MUNI
PHARM

Structure of the Cell Membrane

Biophysics

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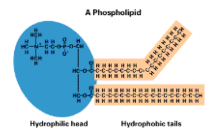
Structure of the Cell Membrane

The cell membrane **physically separates** intracellular components from the extracellular environment. The cell membrane is **selectively permeable** and able to regulate what enters and exits the cell, thus facilitating the transport of materials. Cell membranes are **involved in a number of cellular processes** such as cell adhesion, immune response and cell signalling.

Phospholipids are the most abundant lipids in the cell membrane. A phospholipids spontaneously form a spherical micelles or, at higher concentrations, **phospholipid bilayer** - the building blocks of cell membranes.
In phospholipid bilayer the hydrophilic heads are exposed to the watery environment outside and inside the cell, and the hydrophobic tails are shielded from water.



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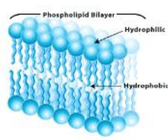
Structure of the Cell Membrane

The cell membrane and non-bonded interactions
Between phospholipids take place hydrophobic interaction and partially Van der Waals forces.
If the molecule carries a charge, electrostatic interactions take place.



Cholesterol (stability of membranes)

The hydroxyl group will associate with the phosphate head groups of phospholipids. The steroid rings and hydrocarbon chain will associate with the fatty acid tails of phospholipids with the same London attraction forces that hold the fatty acids together. The presence of cholesterol in our membranes = protection of membranes from rupture.

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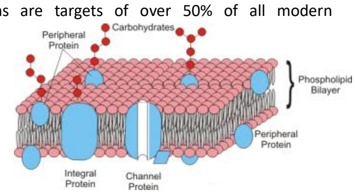
Structure of the Cell Membrane

At membranes, there are multiple factors: the **fluidity** of molecules within the membrane; the maintenance of **membrane integrity** under changing external conditions; and the organization of **membrane proteins**.
Membrane proteins: **Integral** and **peripheral** membrane proteins; determine the specific functions of the membrabe (membrane receptor, membrane enzymes, cell adhesion molecules - immune response, transmembrane transport, membrane potential).
Membrane proteins are targets of over 50% of all modern medicinal drugs.



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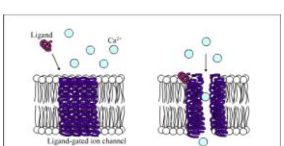
Mechanism of cell membrane transport

Transport proteins

- they are often selectively permeable (only specific ions or molecules may pass through). Selectivity is affected by protein channel characteristics such as size, shape or electrical charge on its surface.
- they can be opened or closed (conformational changes of the protein channel). They are mostly controlled **electrically** (electric potential changes on the membrane) by **ligands** (binding of specific molecules to a protein channel) or **mechanically**.

Classification by ion type:
Na^+, K^+, Ca^{2+}, H^+, Cl^-, nonselective cation channels.



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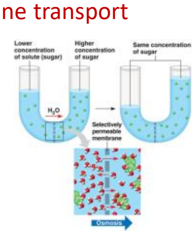
Mechanism of cell membrane transport

Passive transport (requires no energy)
Transport of substances in the direction of the concentration (electrochemical) gradient .

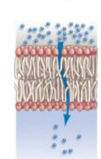
- Osmosis (water)

A type of passive transport that involves the movement of water across a cell membrane. Water crosses cell membranes via special channels called **aquaporins**.



- Simple diffusion (O_2, CO_2, lipophilic molecules)

A lipid soluble substance will diffuse through a cell membrane from the side where it is more concentrated to the side where it is less concentrated.



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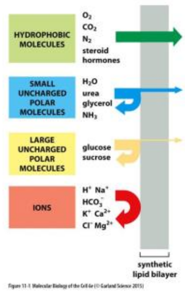
Mechanism of cell membrane transport

There are 4 factors that determine the **membrane permeability**:

1. **Lipid solubility** – is the most important factor in determining a molecule's permeability (hydrophobic molecules can dissolve in the lipid bilayer and cross it with ease).
2. **Polarity** – polar molecules tend to be hydrophilic, and therefore do not pass readily through the membrane (very small molecules that are polar but uncharged, such as water, can pass through the membrane readily).
3. **Molecular size** – larger molecules are less permeable (limited diffusion due to small pore sizes in the membrane).
4. **Charge** – charged molecules are usually hydrophilic and they are surrounded by a hydration shell, which increases the size of the molecule, further impeding movement across the membrane.



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Mechanism of cell membrane transport

Passive transport

- Facilitated diffusion (specific/nonspecific transport proteins)

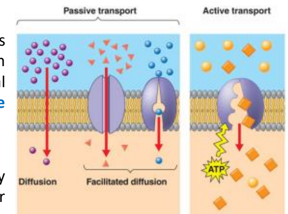
Some molecules cannot pass through the bilayer on their own. Carrier proteins may bind a specific molecule and, as a result, change their own shape, passing the molecule through the middle of the protein to the other side of the membrane.

Active transport

Movement of molecules across a cell membrane in the direction against their electrochemical gradient (**process require energy**).

Primary active transport

- energy from ATP is directly consumed for transport or "pump" mechanism.



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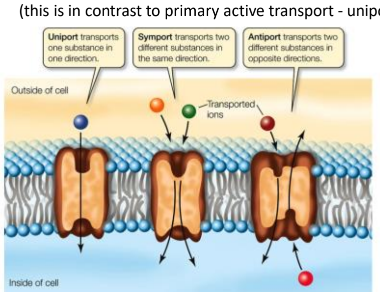
Mechanism of cell membrane transport

Secondary active transport

One molecule/ion moves along its electrochemical gradient, allowing another molecule to move against its own electrochemical gradient (this is in contrast to primary active transport - uniport).



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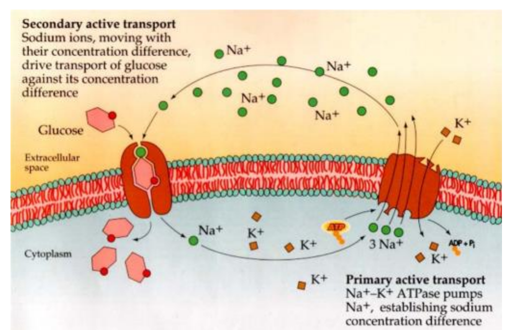
Mechanism of cell membrane transport

Secondary active transport



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Mechanism of cell membrane transport

Rate of diffusion (J)

Simple diffusion (1. Fick law**):**

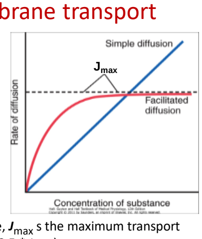
$J = P * A * \Delta C$

ΔC is concentration gradient, A is surface for diffusion and P is permeation koeficient

Facilitated diffusion and Active transport (Michaelis-Menten eq.**):**

$J = J_{max} * C / (K_M + C)$

C is the concentration of the transported substance, J_{max} s the maximum transport rate and K_M is the concentration at half saturation(0,5 * J_{max}).



Facilitated diffusion and active transport:

- They show saturation, i.e. they have a limited capacity
- They mostly transport chemically similar substances (competitive inhibition)
- Different substances have different affinities for the transport system
- When energy supply to the cell is interrupted, they are inhibited (does not apply to facilitated diffusion)

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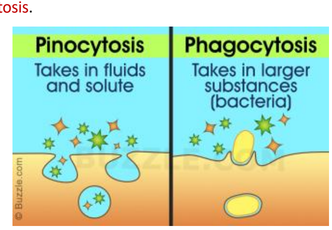
Mechanism of cell membrane transport

Endocytosis and exocytosis

Some molecules or particles are just too large to pass through the plasma membrane or to move through a transport protein. So cells use two other active transport processes to move these large molecules into (endocytosis) or out (exocytosis) of the cell – pinocytosis or phagocytosis.



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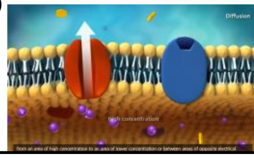
Mechanism of cell membrane transport

Life of the cell depends on the transport mechanisms (metabolic processes, electrical potentials, etc.).

The main tasks of transport mechanism:
- Transfer of nutrients from the environment into the cell
- Regulation of cell volume
- Regulation of pH
- Membrane energetics (proton transport against an electrochemical gradient as a source of energy for ATP synthesis)
- Gradient Na^+, K^+ responsible for membrane potentials (required for the conduction of nerve impulses)



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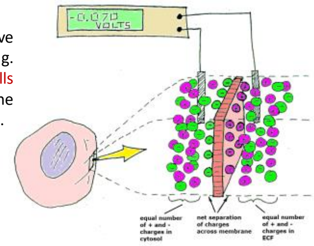
Membrane potential

Membrane potential (**resting** or **action**) is determined by the uneven distribution of ions between the intracellular and the extracellular spaces.
It is created on the cell membranes mainly due to **active transport** as well as **passive transport** of various ions across the cell membrane.

Electrical potentials have an important role in e.g. excitation of muscle cells or in transfer of the information in nerve cells.



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Resting membrane potential

- It is created under conditions of physiological calm; is due to the uneven distribution of basic physiological ions (K^+, Na^+, Cl^- and HCO_3^-) on both sides of the cell membrane.
- Depending on the cell type; it varies in the range of -50 mV to -100 mV.
- The sodium-potassium pump (active transport) is involved in the formation and maintenance of the resting membrane potential.

Intra-cellular concentration	$[K^+]_i$	$[Na^+]_i$	$[Cl^-]_i$	$[proteins^-]_i$	$[HCO_3^-]_i$
	nmol l^{-1}				
Muscle cell	150	15	9	155	1

Sum of cations +165
Sum of anions -165

Exra-cellular concentration	$[K^+]_e$	$[Na^+]_e$	$[Cl^-]_e$	$[proteins^-]_e$	$[HCO_3^-]_e$
	nmol l^{-1}				
Muscle cell	5.5	150	125	7	23.5

Sum of cations +155.5
Sum of anions -155.5

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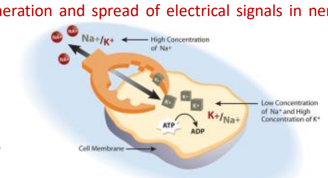
Resting membrane potential

Sodium-potassium pump
- transmembrane protein that transports (due to conformation changes) sodium and potassium ions across the cell membrane against the concentration gradient (consuming ATP).
- **Na^+ ions are pumped out of the cell and K^+ ions inside** (transports 3 Na^+ against 2 K^+).
- The sodium-potassium pump maintains an uneven distribution of sodium and potassium on both sides of the cell membrane. This is essential for the generation and spread of electrical signals in nerve and muscle cells.
- The sodium-potassium pump regulates the cell volume (affects the concentration of ions and thus the osmotic pressure).



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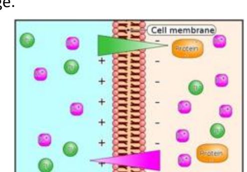
Resting membrane potential

Donnan equilibrium
The usual cause is the presence of a different charged substance that is unable to pass through the membrane (e.g. large anionic proteins) and thus creates an uneven electrical charge.

On the side of the membrane where the not diffusible protein is, the concentration of Cl^- ions will be lower and concentration of K^+ ions will be higher (maintaining electrical neutrality).



K^+, Cl^- - diffusible ions

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Resting membrane potential

The size of the resting membrane potential is approximately determined by the Nernst equation:

$$E_K = \frac{RT}{nF} \ln \frac{[K^+]_e}{[K^+]_i}$$

The cell membrane (in resting state) has limited permeability even for Na^+ and Cl^- ions – the real resting potential differs from the value calculated for K^+ ions. The influence of other ions expressed Goldman equation:

$$E_K = \frac{RT}{nF} \ln \frac{P_K [K^+]_e + P_{Na} [Na^+]_e + P_{Cl} [Cl^-]_i}{P_K [K^+]_i + P_{Na} [Na^+]_i + P_{Cl} [Cl^-]_e}$$

P_K, P_{Na}, P_{Cl} – membrane permeability coefficients.
Approximately: P_K, P_{Na}, P_{Cl} = 1 : 0.04 : 0.45

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Action potential

Excitable cells (e.g. nervous, muscular) have the ability to change ion permeability of the membrane, resulting in significant changes of membrane potential – action potential:

- play a central role in the transmission of information in the nervous system
- is the first step in triggering muscle contraction
- is followed by a refractory period during which it is impossible to evoke another action potential

At the site of excitation, **cell membrane permeability for Na⁺ ions is selectively increased**.
The value of the action potential is (Nernst equation) +20 to +50 mV:

$$E_{Na} = \frac{RT}{F} \ln \frac{[Na^+]_e}{[Na^+]_i}$$

$$E_{Na} = -61 \log \frac{[Na^+]_i}{[Na^+]_e}$$

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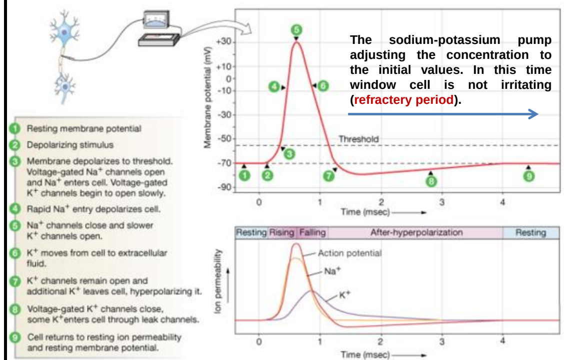
Action Potential



The sodium-potassium pump adjusting the concentration to the initial values. In this time window cell is not irritating (refractery period).

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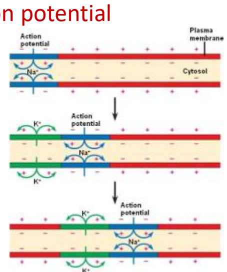
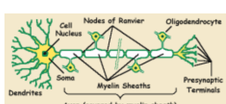
Propagation of action potential

- charge distribution changes inside and on the surface of the membrane: the formation of local electric currents
- these currents have an irritant effect on the neighboring membrane element
- after the threshold is reached, the entire process repeats



Myelinated nerve fibres

- Different action potential propagation.
- The fibers are enveloped by myelin sheath, which is interrupted after 1-3 nm (i.e. nodes of Ranvier).
- Local currents do not pass through the myelin sheath, the impulse spreads by jumping (saltatory conduction).
- Impulses spread up to 100 times faster.



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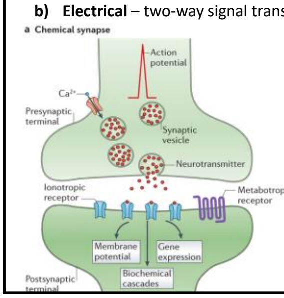
Propagation of action potential

Synapse – mediate the transmission of signals between nerve cells to each other and between nerve and other cells (muscle, glands).

a) **Chemical** – transmission of the impulse from the presynaptic to the postsynaptic membrane by neurotransmitter.

b) **Electrical** – two-way signal transmission (ion channels).



- The action potential releases a transmitter at the chemical synapse, which diffuses through the synaptic cleft (about 30 nm) and binds to the postsynaptic membrane receptors.
- Transmitter release occurs by exocytosis of synaptic vesicles; AP induces the opening of electrically controlled Ca^{2+} channels, thus changing the conformation of proteins in the membrane.
- The postsynaptic membrane may be excited or inhibited.

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Propagation of action potential

Excitatory and inhibitory chemical synapse

a) excitatory – induction of action potential on the postsynaptic membrane (e.g. glutamic acid, acetylcholine).

b) inhibitory – deterioration of conditions for the formation of action potential (e.g. γ-aminobutyric acid).

Depending on the nature of the transmitter, the postsynaptic membrane may be excited or inhibited.

The termination of the effect of transmitters on ion channels is caused either by pumping the transmitters back across the presynaptic membrane or by enzymatic degradation (e.g., acetylcholinesterase).

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MUNI PHARM

Medical and diagnostic methods using electric current

Biophysics

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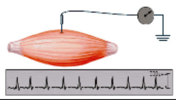
Using action potentials in diagnostics

The time dependence of potential changes can be observed not only on the nerve or muscle cells membrane, but also on the body surface. The resulting record is called electrogram.

Examination	Abbr.	Potentials examined
electrocardiography	ECG	cardiac action potential
electroencephalography	EEG	brain activity potential
electrogastrography	EGG	potentials of smooth muscle (Monitoring of gastric motility)
electrohysterography	EHG	uterine activity potential (Monitoring the uterine contractions during pregnancy and childbirth)
electromyography	EMG	muscle action potential (Examination of neuromuscular excitability)



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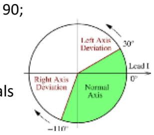
Using action potentials in diagnostics

Electrocardiography (ECG)

- basic diagnostic methods in cardiology - provides a graphical record of the heart's electrical activity (related to the mechanical activity of the heart)
- ECG measure the voltage difference as a manifestation of propagation of the action potential in myocardium

Description of ECG curve:

1. Heart rhythm (sinus or else)
2. Action (regular or irregular)
3. Frequency (strokes/min) normal 60-90; tachycardia> 90; bradycardia <60
4. Electric heart axis (direction of electrical activity during the cardiac contraction; normal 30° to -110°)
5. Analysis of individual waves, oscillations and intervals



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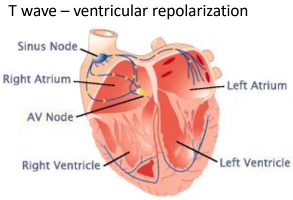
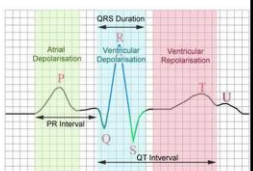
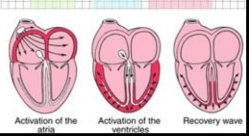
Using action potentials in diagnostics

ECG curve

P wave – atrial depolarization (sinus node)
QRS wave – fast ventricular depolarization (AV node) and atrial repolarization
T wave – ventricular repolarization







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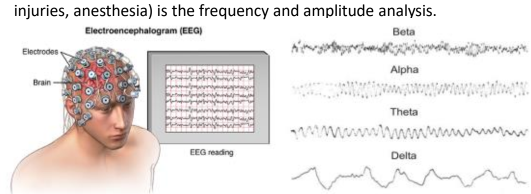
Using action potentials in diagnostics

Electroencephalography (EEG)

The electroencephalographic recording is not nearly as typical as an ECG (sum of the potentials of a large number of neurons near the electrodes). The basis of diagnostic brain disorders (e.g., epilepsy, head injuries, anesthesia) is the frequency and amplitude analysis.



β waves – normal humans rhythm in the waking state
α waves – characteristic for mental and physical rest (relaxation)
θ waves – falling asleep
δ waves – deep sleep

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Therapeutic applications of electric current

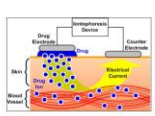
Direct current

Galvanization

Treatment of post-traumatic conditions, muscle pain, nerve problems, degenerative musculoskeletal diseases.
Electric current causes pH changes near the electrodes. At the anode the pH is decreased - reduces pain (analgesia); at the cathode the pH increases - increase irritating effect (i.e. increased blood flow at the site of application of the current and also increased metabolism -> faster healing process).

Iontophoresis

Topical administration of drugs in ionic form into the body by means of direct current. The anions are administered from the cathode (eg. I^-, ascorbic acid), cations from the anode (magnesium, calcium, mezokain). Use eg. in the skin desensitisation (skin disease), improvement in blood circulation, softening of fibrous tissue.



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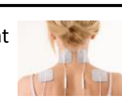
Therapeutic applications of electric current



Alternating current

TENS (transcutaneous electrical nerve stimulation) – irritation of nerve fibers. Used for the suppression of painful musculoskeletal disorders, maintaining muscle tension of injured muscle, atrophy prevention, etc.

Cardiostimulation

Maintaining heart rhythm in physiological values. Pacemaker: when bradycardia occurs (<60 strokes/min), it automatically turn on; it turn off when faster heart rate is restored.

Defibrilation

The most effective (and often only) life-saving treatment of ventricular fibrillation. The electrical discharge simultaneously depolarizes all myocardial cells and thereby induces the conditions for the use physiological centers for the impulse propagation.

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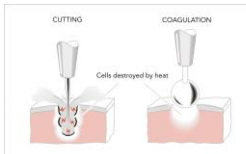
Therapeutic use of electric current

Alternating current

Diathermy

It uses the thermal effect of high-frequency current (MHz, no irritation effects). It can be used in the treatment of the musculoskeletal system diseases in the chronic stage, back pains, blood circulation disorders. The main effects are dilatation of bloodstream, improvement of tissue nutrition and relaxation of muscle spasms. Other application is surgical diathermy (helping to prevent bleeding).

DIATHERMY SHOULDER TREATMENT



Two types of surgical diathermy

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