additional hydroxyl group is added to the aromatic ring.
- Tyrosine hydroxylation is the rate limiting step in the synthesis of catecholamines and is subject to feedback inhibition by the end products.
Catecholamines (dopamine, NA, A)

- DOPA decarboxylation

- DOPA is used in the treatment of Parkinson's disease
Catecholamines (dopamine, NA, A)

• Dopamine hydroxylation

• DOPAMINE in catecholaminergic nerves is taken up into synaptic vesicles and is converted to norepinephrine (NE) by the addition of a hydroxyl group on the carbon second (beta) from the amino group
Catecholamines (dopamine, NA, A)

\[
\text{N-methylation}
\]

\[
\text{phenylethanolamine-N-methyl-transferase enzyme}
\]
adrenergic receptors

• are a class of G protein-coupled receptors that are targets of the catecholamines

• There are several types of adrenergic receptors, but there are two main groups: α-Adrenergic and β-Adrenergic.

• receptors bind norepinephrine and epinephrine
Roles in Circulation

- Epinephrine reacts with both α- and β-adrenoreceptors, causing vasoconstriction and vasodilation, respectively.
- Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by β-adrenoreceptors.
- The result is that high levels of circulating epinephrine cause vasoconstriction.
- At lower levels of circulating epinephrine, β-adrenoreceptor stimulation dominates, producing an overall vasodilation.
Inactivation of catecholamines

• Occurs by the action of 2 enzymes:
  1. Monoamino-Oxidase (MAO)
     - MAO-A is present in extraneuronal tissues
     - MAO-B is a characteristic enzyme of the outer mitochondrial membrane of neurons
  2. Catechol-O-methyl transferase (COMT)
COMT

- It is present in glial cells and several extraneuronal tissues
- It methylates phenolic OH groups on catecholamines
- From epinephrine and norepinephrine

\[ \text{MAO,COMT} \rightarrow \text{VANILLYLMANDELIC ACID} \]

From Dopamin

\[ \text{MAO,COMT} \rightarrow \text{Homovanillinic acid} \]
Dopamine receptors

- are a class of [metabotropic G protein-coupled receptors](#) that are prominent in the [vertebrate central nervous system](#) (CNS).
- The [neurotransmitter dopamine](#) is the primary [endogenous ligand](#) for dopamine receptors.
- There are five subtypes of dopamine receptors, D1, D2, D3, D4, and D5.
Patobiochemistry

• Defects of dopamine synthesis in substantia nigra results in Parkinsonism
• Therapy: L-DOPA
• Increased dopamine synthesis results in schizophrenia
Serotonin

- Tryptophan $\rightarrow$ 5-hydroxytryptophan $\rightarrow$ serotonin (5-hydroxytryptamine)
- tryptophan hydroxylase, amino acid decarboxylase
- Receptors 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$, 5-HT$_7$
- 5-HT receptors, are a group of G protein-coupled receptors
- Except 5-HT$_3$, it is a ligand gated ion channel
- central and peripheral nervous systems
Serotonin

- Psychedelic drugs
  - Psilocybin (psilocybin mushrooms), mescaline (San Pedro cactus), LSD are agonists, primarily at $5\text{HT}_{2A/2C}$ receptors

- Antidepressants
  - Selective serotonin re-uptake inhibitors
    - Citalopram, Fluoxetine
  - Monoamine oxidase inhibitors
    - Benmoxin, …

- Antiemetics
  - 5-HT3 antagonists
    - ondansetron, granisetron, tropisetron
Histamine

- Histidine → histamine
- histidine decarboxylase
- histamine receptors are a class of G protein-coupled receptors
  - $H_1$ receptor
    - smooth muscles, glands, vascular endothelial cells, central nervous system
    - Allergic reactions, activity of CNS
    - Loratadine, Desloratadine
    - Hydroxyzine (ATARAX)
  - $H_2$ receptor
    - mast cells, enterochromaffin-like cells, and neurons
    - gastric acid secretion
    - Ranitidine, ...
  - $H_3$, $H_4$ receptors