

A sejtmembrán

Foszfolipid kettős réteg
Poláros fej, apoláros láncok

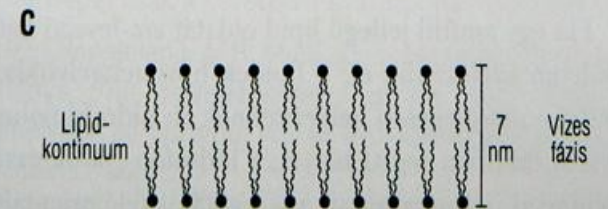
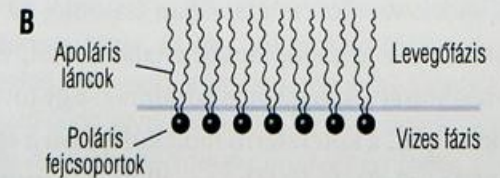
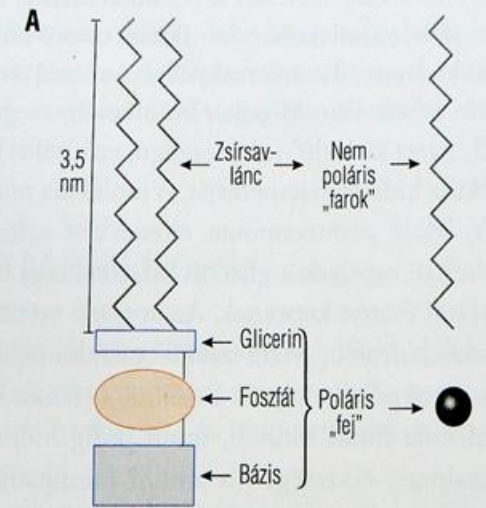
Molekulák átjutásának feltételei a membránon?

Folyékony mozaik modell

Hogyan jön létre a sejtmembrán?

Hogyan jött létre az első sejt membrán?

Extra linkek: [Lipidek](#) [Membránok](#)



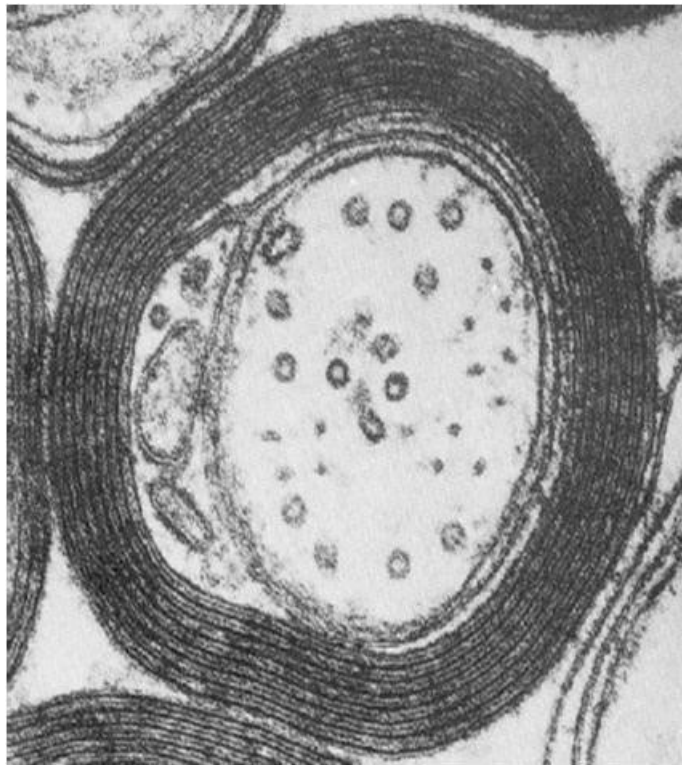
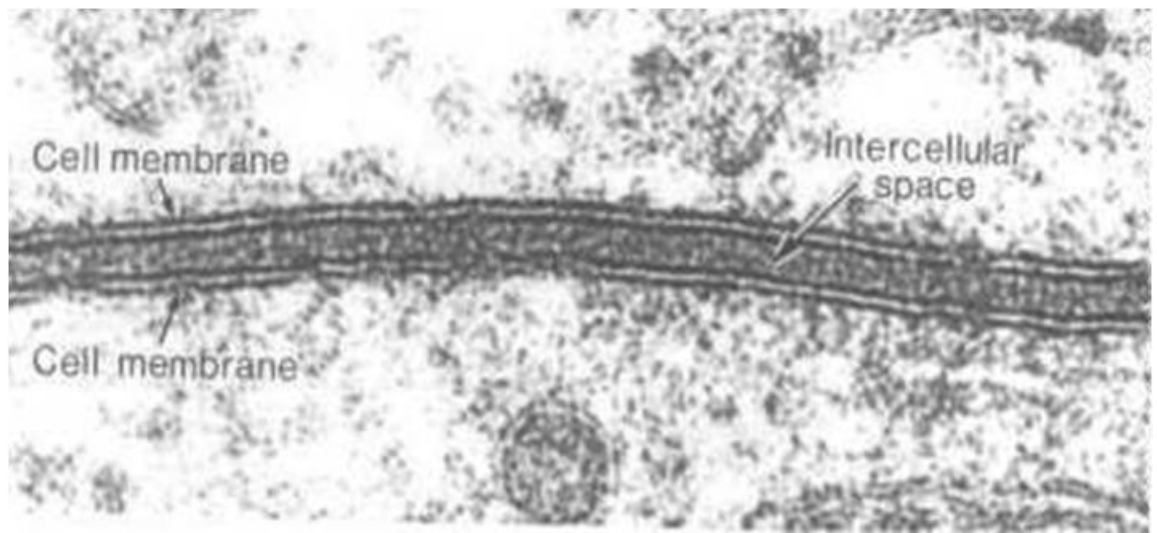
2-1. ábra

Az amfipatikus foszfolipidek szerkezete, a monomolekuláris réteg és a lipid kettős réteg membrán

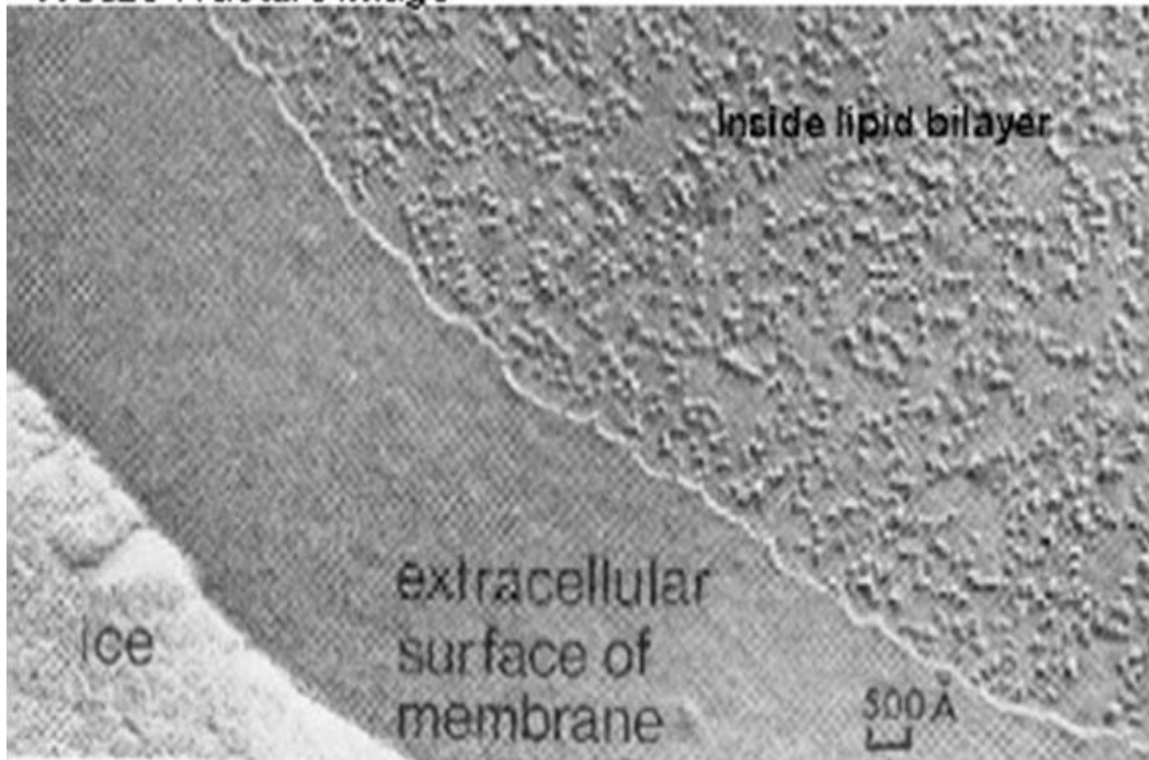
- A) Egy amfipatikus foszfolipidmolekula és jelképes ábrázolása
Bal oldalon a foszfollipid alkotóelemei, jobb oldalon általánosan használt jelképük látható
- B) Monomolekuláris foszfollipidréteg (monoréteg) elhelyezkedése víz-levegő határfelületen
- C) Két vizes fázist elválasztó lipid kettős réteg

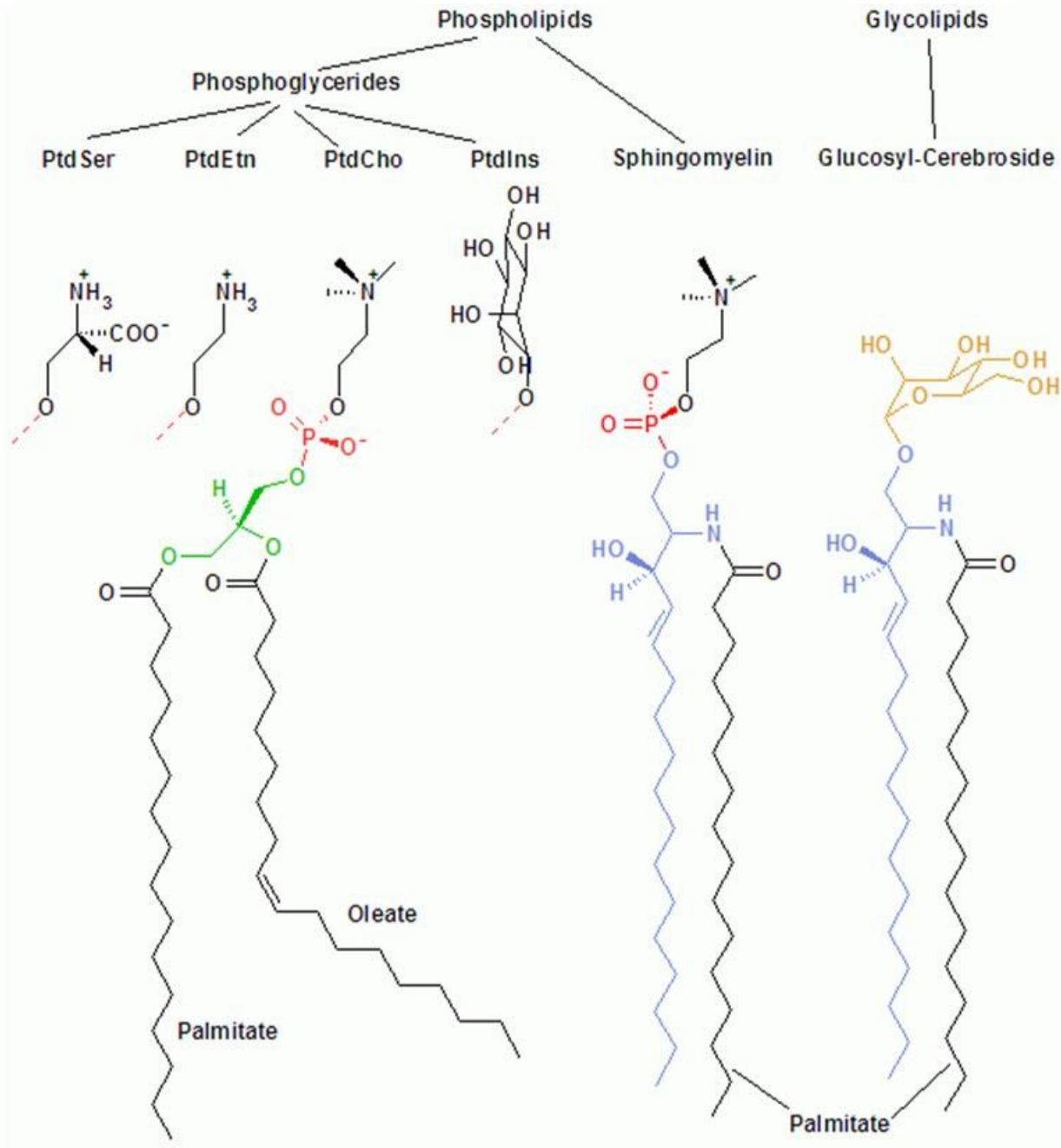
A biológiai membránok

- a sejtek felszínét, de a sejtservecskéket is membrán borítja - **kompartmentalizáció**
- Karl Wilhelm von Nägeli XIX szd. közepe - festékekkel szembeni barrier a sejtfelszínen - duzzadás és zsugorodás - plazma membrán
- EM megjelenésével bizonyították csak
- Singer és Nicholson (1972): **folyékony mozaik** \square
- 6-8 nm vastag kettős lipid réteg + fehérjék
- **mozaik**, mert a fehérjék csoportosulnak
- **folyékony**, mert oldalirányban elmozdulhatnak
- arány változó: mielin illetve mitokondrium
- 10^6 lipid molekula/négyzetmikron



Freeze-Fracture image





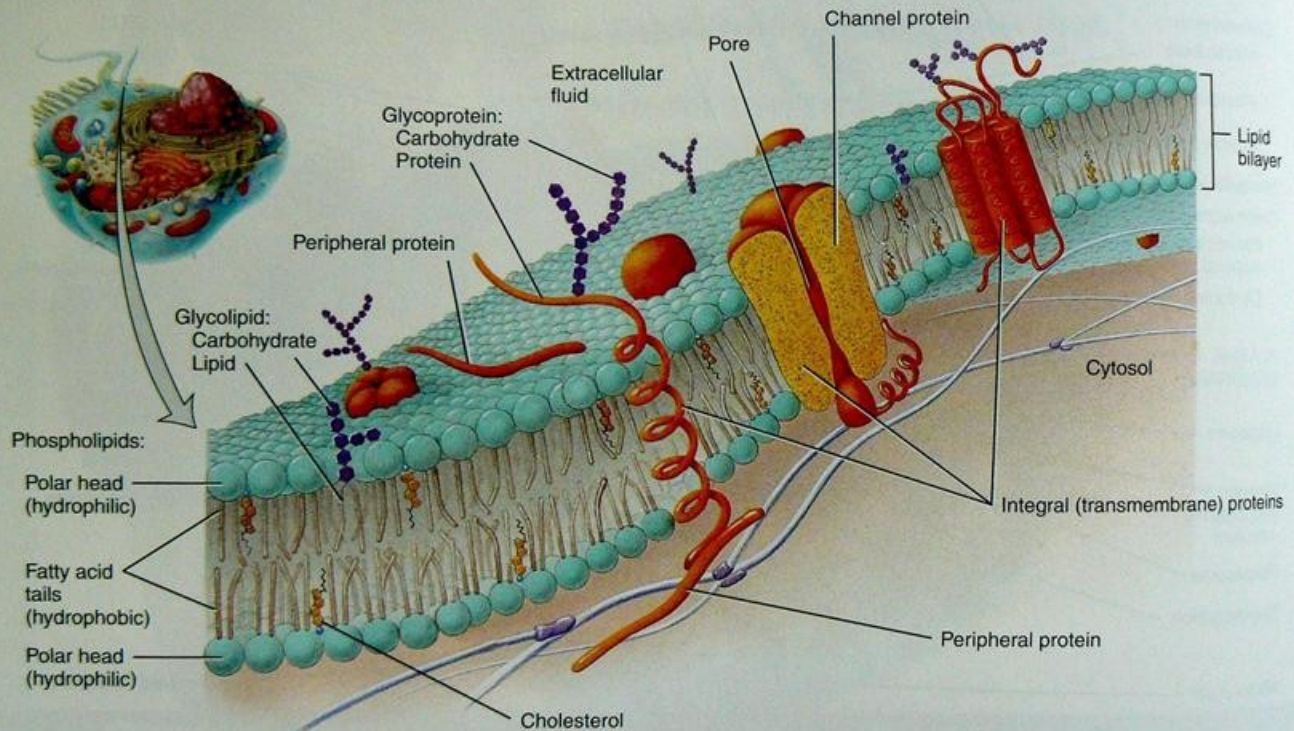
A sejtmembrán - elválasztja a sejt belsejét az extracelluláris tértől kompartmentek

1. List the three main parts of a cell and explain their functions.

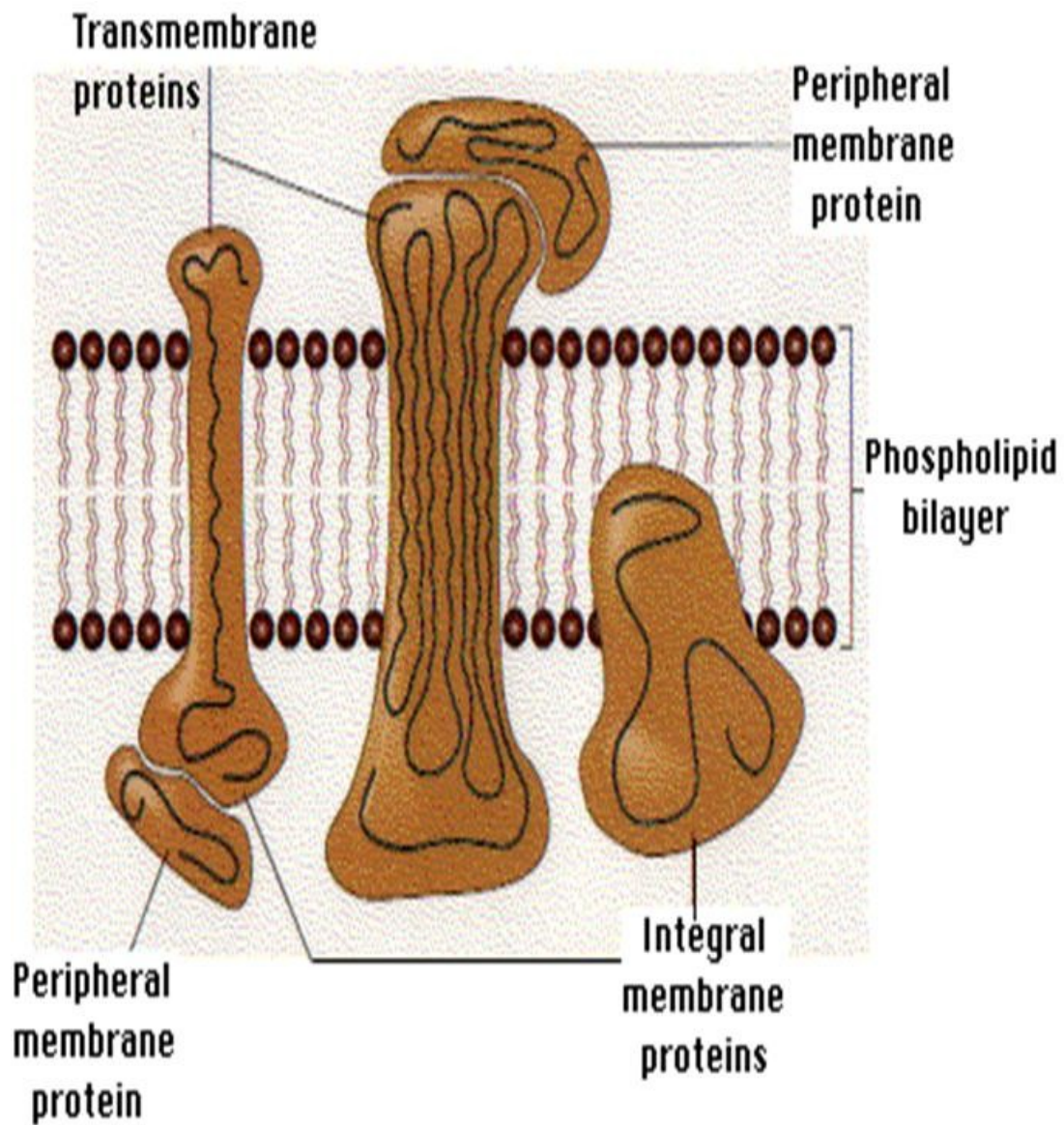
molecules.

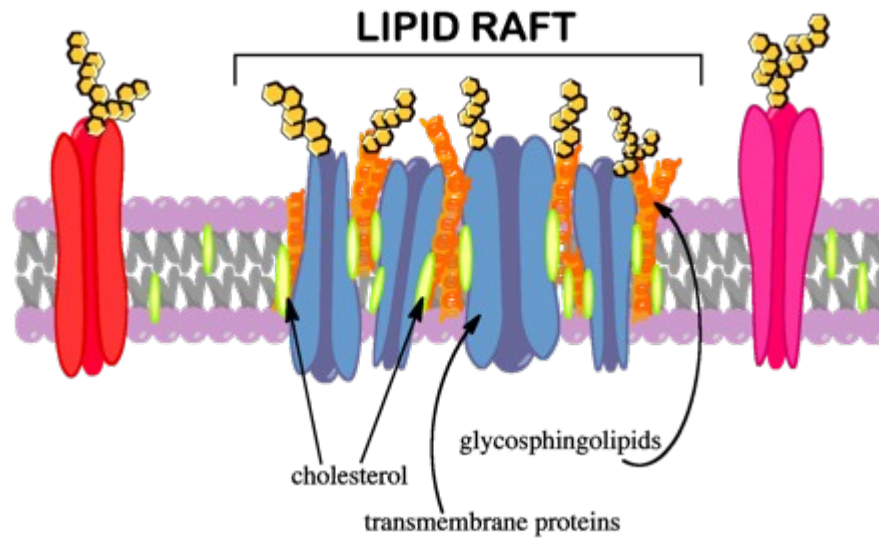
Figure 3.2 The fluid mosaic arrangement of lipids and proteins in the plasma membrane.

Membranes are fluid structures because the lipids and many of the proteins are free to rotate and move sideways in their own half of the bilayer.



? What is the glycocalyx?





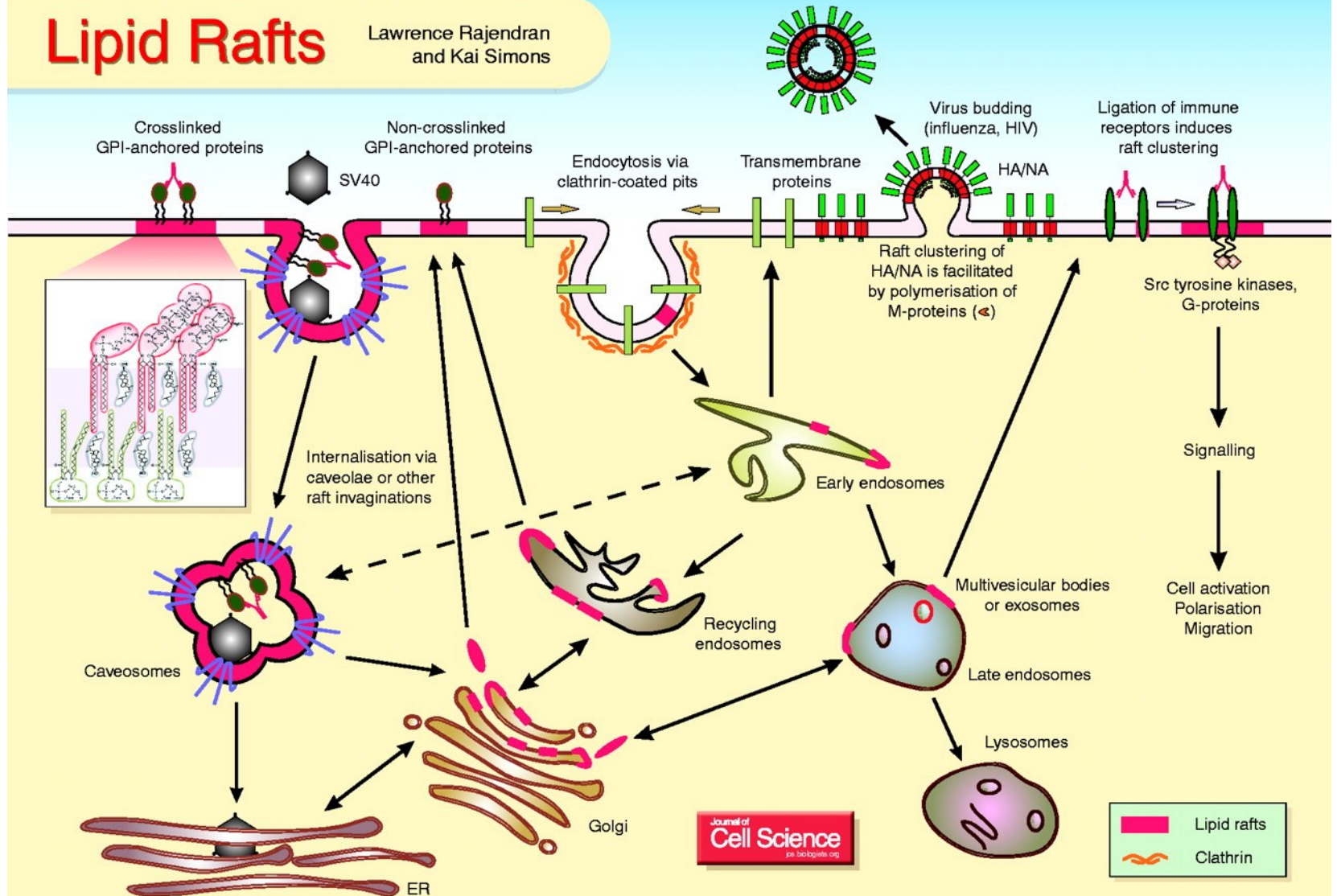
Rafts are liquid-ordered domains that are more tightly packed than the surrounding non-raft phase of the bilayer. The tighter packing is due to the saturated hydrocarbon chains in raft sphingolipids and phospholipids compared with the unsaturated fatty acids of phospholipids in the non-raft phase

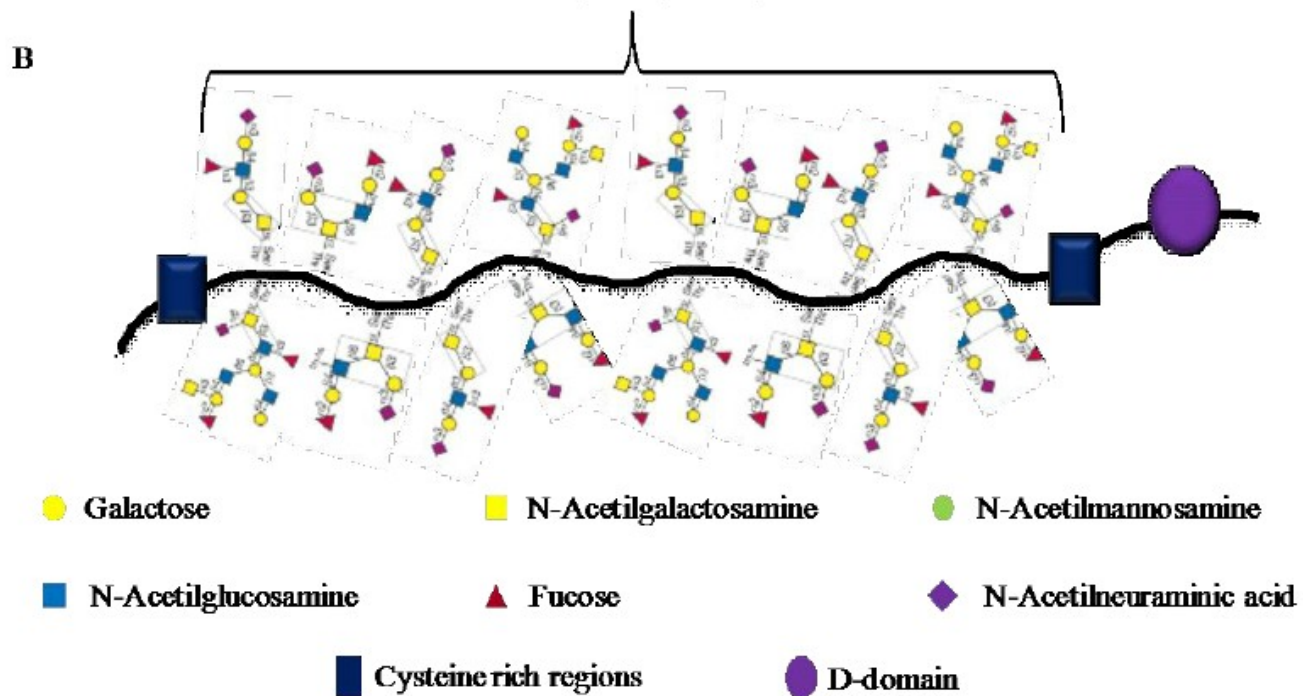
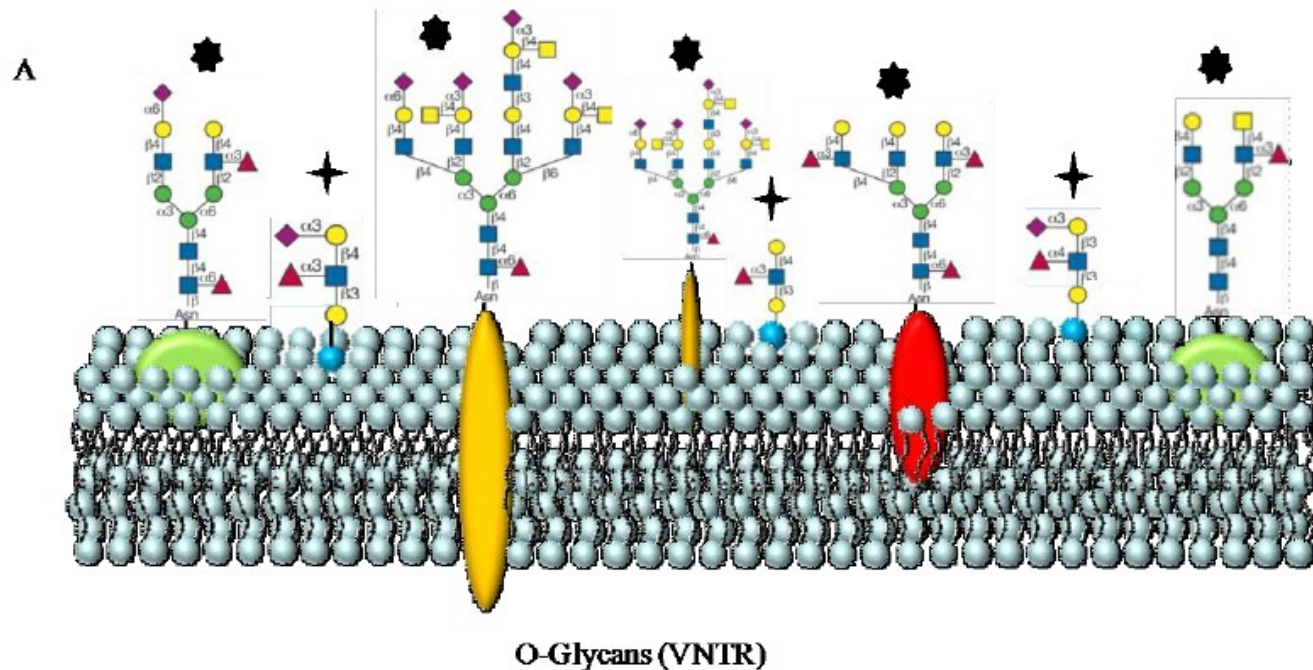
Jelentőségük: platform egyes fehérjék felszíni sűrűségének növelésére, fehérje komplexek kialakulására és stabilizálására (jelátvitel, endo-/exocitózis, stb.)

Membrán rafts

Lipid Rafts

Lawrence Rajendran
and Kai Simons

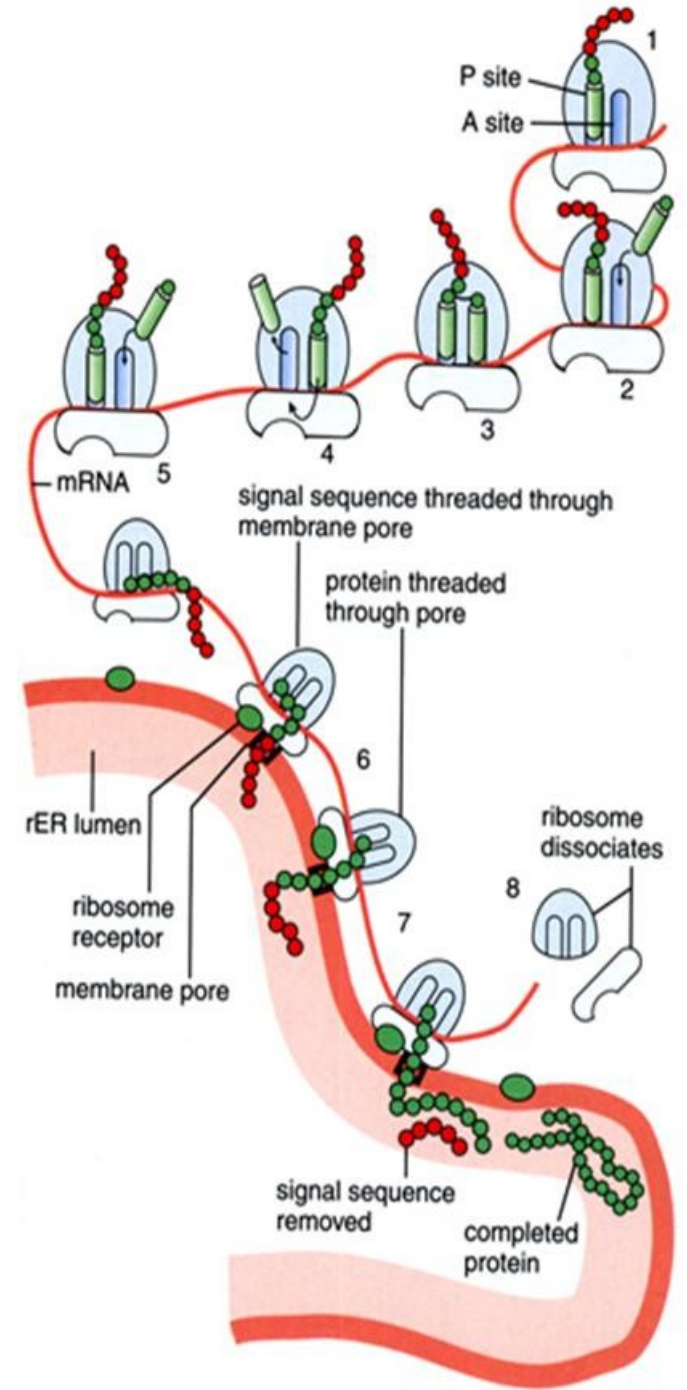
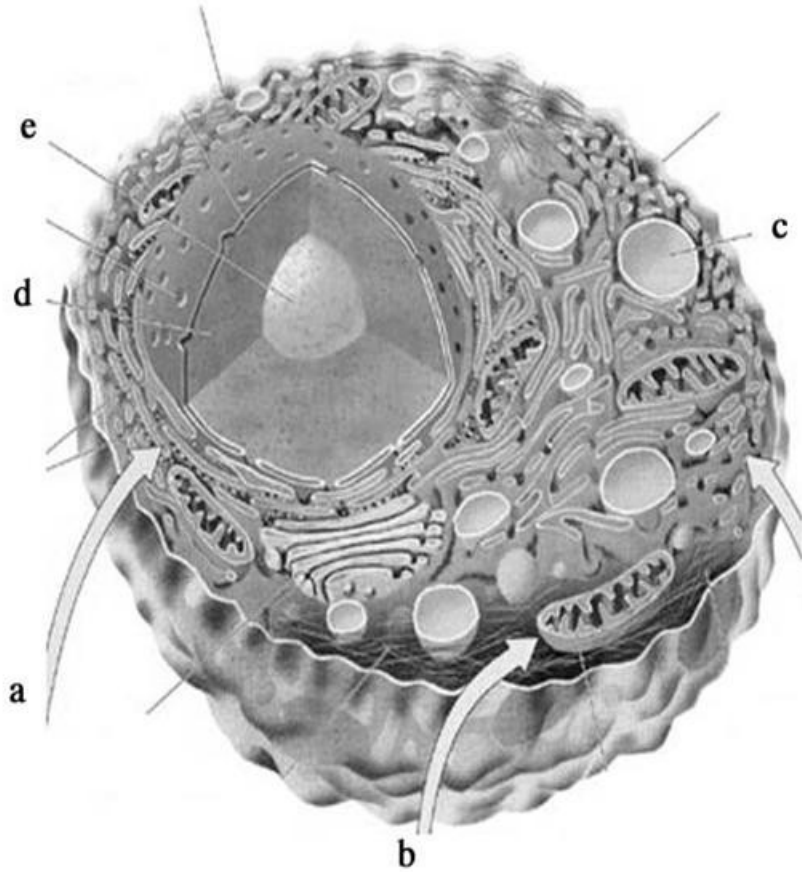




Glikoproteinek

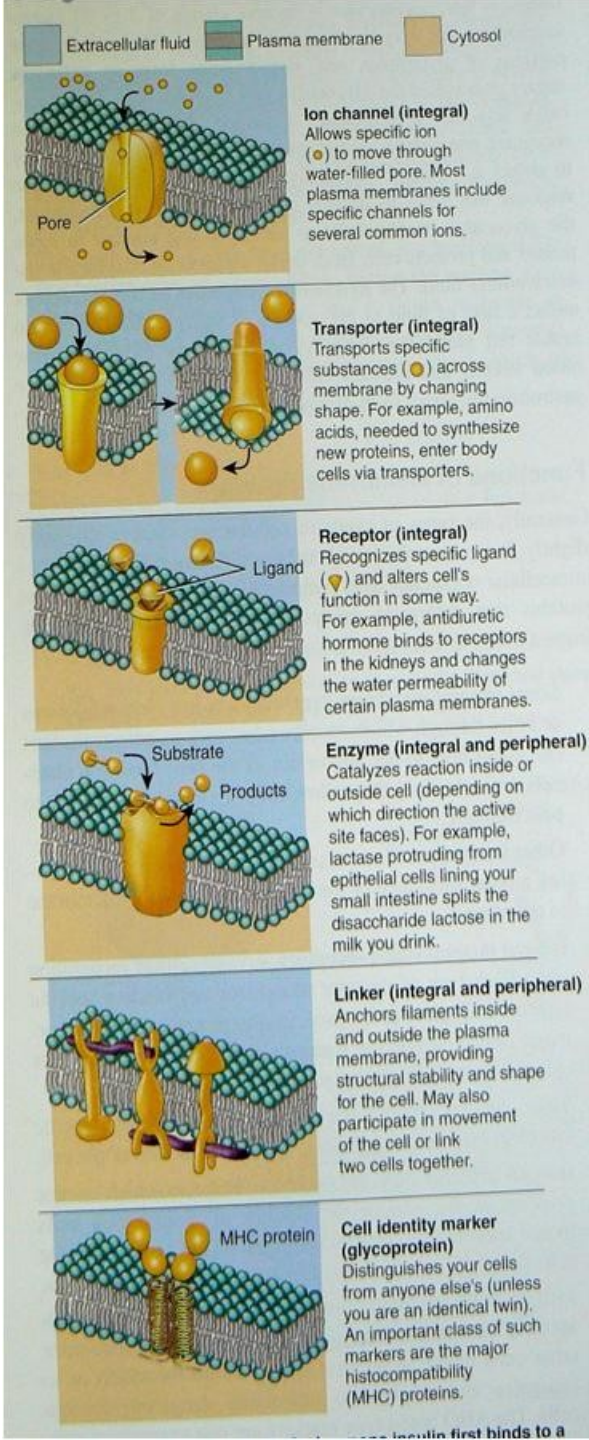
- A cukrok biológiai szerepével foglalkozó glikobiológia (a biokémia egy ága) a reneszánszát éli, köszönhetően annak a felismerésnek, hogy a glikokonjugátumok monoszacharid egységei változatosságuk folytán biológiai információt hordozhatnak – ezt nevezik manapság „cukorkódnak”. Az információtartalom méretére egy példa: 20 féle monoszacharidból $6,4 \times 10^7$ hexamert (ez a glikoproteinek oligoszacharid-csoportjainak átlagos monomer száma) lehet alkotni.
- Az oligoszacharid-csoportoknak szerepük lehet a fehérjék intracelluláris célbajuttatásában (targeting), a sejt-sejt kapcsolatok kialakításában, a sejt- és szöveti differenciálódásban és általában az extracelluláris jeltovábbító rendszerekben.
- A cukorkód megfejtését az tette lehetővé, hogy az oligoszacharid-csoportokat „szekvenálni” lehet, azaz a glikoproteineken (glikolipideken) a cukoregységek sorrendjét, elágazásait meg lehet határozni. A szekvenálás alapja, hogy az oligoszacharidokat speciális N- és O-glikozid specifikus glikoziláz enzimekkel le lehet hasítani a glikokonjugátumokról. A hidrolizátum komponensei szeparálás után tömegspektrometriával azonosíthatók. Az 10.14. ábra egy tömegspektrogramot mutat be (a 7 és 19 monomer közötti méretű oligoszacharidok tömegét és összetételét is feltüntettük). Egy organizmus teljes cukorkészletével, beleértve az glikoproteinek glikán-csoportjait is, a rendszerbiológia része, a glikomika foglalkozik.

Signals for directing proteins to the appropriate locations



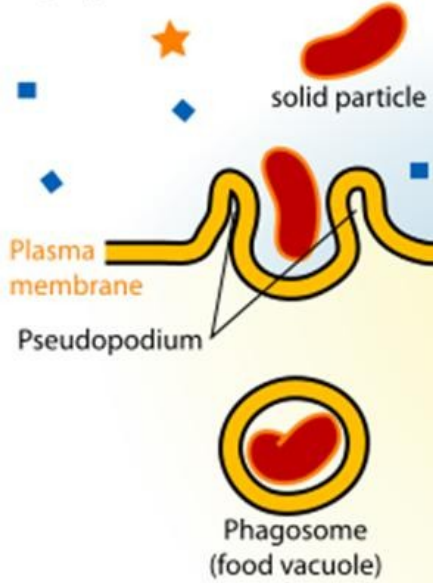
A membránon való átjutás szabályozott

- Endocytosis
- Ion csatornák
- Transzporterek
- Receptorok
- Enzimek
- Sejt adhéziós molekulák
- Fehérjék - cukrok



Endocytosis

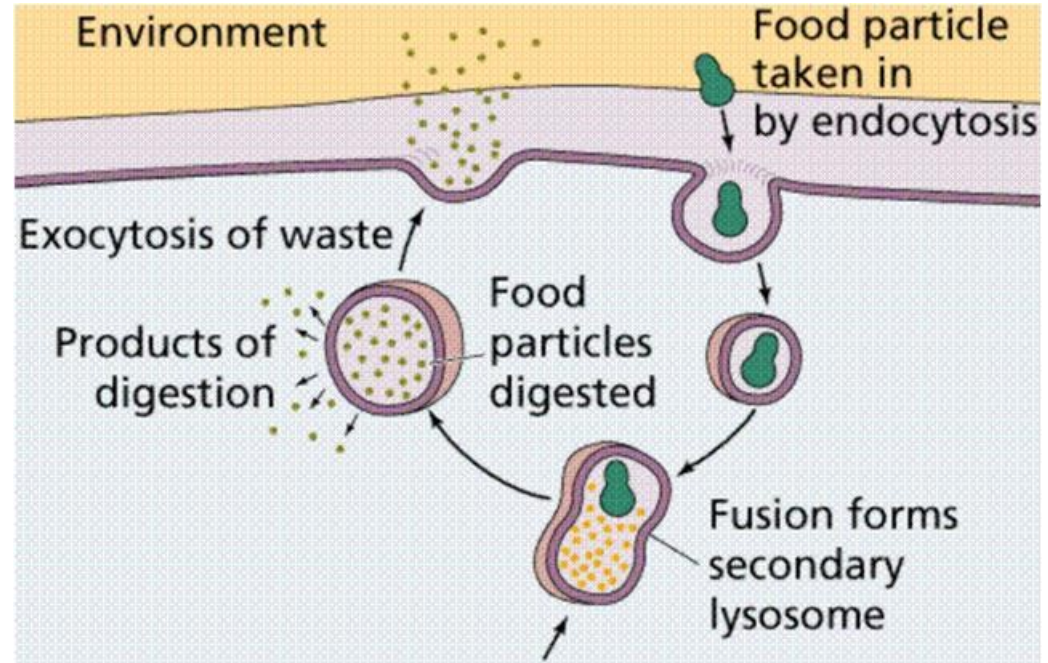
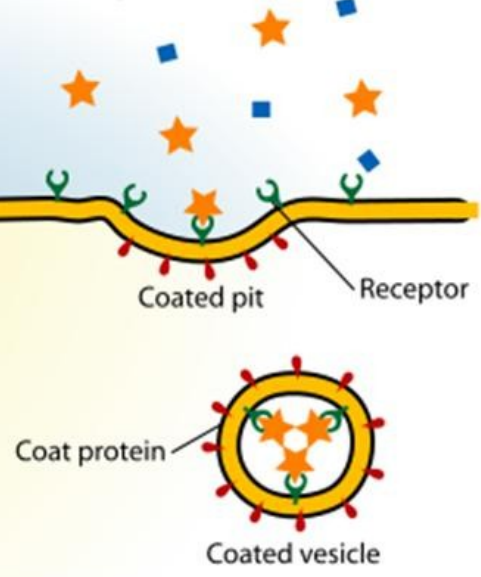
Phagocytosis



Pinocytosis

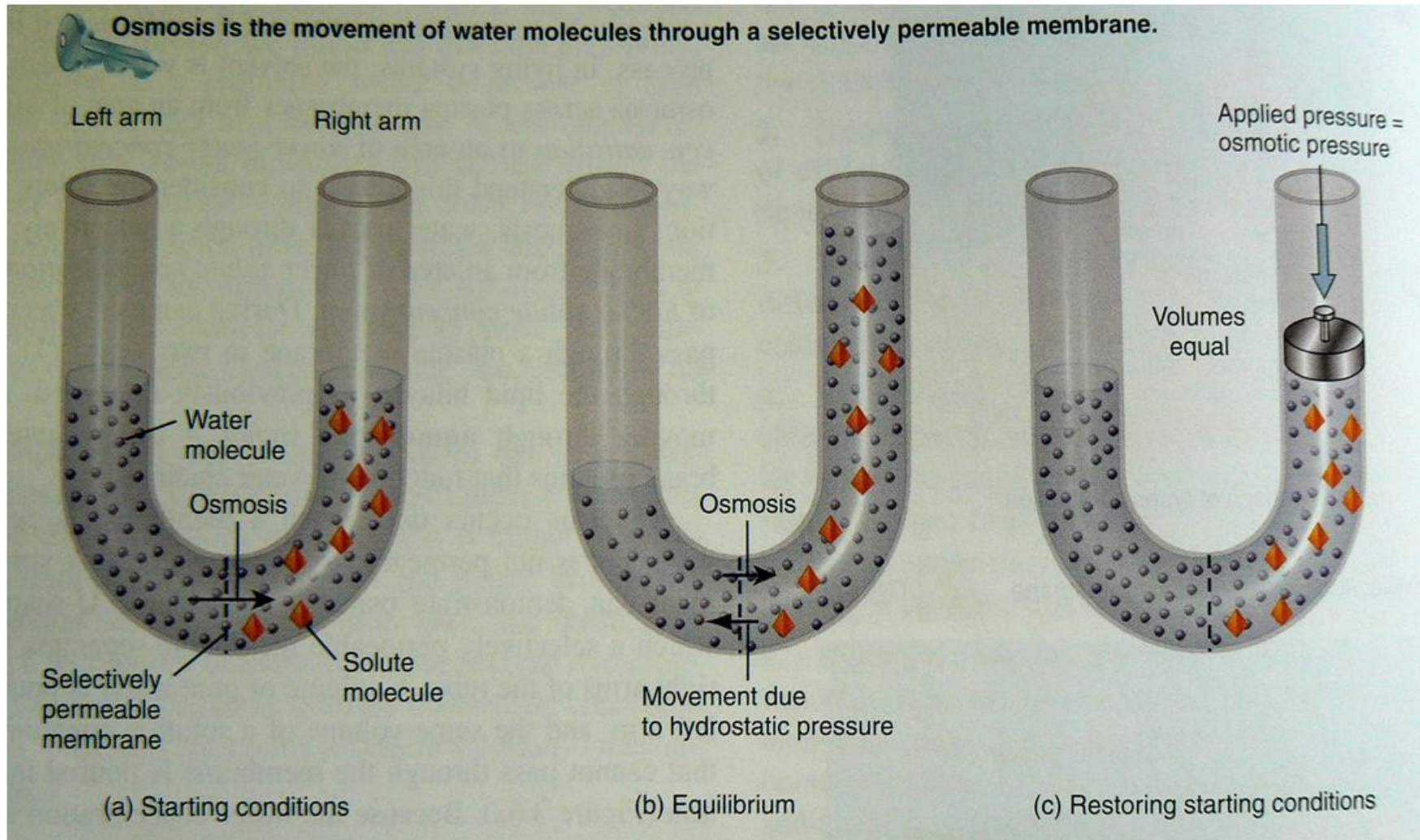


Receptor-mediated endocytosis



Vizháztartás - Ozmózis

Ozmolaritás - Ozmolalitás!



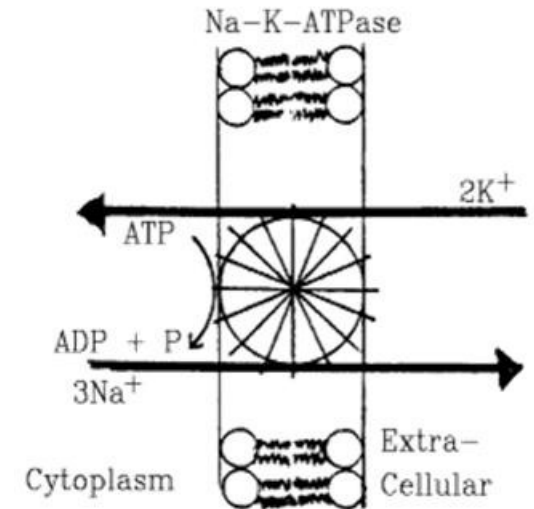
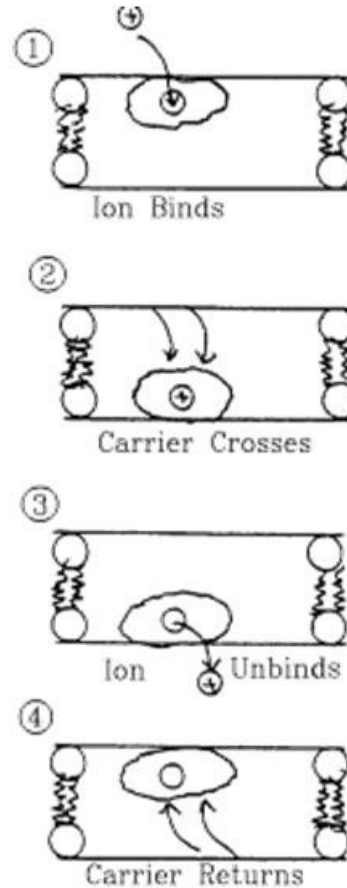
Transzport Mechanizmusok (Transzporterek)

Facilitated Diffusion Primary Active Transport

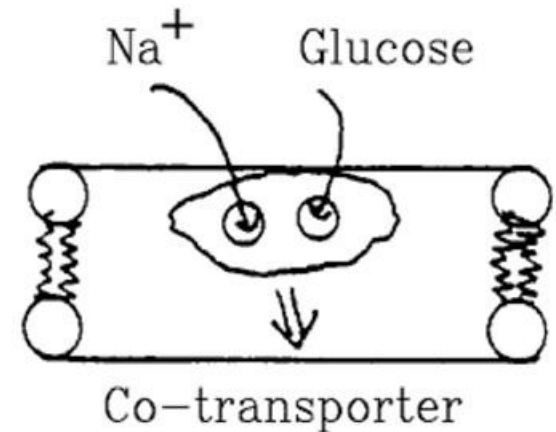
Koncentráció gradiens alapján:

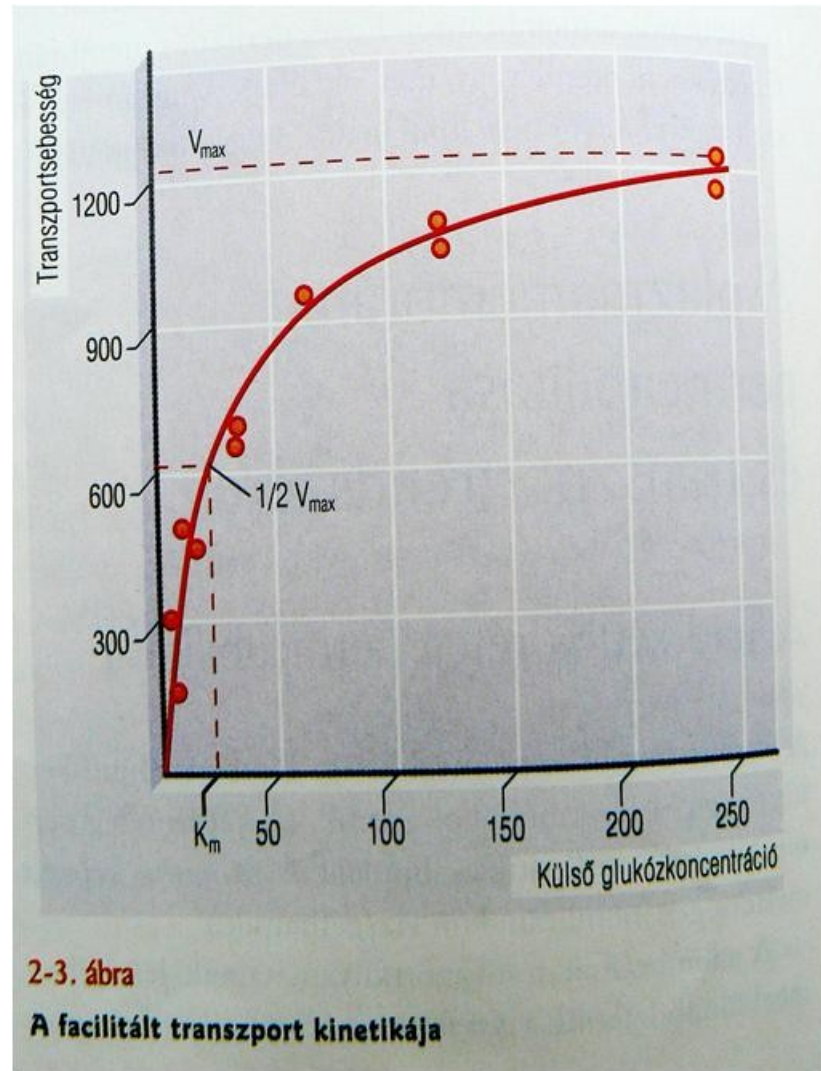
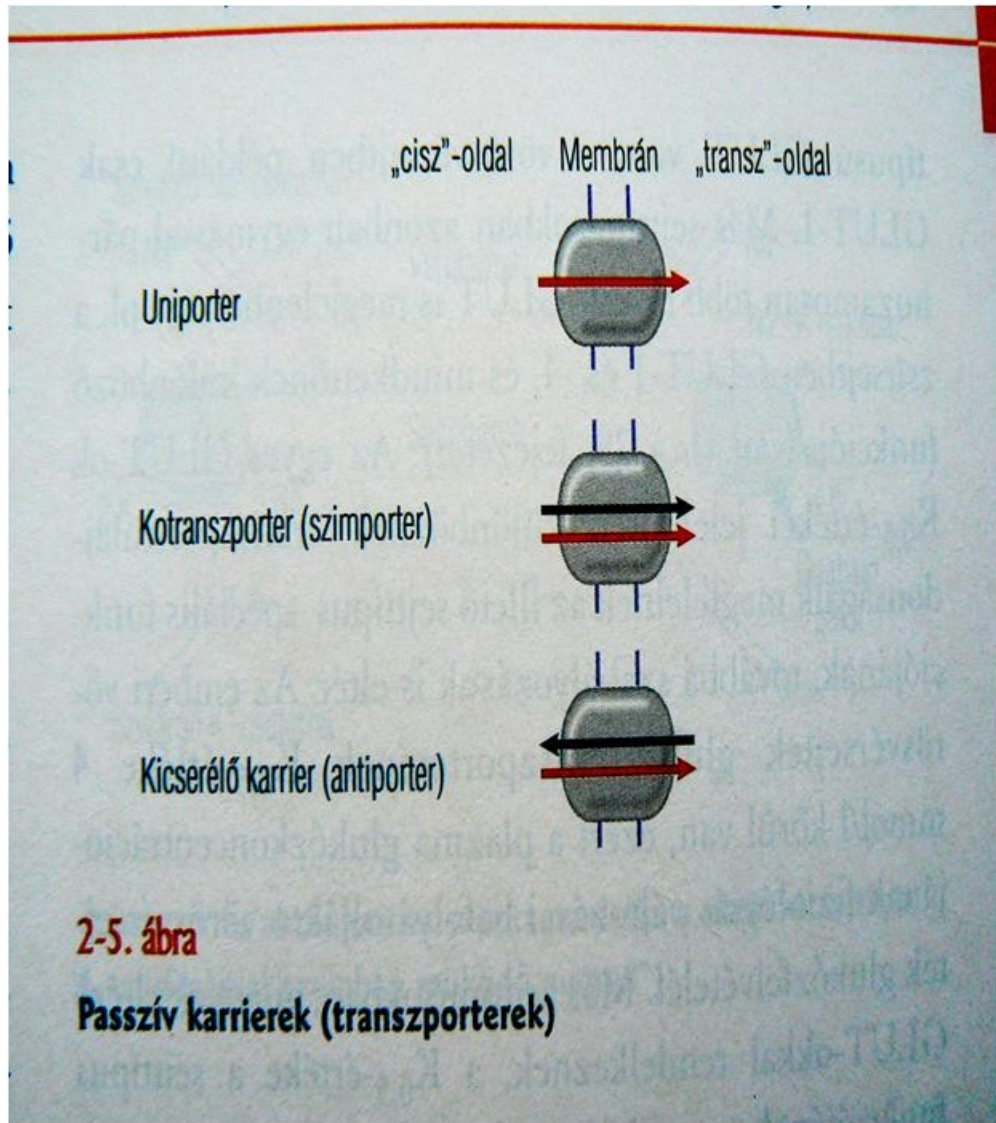
Aktiv és Passzív transzport

- Diffúzió
- Facilitált Diffúzió
- Elsődleges Aktiv Transzport
- Másodlagos Aktiv Transzport (Co-transzport)



Secondary Active Transport





ATPase PUMPS

ION EXCHANGERS

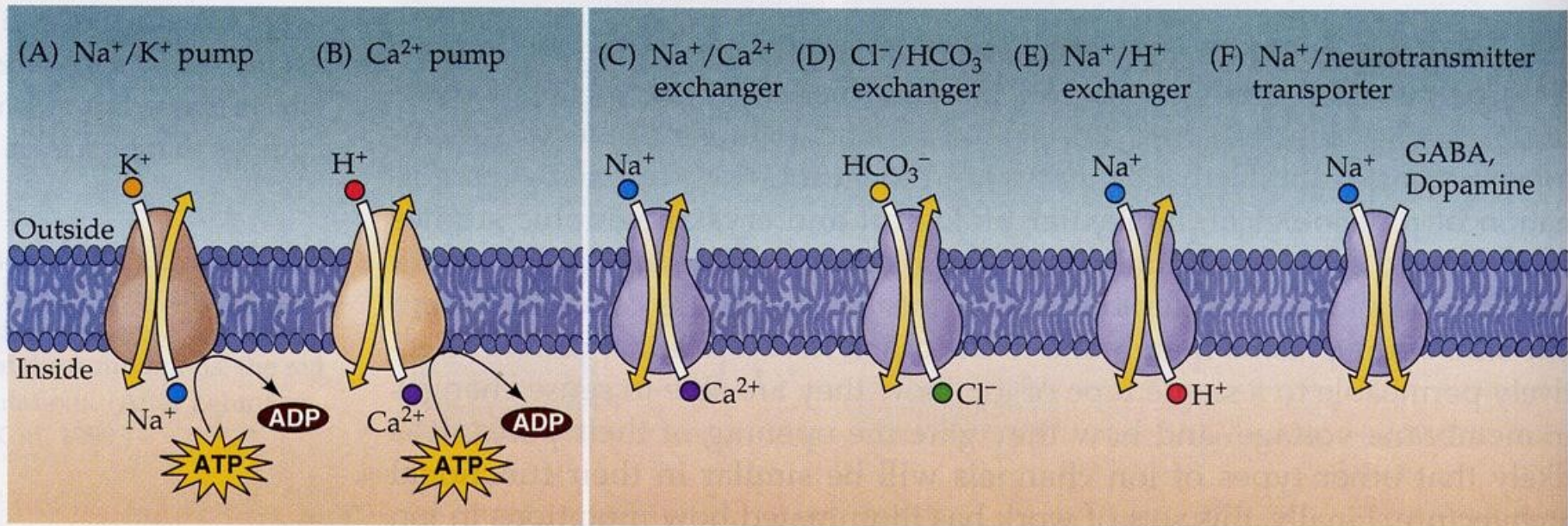


Figure 4.10 Examples of ion transporters found in cell membranes. (A,B) Some transporters are powered by the hydrolysis of ATP (ATPase pumps), whereas others (C–F) use the electrochemical gradients of co-transported ions as a source of energy (ion exchangers).

ban cseréli ki a *transz* oldalon helyet foglaló bikarbonat-

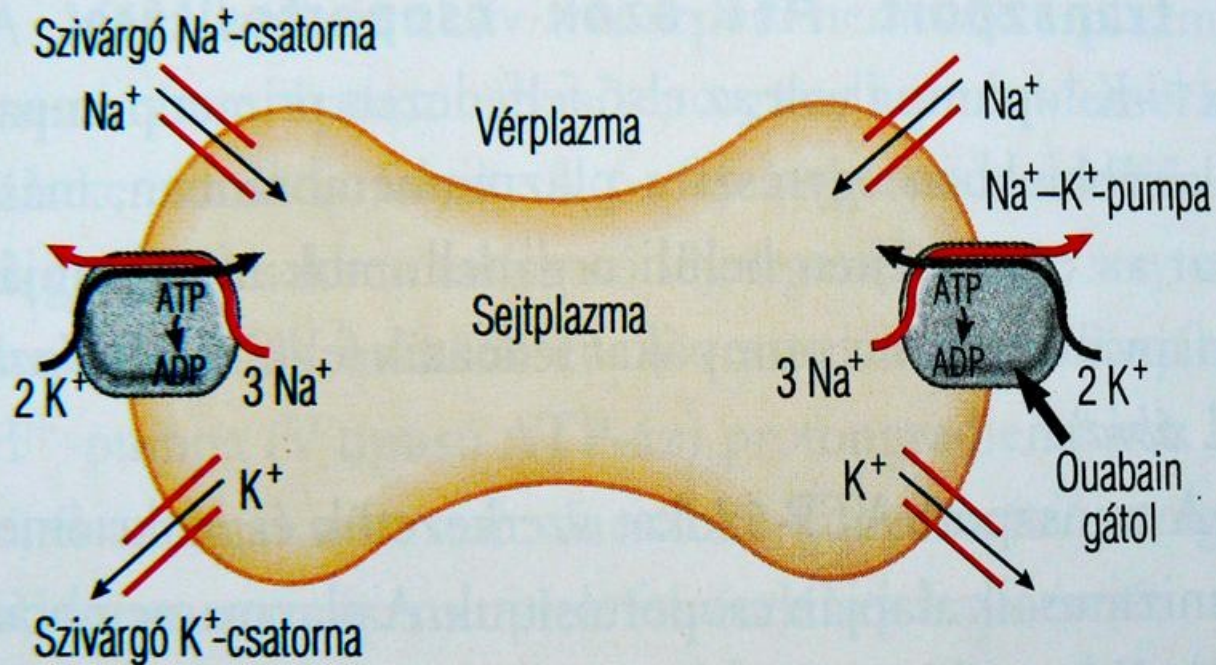
2-1. táblázat

A plazmamembrán facilitatív glukóztranszporterei (uniporterek)

Név	Előfordulás	Szerep
GLUT-1	Vörösvérsejt Kapillárisendothelium	Glukózfelvétel Glukóztranszport a vér-agy gáton keresztül
GLUT-2	Máj Vese Bélhám Pancreas β -sejt	Glukózfelvétel és -leadás Glukózleadás Glukózleadás Inzulinszekréció szabályozása
GLUT-3	Idegsejt	Glukózfelvétel
GLUT-4*	Izom Zsírsejt	Inzulinnal szabályozott glukózfelvétel Inzulinnal szabályozott glukózfelvétel
GLUT-5	Bélhámsejt	Fruktózfelszívás (luminalis)
GLUT-6	?	?
GLUT-7	?	?

A GLUT-1 és a GLUT-3 az agyi neuronok glukózfelvételében sorba kapcsoltan működnek együtt

* A GLUT-4 reverzibilis áthelyeződését a plazmamembrán és az endoszómák között a 29. fejezetben írjuk le



2-6. ábra

A passzív és aktív iontranszport modellje a vörösvérsejtben („szivárgással szemben működő pumpa”)

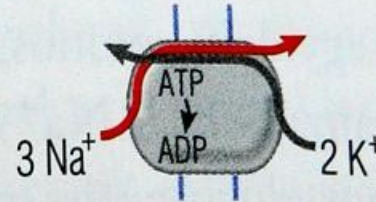
Az aktív transzport energiát igényel, amelyet a sejt

„cisz”-oldal

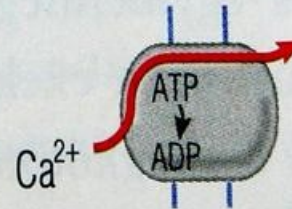
Membrán

„transz”-oldal

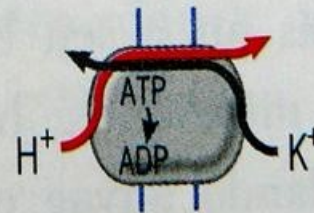
Na^+ - K^+ -pumpa (Na^+ - K^+ -ATP-áz)



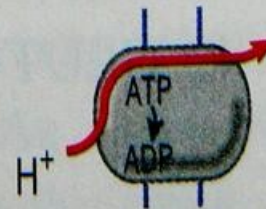
Ca^{2+} -pumpa (Ca^{2+} -ATP-áz)



H^+ - K^+ -pumpa (H^+ - K^+ -ATP-áz)



H^+ -pumpa (H^+ -ATP-áz)



2-7. ábra

Primer pumpák a membránban

A plazmamembrán és az intracelluláris organellek primer pumpái**A) A plazmamembrán primer pumpái**

Név	Előfordulás*	Funkció
Na ⁺ -K ⁺ -pumpa (Na ⁺ -K ⁺ -ATP-áz)	Minden sejt	Egyenlőtlen Na ⁺ - és K ⁺ - megoszlás létrehozása
Ca ²⁺ -pumpa (Ca ²⁺ -ATP-áz)	Vörösvérsejtek	Alacsony Ca ²⁺ -koncentráció a sejtplazmában
	Felszívó hámsejtek	Ca ²⁺ -felszívás
H ⁺ -pumpa (protonpumpa, H ⁺ -ATP-áz)	Vese gyűjtőcsatornák	H ⁺ -szekréció
H ⁺ -K ⁺ -pumpa (H ⁺ -K ⁺ -ATP-áz)	Gyomornyálkahártya fedősejtjei	H ⁺ -szekréció
	Vese gyűjtőcsatornák	H ⁺ -szekréció

B) Az intracelluláris organellek primer pumpái

Név	Előfordulás*	Funkció
Ca ²⁺ -pumpa (Ca ²⁺ -ATP-áz)	Sarcoplasma-reticulum	Kiáramlott Ca ²⁺ visszavétele
	Endoplasma-reticulum	Kiáramlott Ca ²⁺ visszavétele
H ⁺ -pumpa (H ⁺ -ATP-áz)	Lizoszóma	Az organellek belsejének savanyítása
	Szekréciós granulum	A granulum belsejének savanyítása
	Synapticus vesicula	Neurotranszmitter felvétele a vesiculába

A táblázatban nem szerepelnek az ABC-transzporterek

* A felsorolás nem teljes

Transzporterek szabályozása

- Recycling - újrahasznosítás

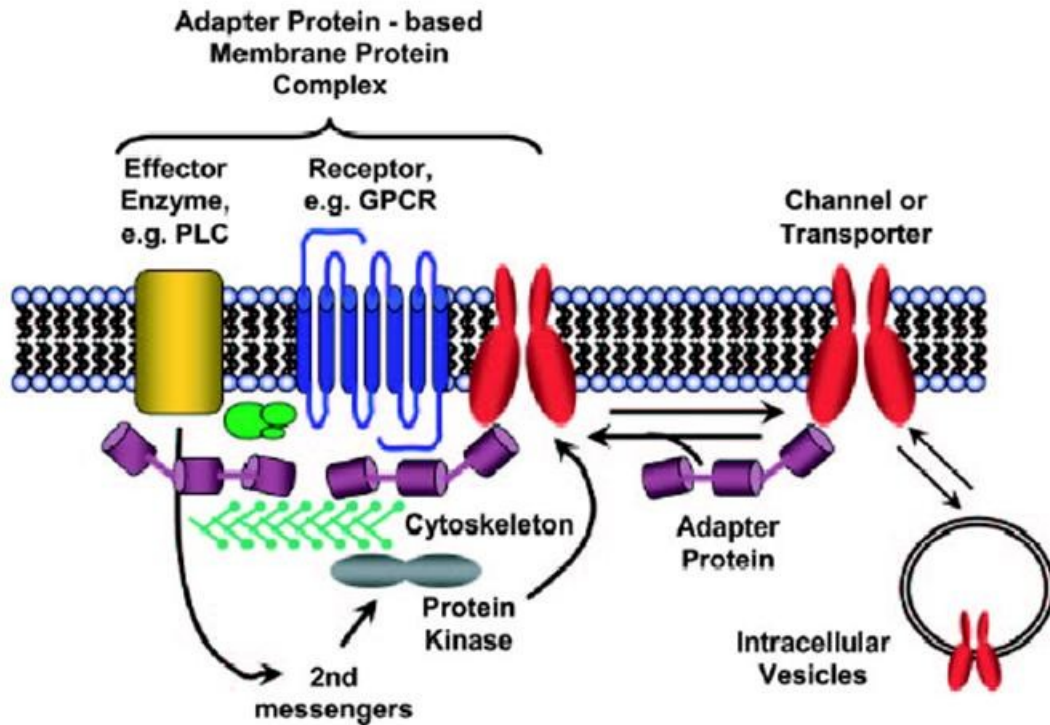
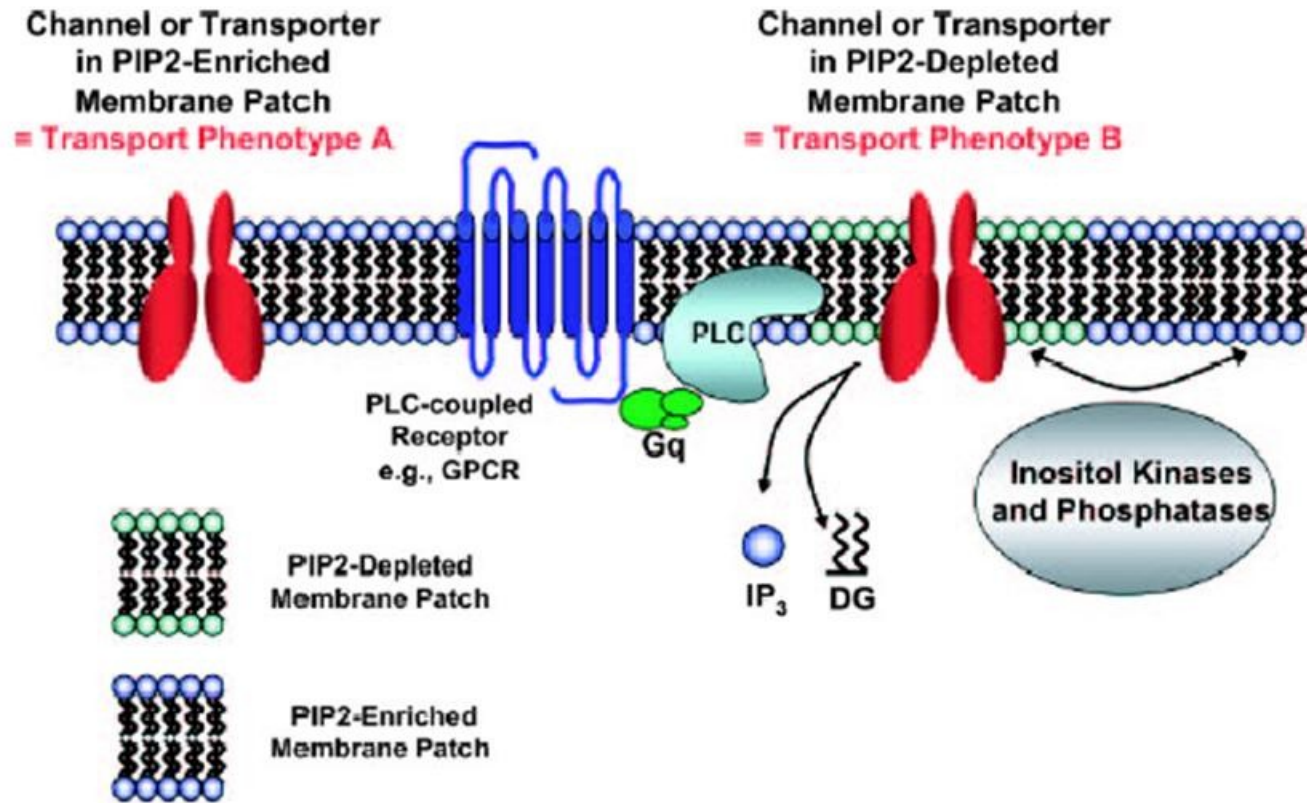


Fig. 3. Schema of how adapter proteins can regulate the trafficking of ion transport proteins and the assembly of the signaling complexes that include ion transport proteins, receptors, effector enzymes, and cytoskeletal proteins. PLC, phospholipase C; GPCR, G protein-coupled receptor.

Fig. 5. Schema of how local changes in phosphatidylinositol 4,5-bisphosphate (PIP₂) levels can regulate the functional characteristics of a nearby ion transport protein.



Lipid összetétel változtatása

Adapter molekulával

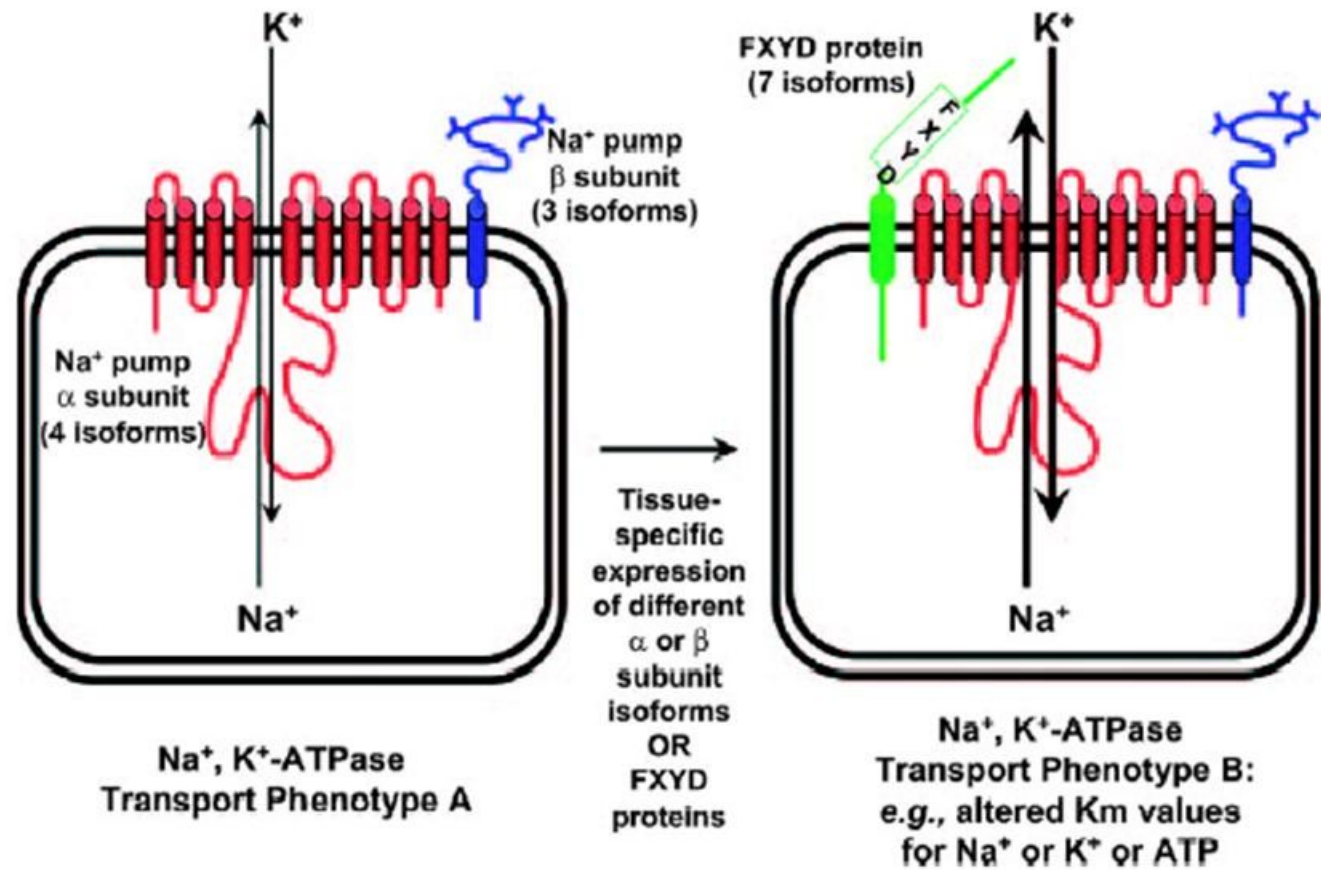
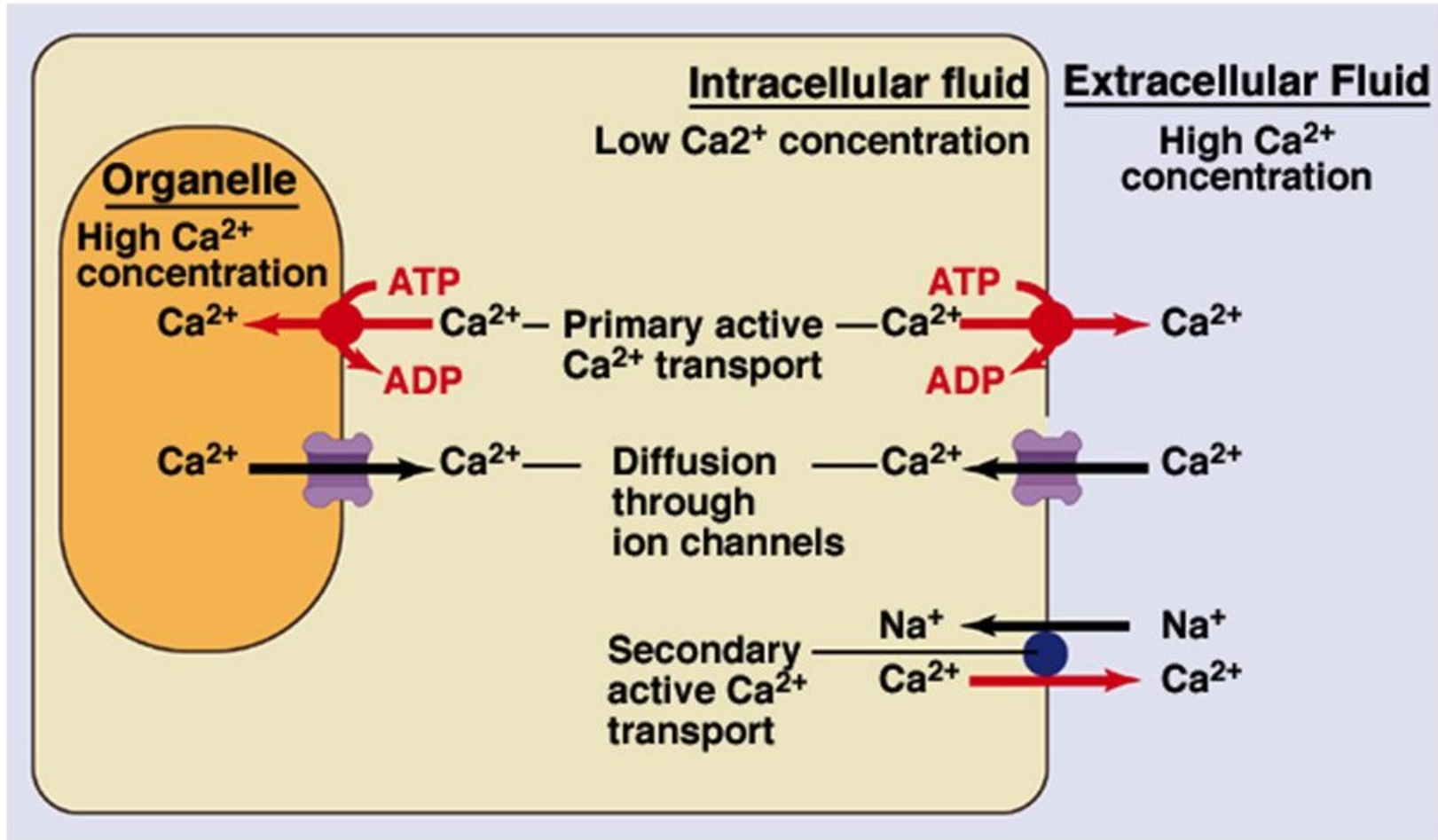


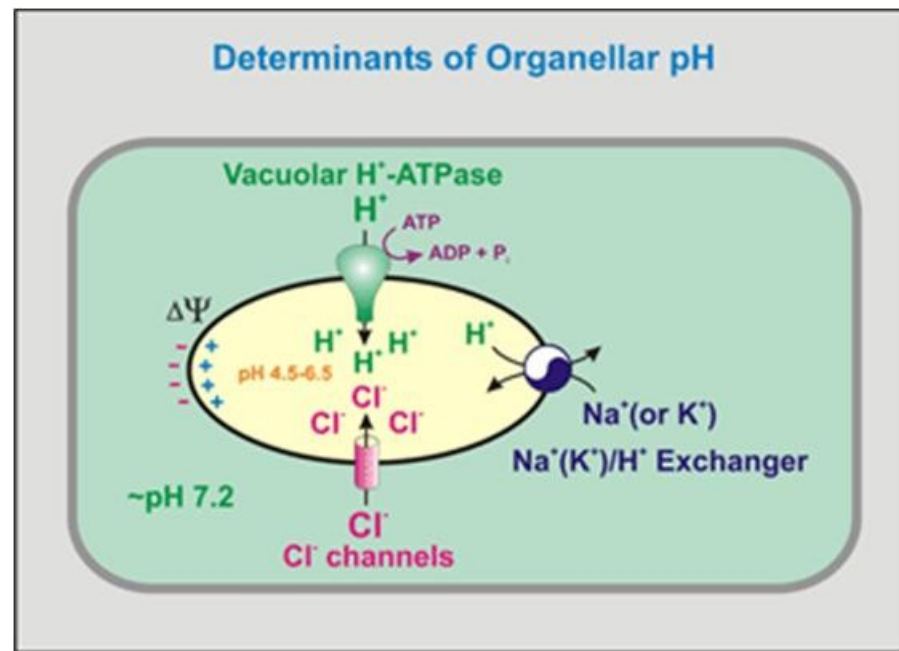
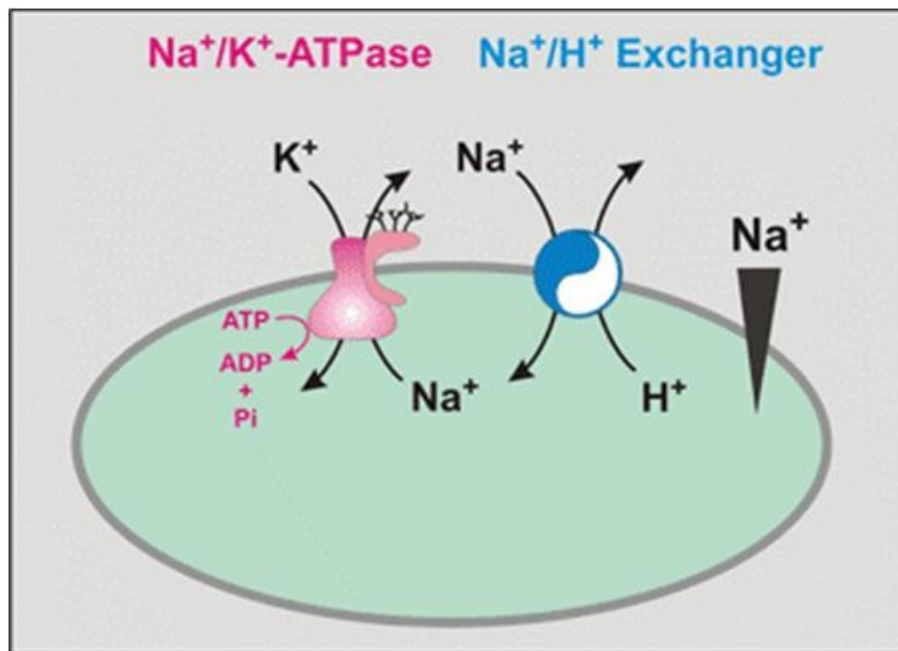
Fig. 8. Cell biology of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ in terms of the tissue-specific synthesis of α - and β -subunits and modulation by coexpressed FXYP proteins [adapted from Crambert and Geering (8)].

Na/Ca exchanger

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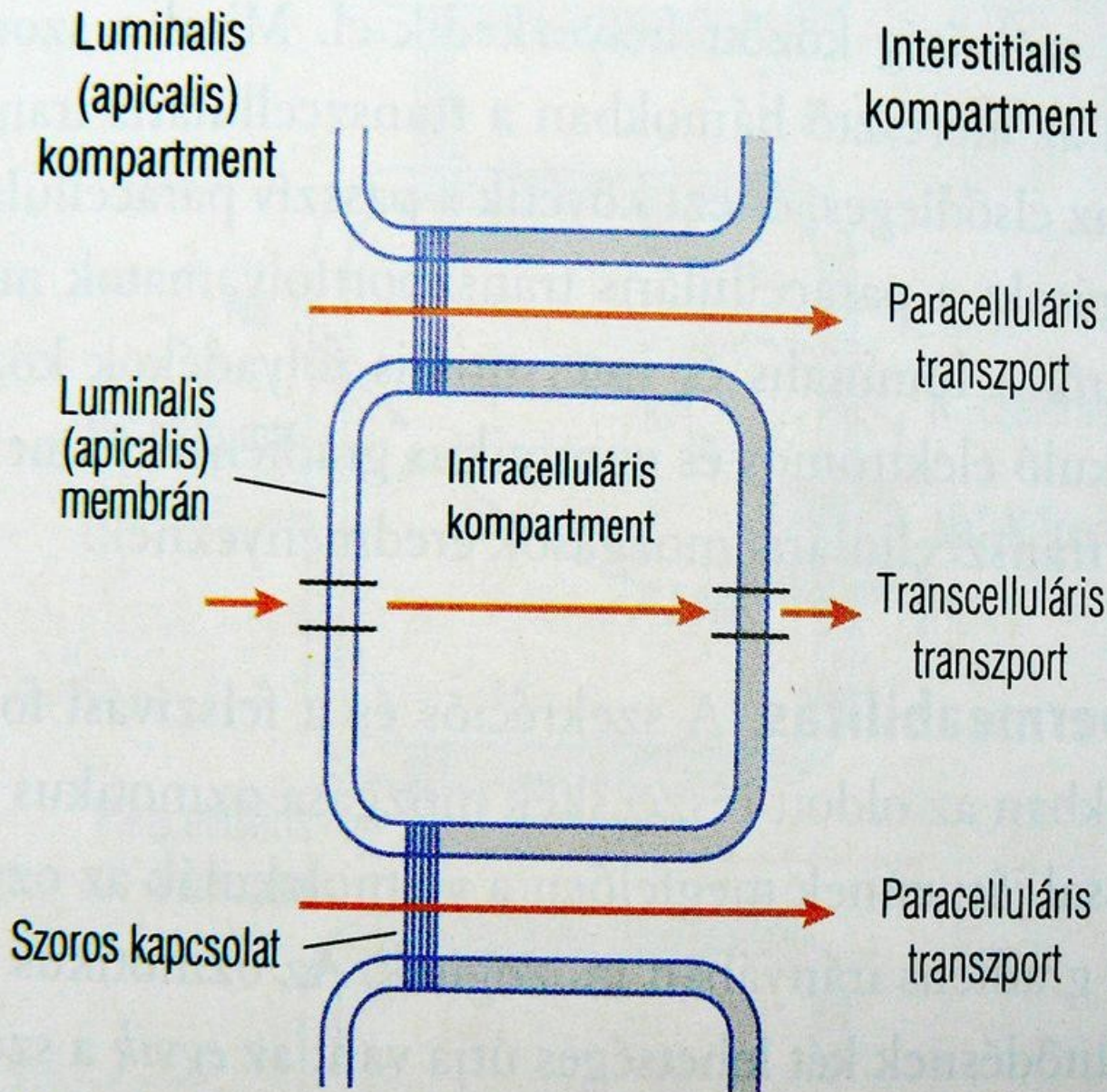
Cytosolic calcium concentration





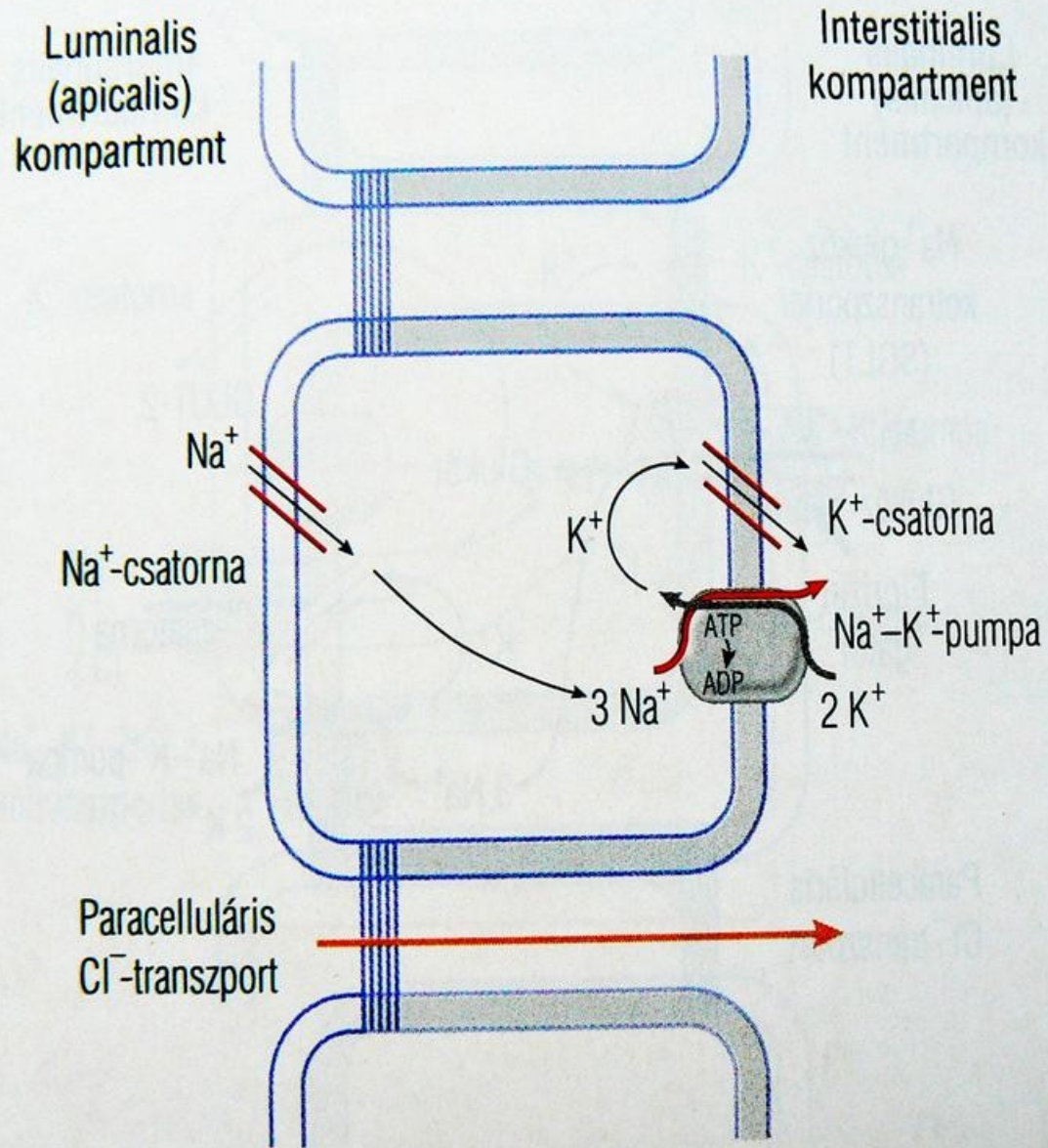
Balra: Nátrium/proton pumpa. Nátrium/kálium kicserélő pumpa biztosítja hozzá az energiát.

Jobbra: Ion csatornák, pumpák és transzporterek, amelyek a sejtalkotók pH-ját szabályozzák



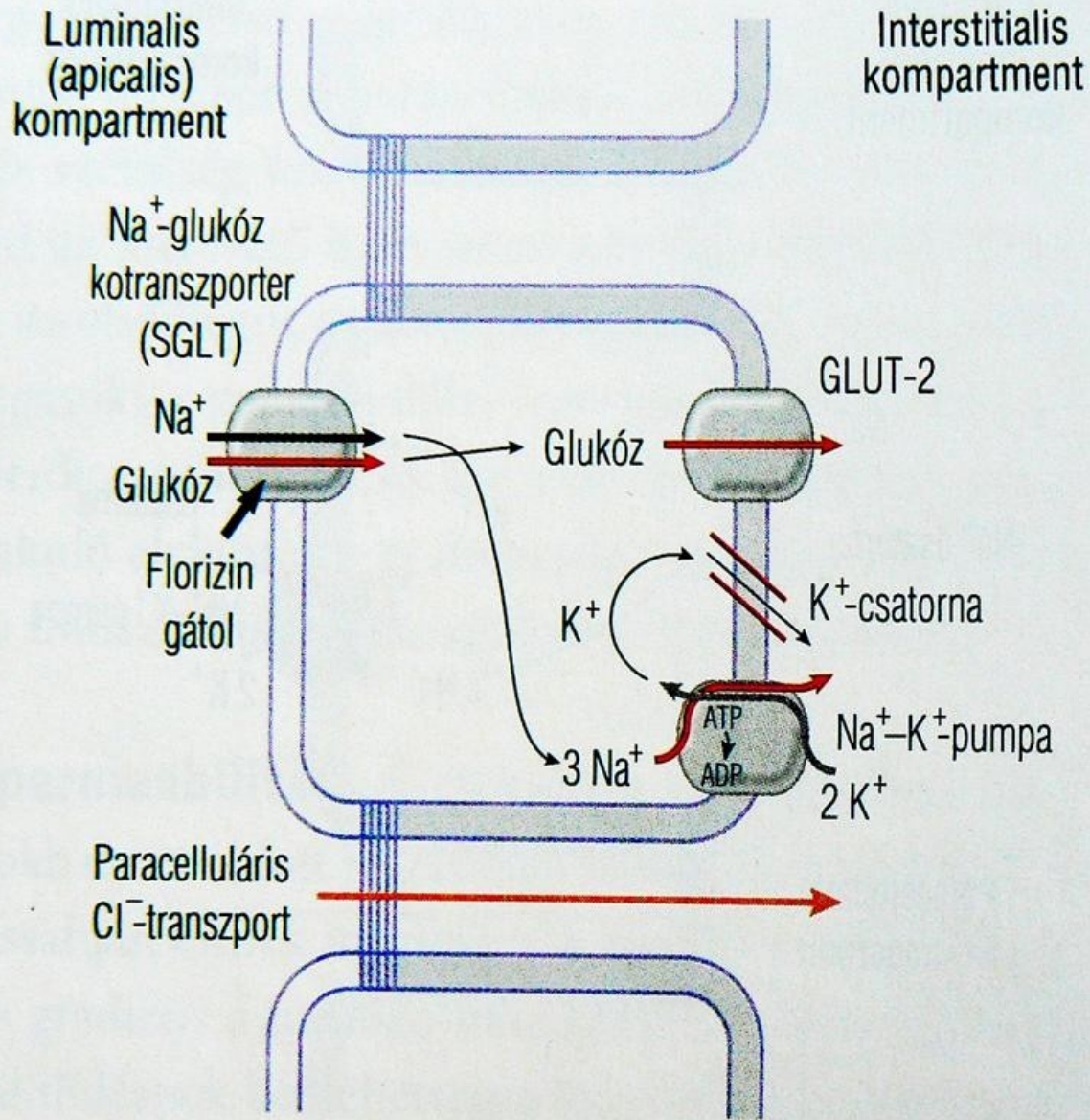
4-1. ábra

Transzcelluláris és paracelluláris transzport hámokban



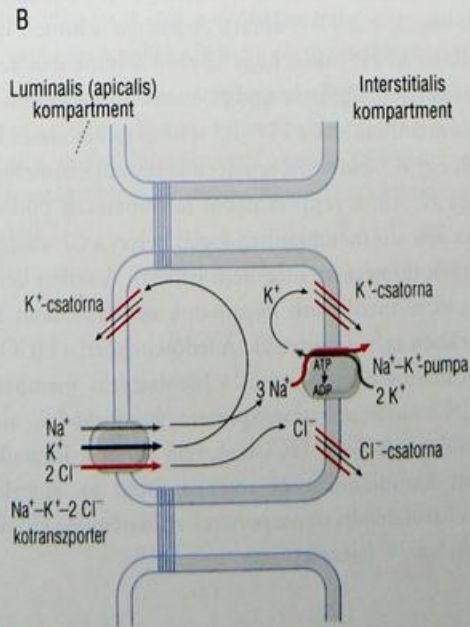
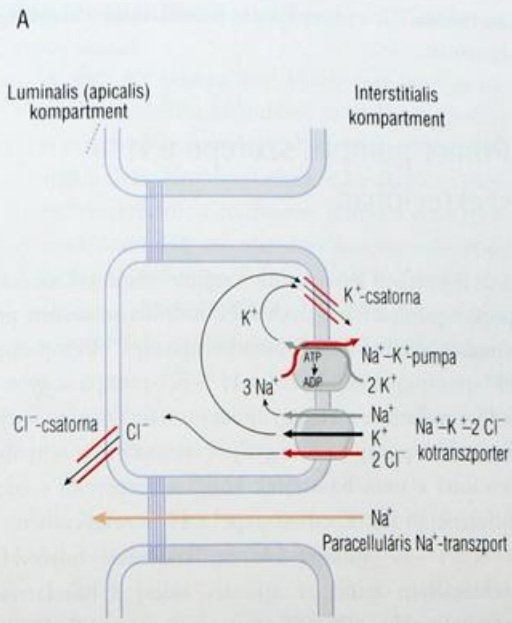
4-2. ábra

Transepithelialis NaCl -transzport



4-3. ábra

A glukóz másodlagosan aktív transzportja a hámsejtekben



4-4. ábra

A) Másodlagosan aktív kloridszekréció

B) Másodlagosan aktív kloridfelszívás

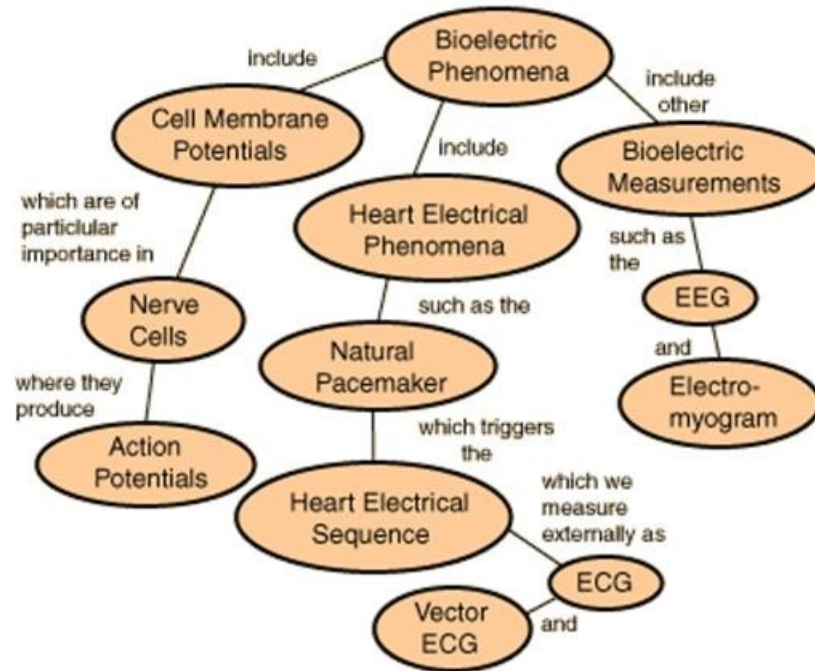
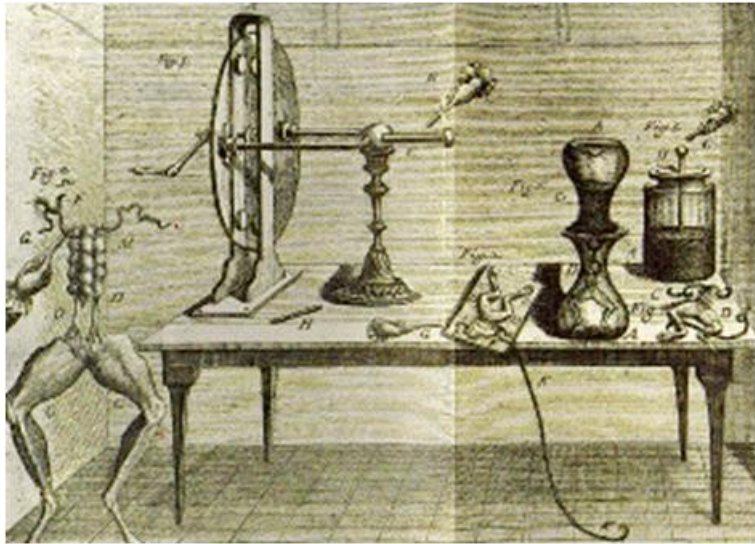
4-1. táblázat

A hámsejtek plazmamembránjának fontosabb transzportelemei

Primer pumpa	Uniporter	Kotranszporter	Antiporter (kicserélő karrier)	Csatorna
Na ⁺ -K ⁺ -pumpa (P típusú ATP-áz)	GLUT típusú transzporterek	Na ⁺ -glukóz (SGLT 1 és 2)*	Na ⁺ /H ⁺ Cl ⁻ /HCO ₃ ⁻ (anioncserélő fehérje)	Vízcsatornák (aquaporinok)
Ca ²⁺ -pumpa (P típusú ATP-áz)	Facilitatív aminosav transzporterek	Na ⁺ -aminosav (többféle)		Ioncsatornák Na ⁺ -csatorna (amiloridérzékeny)
H ⁺ -K ⁺ -pumpa (P típusú ATP-áz)		Na ⁺ -oligopeptid (többféle)		K ⁺ -csatorna
H ⁺ -pumpa (V típusú ATP-áz)		Na ⁺ -epesavas só Na ⁺ -HCO ₃ ⁻		Cl ⁻ -csatorna (CFTR)
ABC-transzporterek (MDR, MRP, SPGP)		Na ⁺ -Cl ⁻ Na ⁺ -K ⁺ -2 Cl ⁻ Na ⁺ -foszfát		Ca ²⁺ -nal aktivált Cl ⁻ -csatorna

* SGLT a „sodium glucose transporter”-ből képzett betűszó

Membrán potenciál



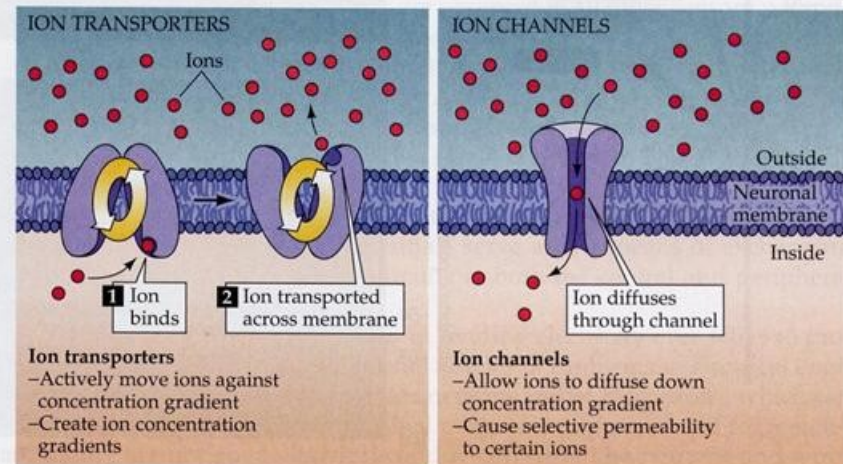
<http://hyperphysics.phy-astr.gsu.edu/hbase/electric/bioelcon#c1>

Luigi Galvani

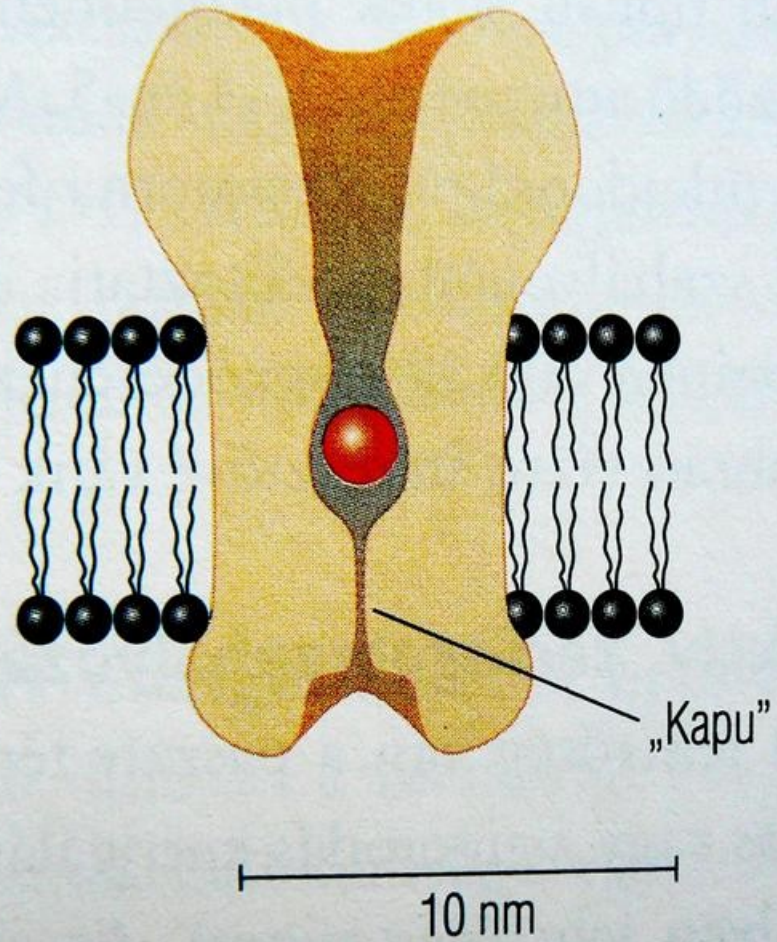
b. Sept. 9, 1737, Bologna, Papal States (Italy)

d. Dec. 4, 1798, Bologna, Cisalpine Republic

Figure 2.3 Ion transporters and ion channels are responsible for ionic movements across neuronal membranes. Transporters create ion concentration differences by actively transporting ions against their chemical gradients. Channels take advantage of these concentration gradients, allowing selected ions to move, via diffusion, down their chemical gradients.



<http://video.yahoo.com/video/play?vid=1080449&fr=yfp-t-471>



2-4. ábra

loncsatorna modell

A membrán potenciál eredete: Eltérő ionkoncentrációk a membrán két oldalán

Nernst equation:

$$E = E^0 - \frac{0.0591}{n} \log \frac{[\text{ion out of cell}]}{[\text{ion inside cell}]}$$

Electrochemical potential:

$$m = m' + zFy$$

$$Dm(2-1) = Dm'(2-1) + zFDy(2-1)$$

$$Dm(2-1) = RT \ln aA2 / aA1 + zFDy(2-1)$$

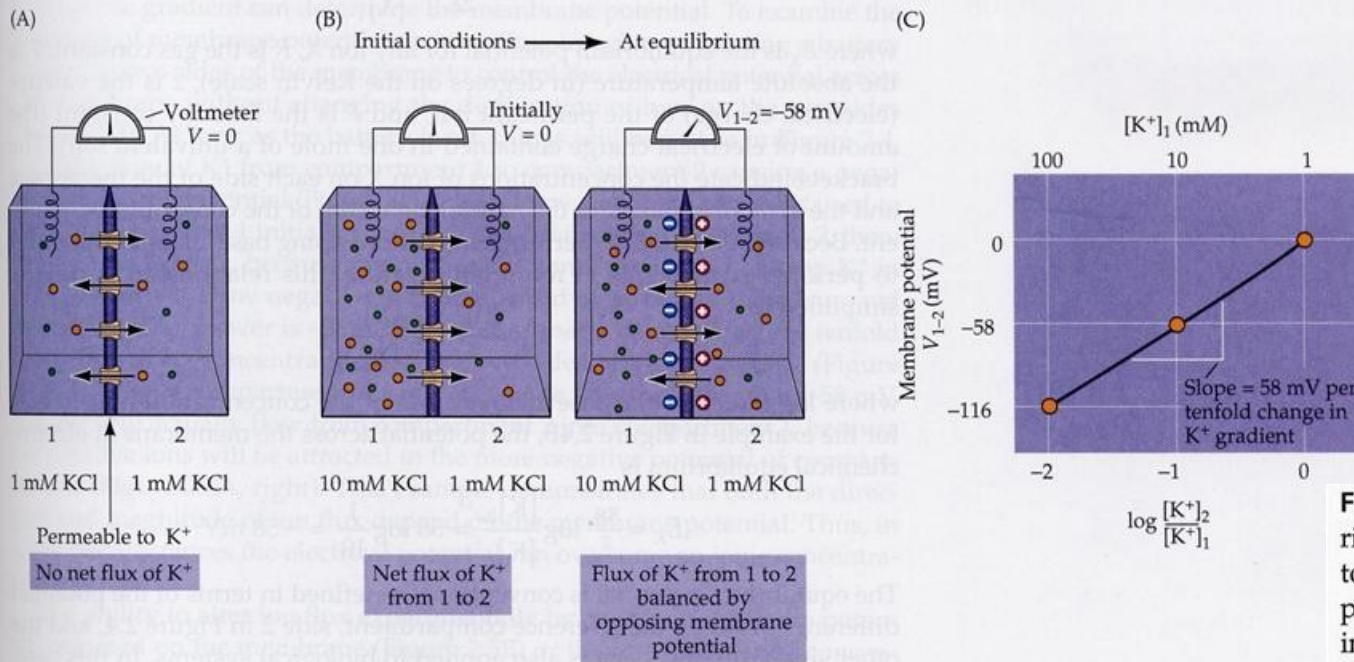


Figure 2.4 Electrochemical equilibrium. (A) A membrane permeable only to K⁺ (yellow spheres) separates compartments 1 and 2, which contain the indicated concentrations of KCl. (B) Increasing the KCl concentration in compartment 1 to 10 mM initially causes a small movement of K⁺ into compartment 2 (initial conditions) until the electromotive force acting on K⁺ balances the concentration gradient, and the net movement of K⁺ becomes zero (at equilibrium). (C) The relationship between the transmembrane concentration gradient ($[K^+]_2/[K^+]_1$) and the membrane potential. As predicted by the Nernst equation, this relationship is linear when plotted on semi-logarithmic coordinates, with a slope of 58 mV per tenfold difference in the concentration gradient.

Such an equation was developed by David Goldman in 1943. For the case most relevant to neurons, in which K⁺, Na⁺, and Cl⁻ are the primary permeant ions, the **Goldman equation** is written

$$V = 58 \log \frac{P_K [K]_2 + P_{Na} [Na]_2 + P_{Cl} [Cl]_1}{P_K [K]_1 + P_{Na} [Na]_1 + P_{Cl} [Cl]_2}$$

where V is the voltage across the membrane (again, compartment 1 relative to the reference compartment 2) and P indicates the permeability of the

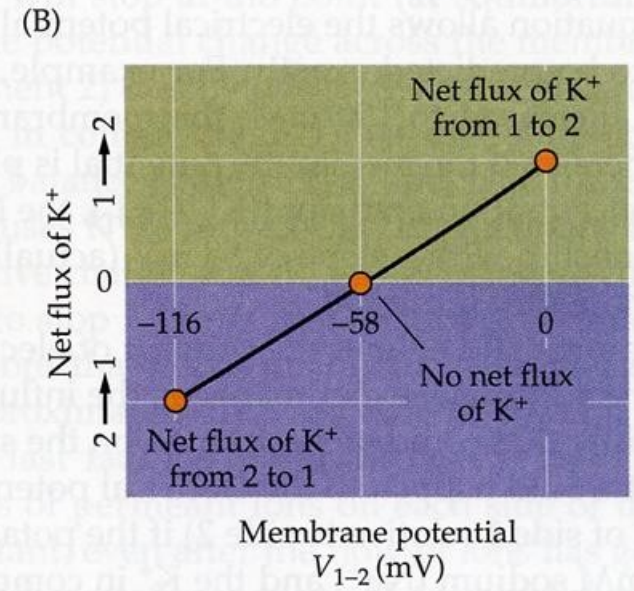
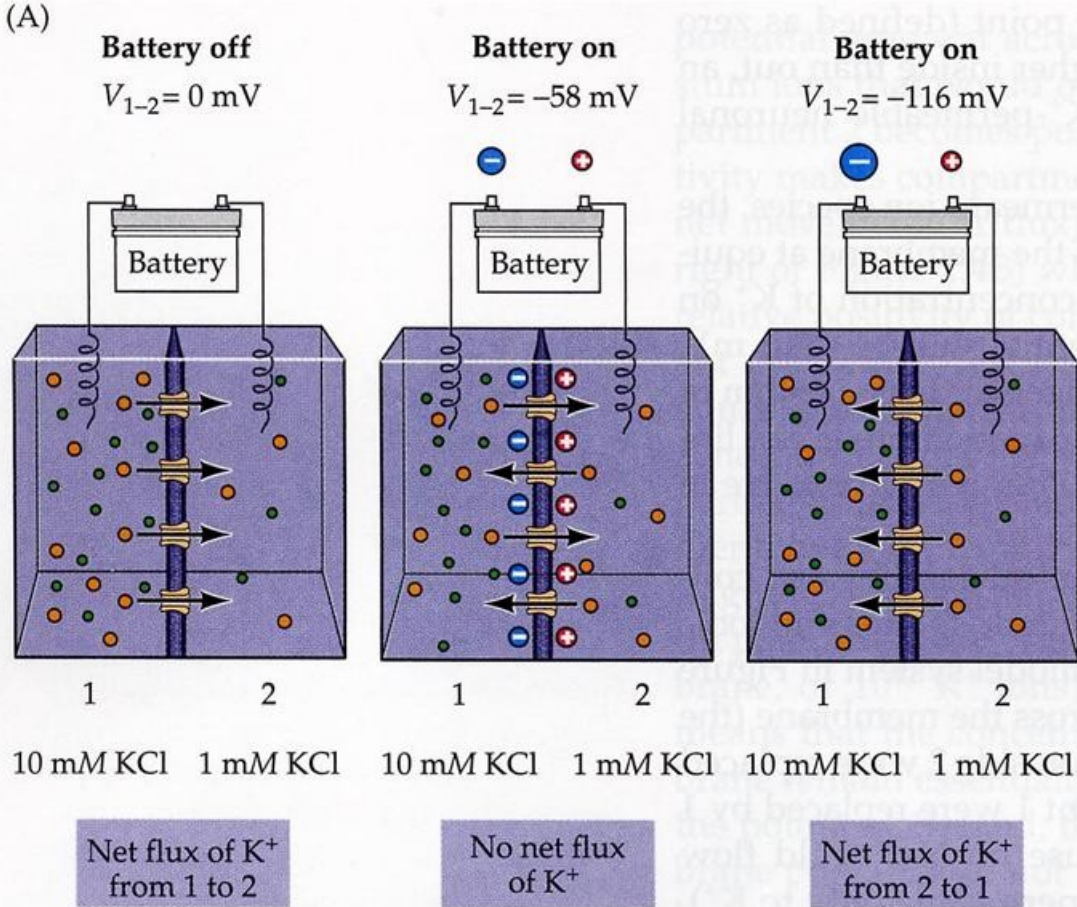


Figure 2.5 Membrane potential influences ion fluxes. (A) Connecting a battery across the K^+ -permeable membrane allows direct control of membrane potential. When the battery is turned off (left), K^+ ions (yellow) flow simply according to their concentration gradient. Setting the initial membrane potential (V_{1-2}) at the equilibrium potential for K^+ (center) yields no net flux of K^+ , while making the membrane potential more negative than the K^+ equilibrium potential (right) causes K^+ to flow against its concentration gradient. (B) Relationship between membrane potential and direction of K^+ flux.

$$I_{ion} = g_{ion}(E_m - E_{ion})$$

Ionic concentrations in cells

TABLE 2.1

Extracellular and Intracellular Ion Concentrations

<i>Ion</i>	<i>Concentration (mM)</i>	
	<i>Intracellular</i>	<i>Extracellular</i>
Squid neuron		
Potassium (K ⁺)	400	20
Sodium (Na ⁺)	50	440
Chloride (Cl ⁻)	40–150	560
Calcium (Ca ²⁺)	0.0001	10
Mammalian neuron		
Potassium (K ⁺)	140	5
Sodium (Na ⁺)	5–15	145
Chloride (Cl ⁻)	4–30	110
Calcium (Ca ²⁺)	0.0001	1–2

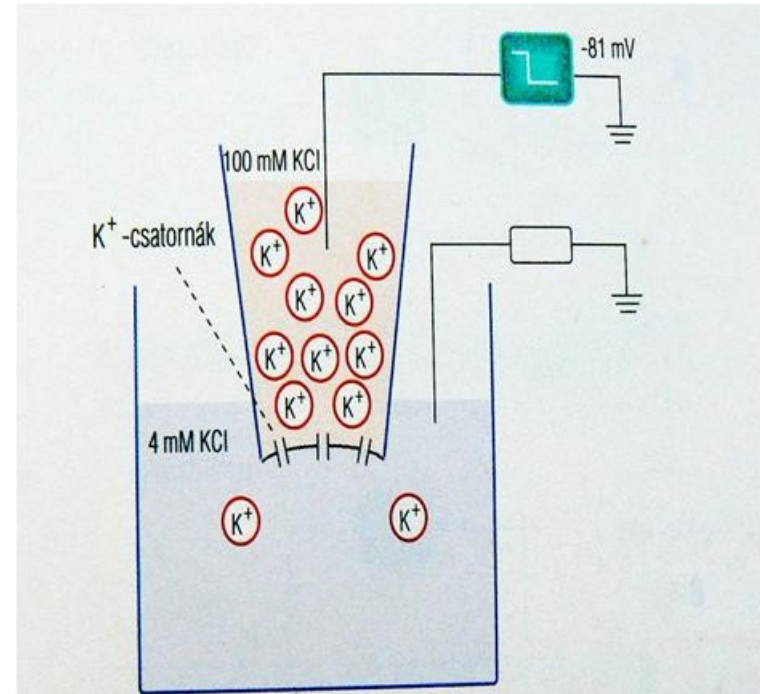
Reversal
Potential:
-80 mV
+60 mV
-60 mV
+60 mV

Resting:
-70 mV

3-1. táblázat

Közelítő nyugalmi membránpotenciál értékek

Sejt	Nyugalmi membránpotenciál (mV)
Simaizomsejt (emlős)	-35-től -55-ig
Szív nodalis szövet (emlős)	-55-től -65-ig
Óriásidegrost (tintahal)	-60
Idegsejt (emlős gerincvelői motoneuron)	kb. -70
Kamraizomrost (emlős)	-80
Vázizomrost (emlős)	-80
Vázizomrost (béka)	-90



3-5. ábra

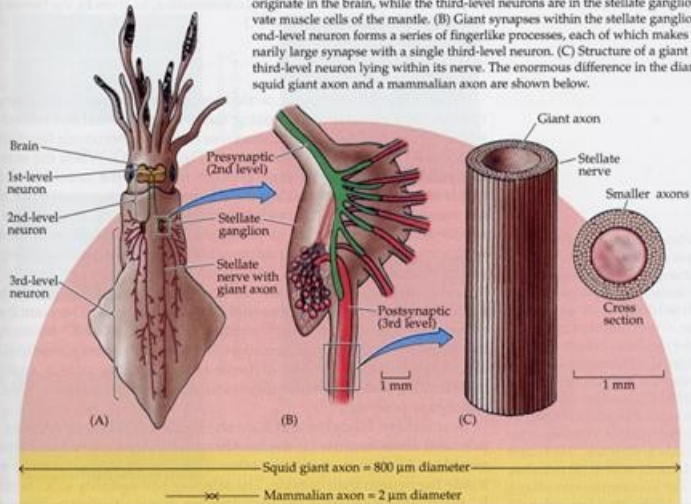
Az egyensúlyi potenciál kialakulásának szemléltetése

A pipetában lévő folyadék 100 mM, a fürdőben lévő 4 mM káliumion, a membrán csak K⁺-csatornákat tartalmaz. A K⁺-ok nettó áramlása a pipetából a fürdőbe akkor szűnik meg, amikor a pipetában a potenciálérték -81 mV-ra áll be ($58 \times \log 4/100 = -81$, l. a szöveget); ekkor a kémiai gradiens egyensúlyt tart az elektromos gradienssel

A Hodgkin-Huxley kísérlet fő eredményei – a HH Model

<http://osiris.sunderland.ac.uk/~cs0her/iBoGpdf/chapt4.pdf>

(A) Diagram of a squid, showing the location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second-level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle. (B) Giant synapses within the stellate ganglion. The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron. (C) Structure of a giant axon of a third-level neuron lying within its nerve. The enormous difference in the diameters of a squid giant axon and a mammalian axon are shown below.



Az ioncsatornák ionszelektivitásának megállapítása. Az ioncsatornák elkülönítése ez alapján

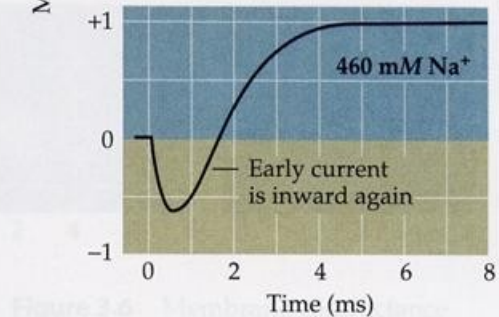
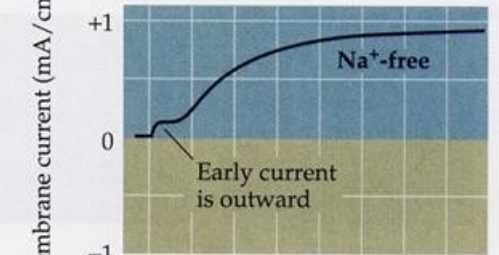
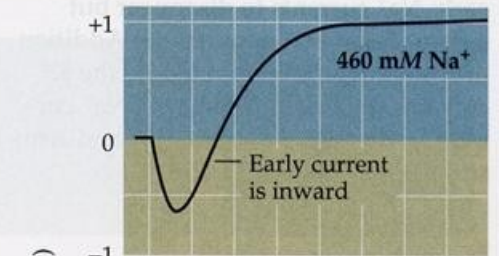
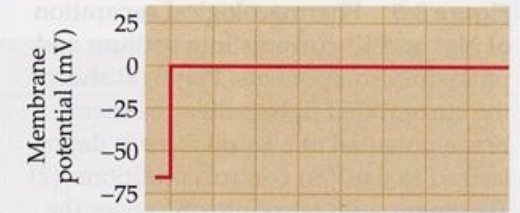
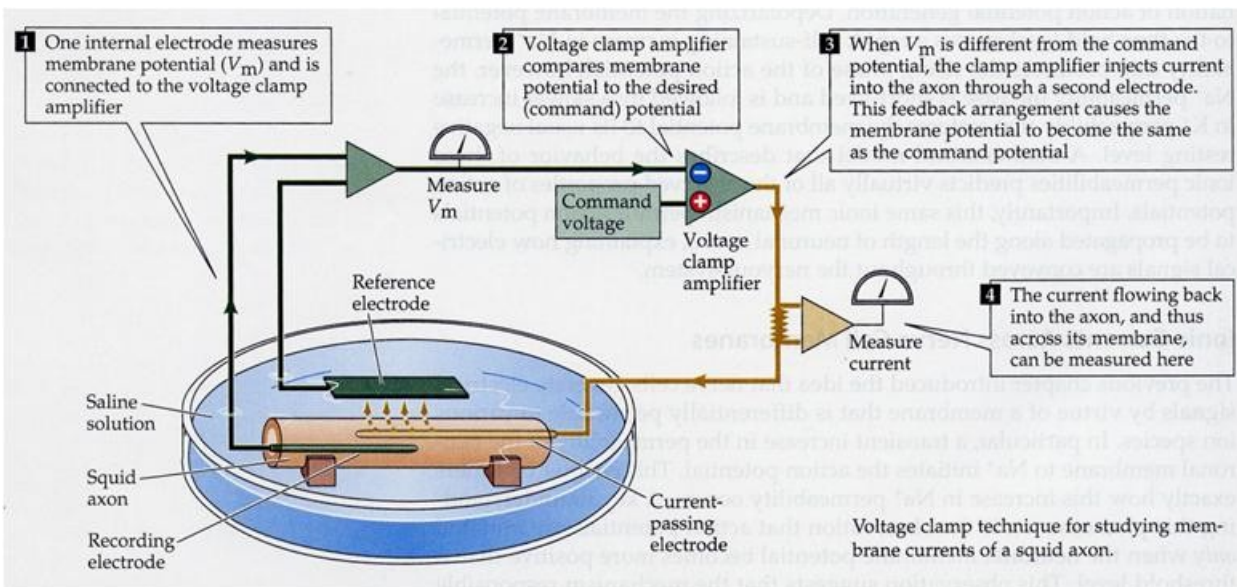
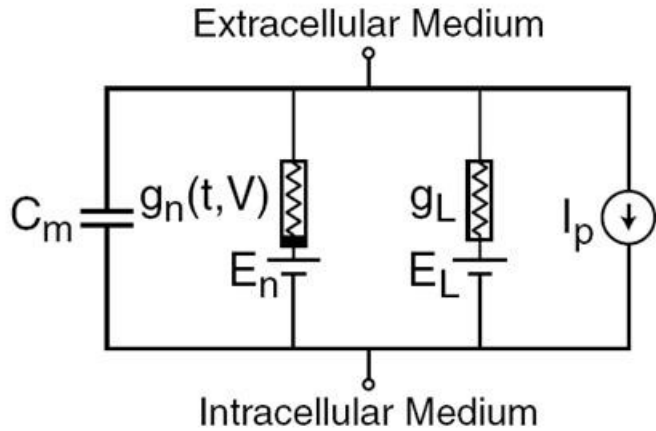


Figure 2.6

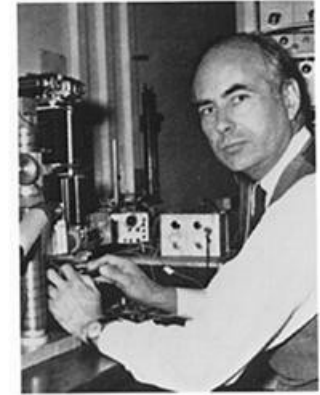
A feszültség zár (Voltage clamp) módszer létrehozása : Ioncsatornák feszültségfüggésének a mérése



Hodgkin-Huxley formalizmus



Sir Alan Hodgkin, 1949



Sir Andrew Huxley, 1974

$$I = C_M \frac{dV}{dt} + I_i,$$

$$I_{Na} = g_{Na} (V - V_{Na}),$$

$$I_K = g_K (V - V_K),$$

$$I_l = \bar{g}_l (V - V_l),$$

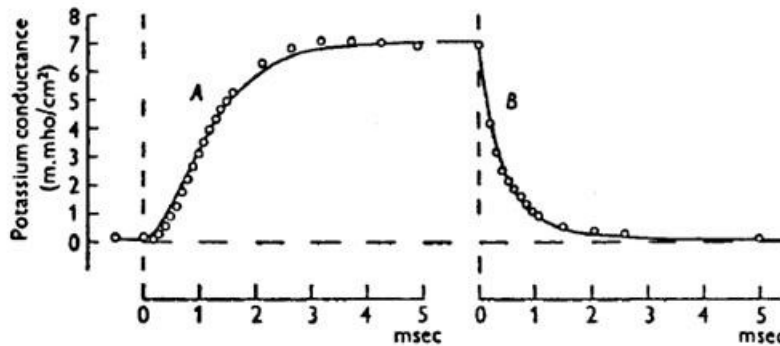


Fig. 2. *A*, rise of potassium conductance associated with depolarization of 25 mV; *B*, fall of potassium conductance associated with repolarization to the resting potential. Circles: experimental points replotted from Hodgkin & Huxley (1952*b*, Fig. 13). The last point of *A* is the same as the first point in *B*. Axon 18, 21° C in choline sea water. The smooth curve is drawn according to eqn. (11) with the following parameters:

$$g_K = \bar{g}_K n^4,$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

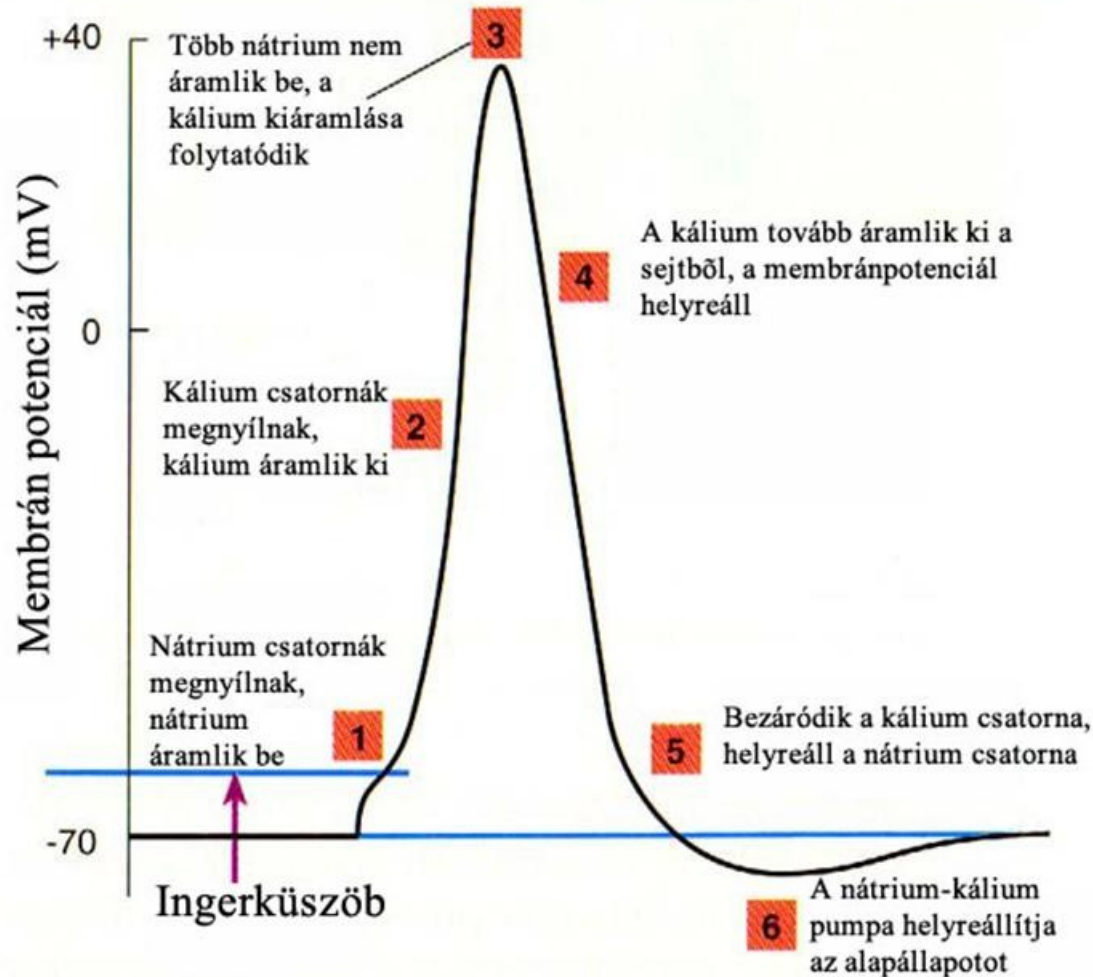
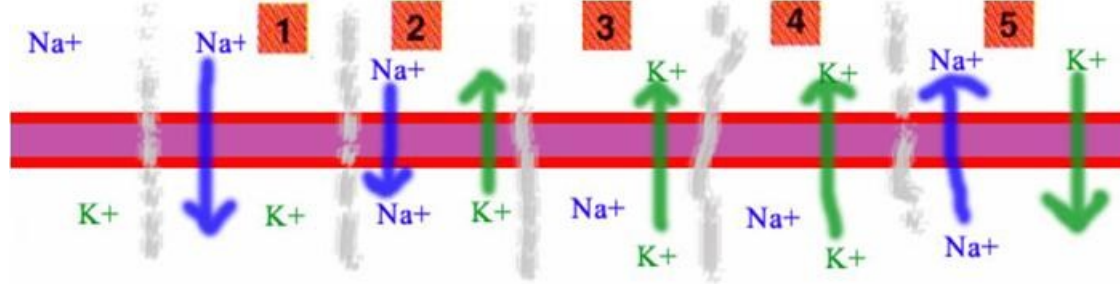
$$\alpha_n = 0.01 (V + 10) / \left[\exp \frac{V + 10}{10} - 1 \right],$$

$$\beta_n = 0.125 \exp (V/80),$$

J. Physiol. (1952) 117, 500-544

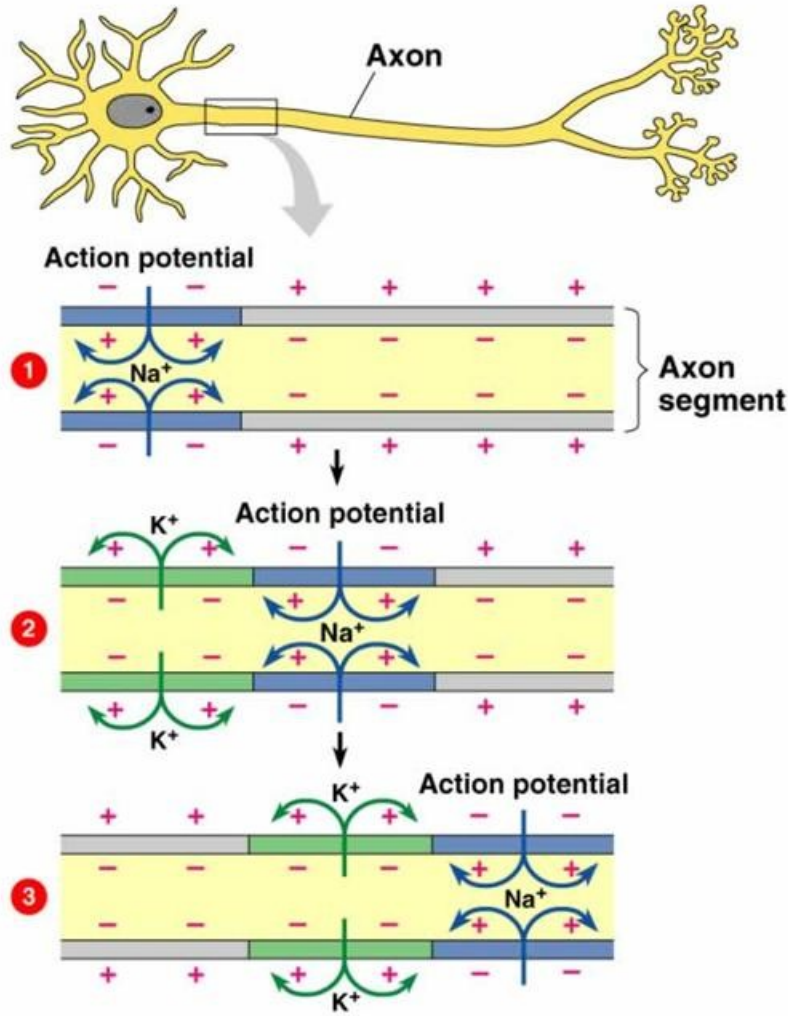
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN AND A. F. HUXLEY



Akciós potenciál

Tovaterjedő akciós potenciál



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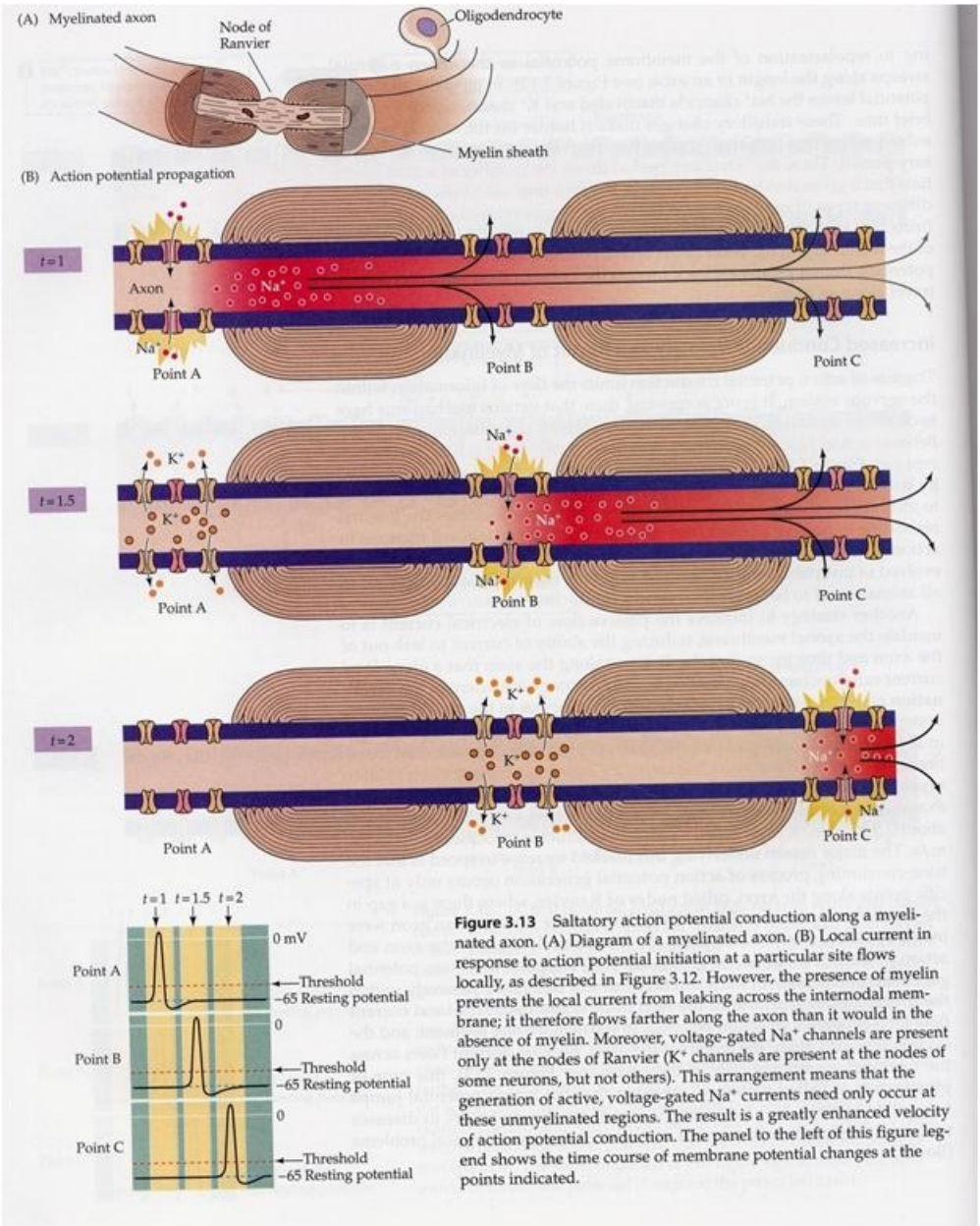


Figure 3.13 Saltatory action potential conduction along a myelinated axon. (A) Diagram of a myelinated axon. (B) Local current in response to action potential initiation at a particular site flows locally, as described in Figure 3.12. However, the presence of myelin prevents the local current from leaking across the internodal membrane; it therefore flows farther along the axon than it would in the absence of myelin. Moreover, voltage-gated Na^+ channels are present only at the nodes of Ranvier (K^+ channels are present at the nodes of some neurons, but not others). This arrangement means that the generation of active, voltage-gated Na^+ currents need only occur at these unmyelinated regions. The result is a greatly enhanced velocity of action potential conduction. The panel to the left of this figure legend shows the time course of membrane potential changes at the points indicated.

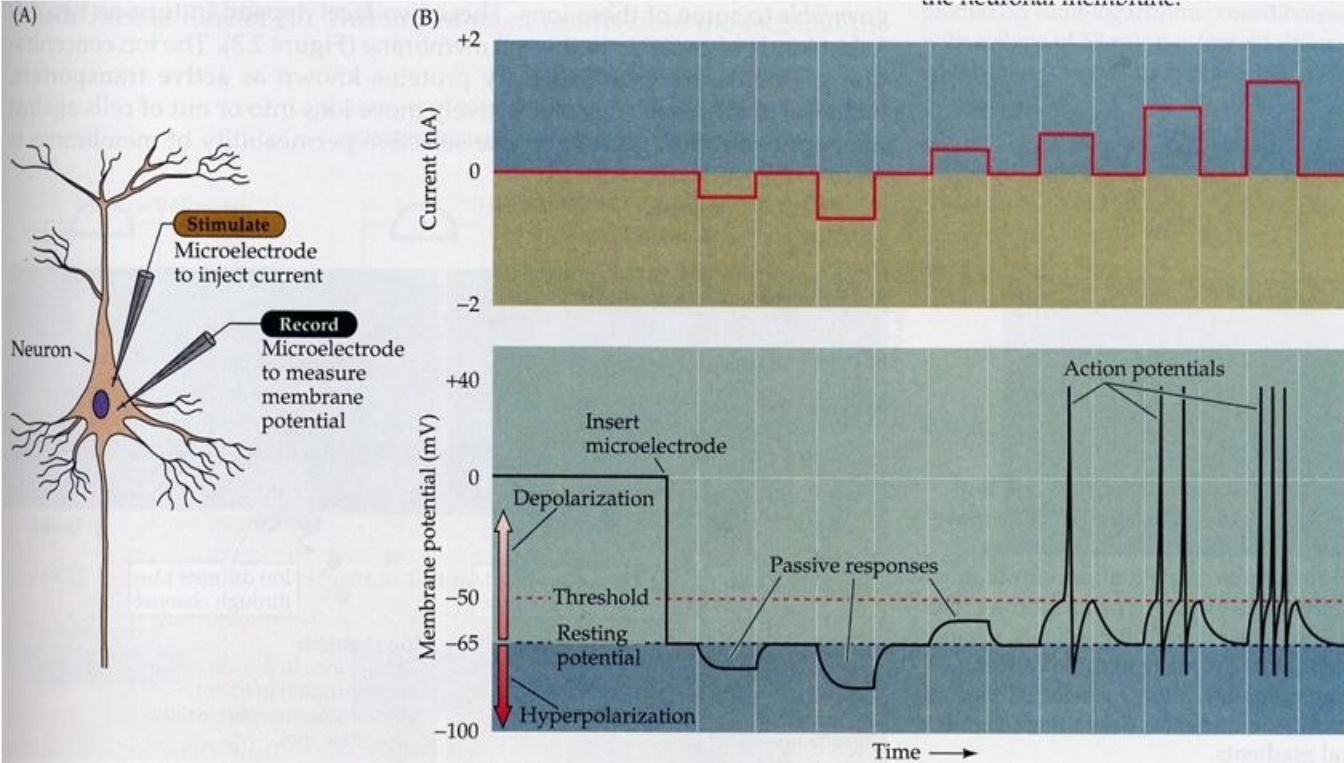
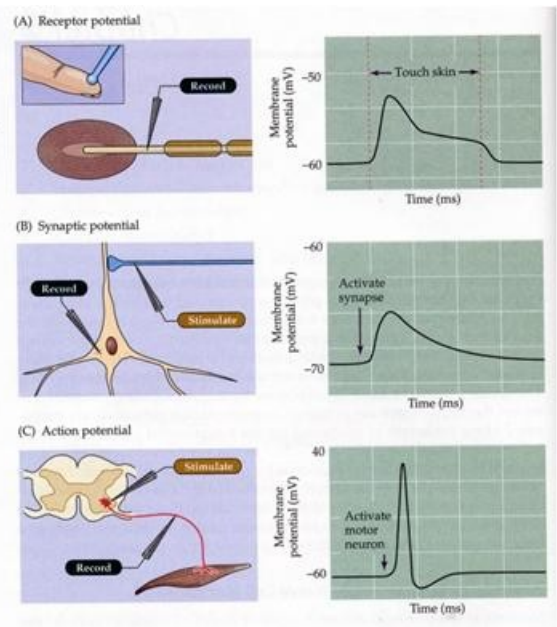


Figure 2.2 Recording passive and active electrical signals in a nerve cell. Two microelectrodes are inserted into a neuron; one of these measures membrane potential while the other injects current into the neuron. (B) Inserting the voltage-measuring microelectrode into the neuron reveals a negative potential, the resting membrane potential. Injecting current through the current-passing microelectrode alters neuronal membrane potential. Depolarizing current pulses produce passive changes in the membrane potential. While small depolarizing currents also elicit only passive responses, depolarizations that cause the membrane potential to meet or exceed threshold additionally evoke action potentials. Action potentials are active responses in the sense that they are generated by changes in the permeability of the neuronal membrane.

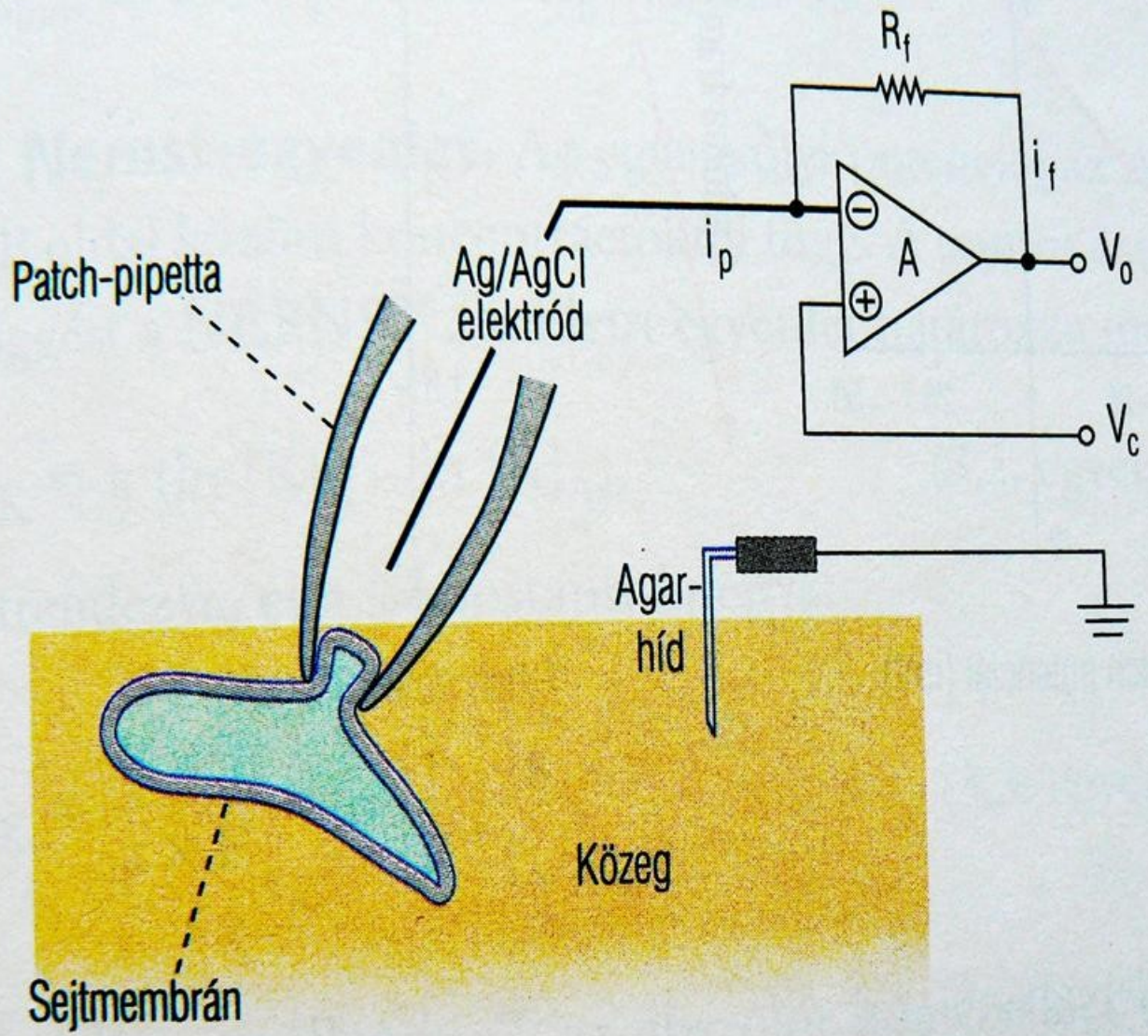
Figure 2.1 Types of neuronal electrical signals. In all cases, microelectrodes are used to measure changes in the resting membrane potential during the indicated signals. (A) A brief touch causes a receptor potential in a Pacinian corpuscle in the skin. (B) Activation of a synaptic contact onto a hippocampal pyramidal neuron elicits a synaptic potential. (C) Stimulation of a spinal reflex produces an action potential in a spinal motor neuron.



Akciós potenciál generálása – membrán depolarizáció – összegzés – akciós potenciál küszöb – regenerálódó akciós potenciál

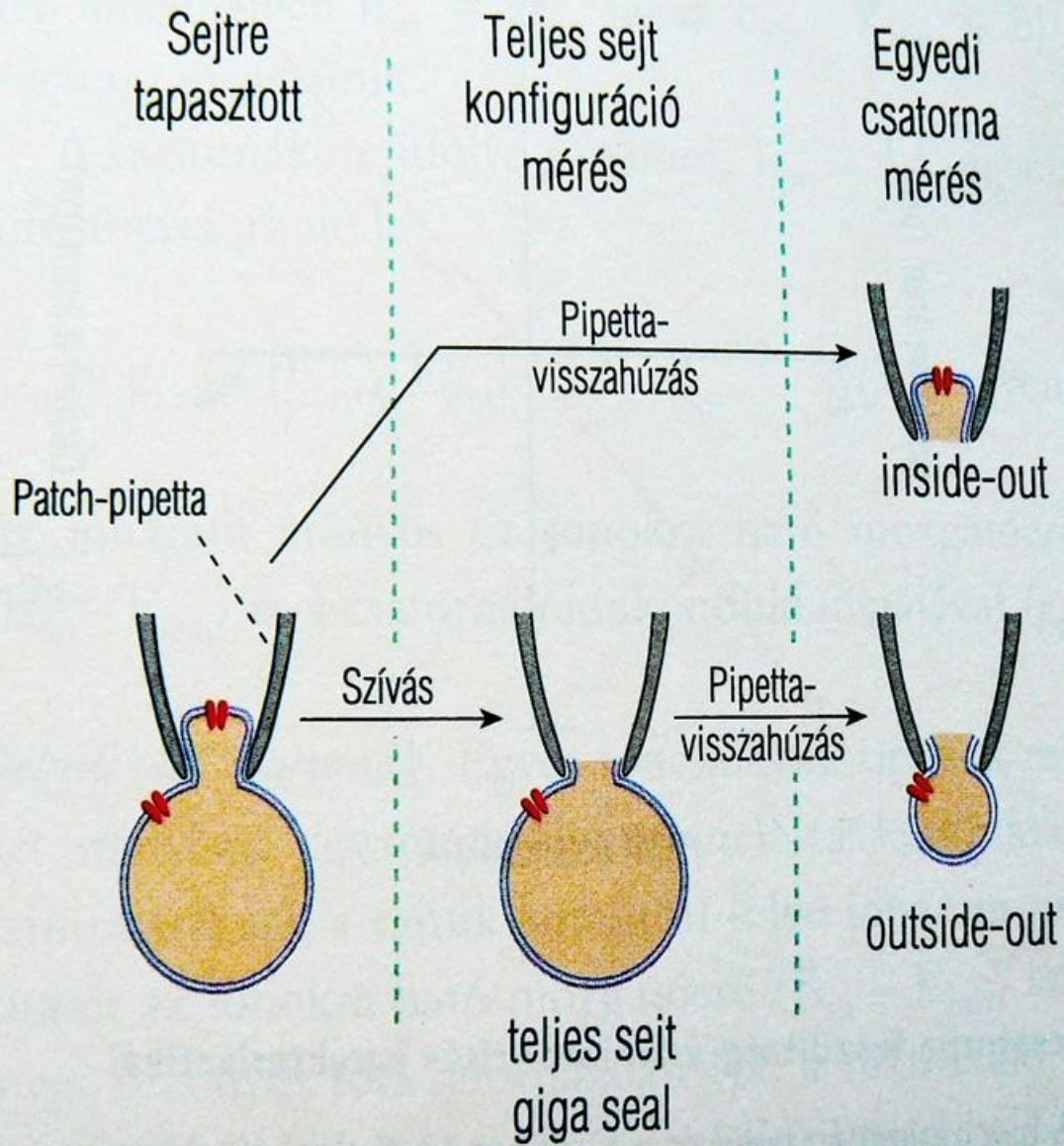
$$V(x) = V_0 e^{-x/\lambda}$$

Published as:
Carnevale, N.T., Tsai, K.Y., Claiborne, B.J., and Brown, T.H.. The electrotonic transformation: a tool for relating neuronal form to function. In: *Advances in Neural Information Processing Systems*, vol. 7, eds. Tesauro, G., Touretzky, D.S., and Leen, T.K.. MIT Press, Cambridge, MA, 1995, pp. 69–76.



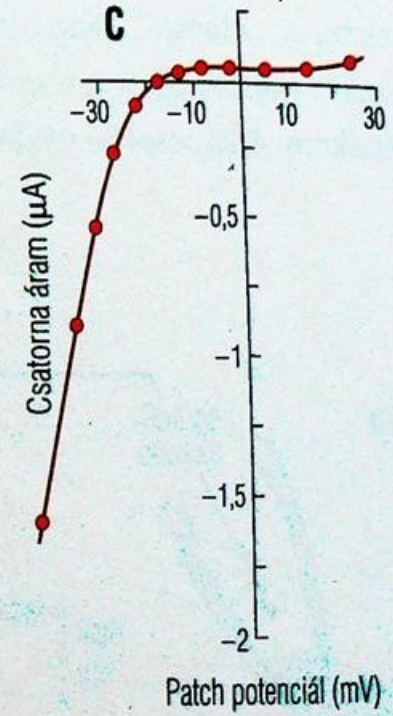
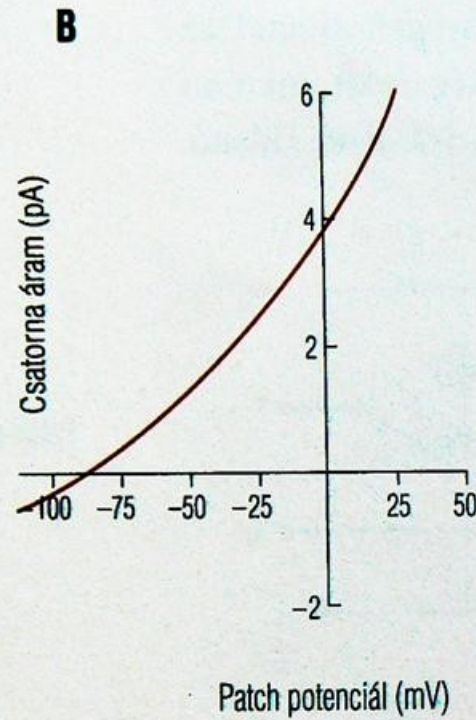
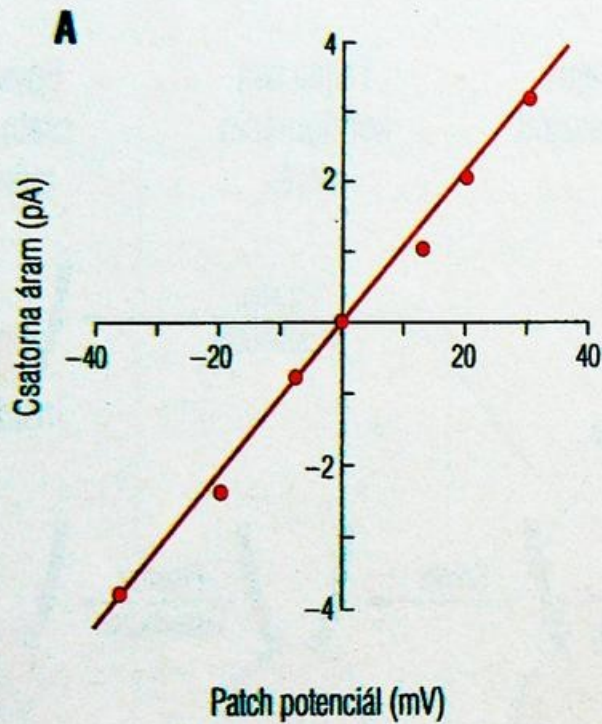
3-1. ábra

A „patch-clamp” regisztrálás elve



3-2. ábra

A „patch-clamp” regisztrálás különböző konfigurációi



3-4. ábra

K⁺-csatorna feszültség-áramintenzitás karakterisztikái

A) A patch-pipettán belül és a fürdőben lévő oldat K⁺-koncentrációi azonosak

B) A patch-pipettán belüli K⁺-koncentráció megfelel az intracelluláris, a fürdő K⁺-koncentrációja az extracelluláris K⁺-koncentrációnak. Az áramintenzitás a K⁺-ok egyensúlyi potenciálja mellett válik zérussá

C) Befelé rektifikáló K⁺-csatorna feszültség-áramintenzitás karakterisztikája

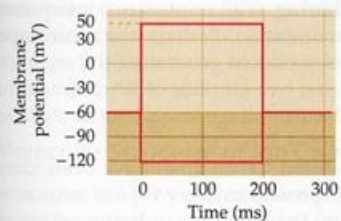
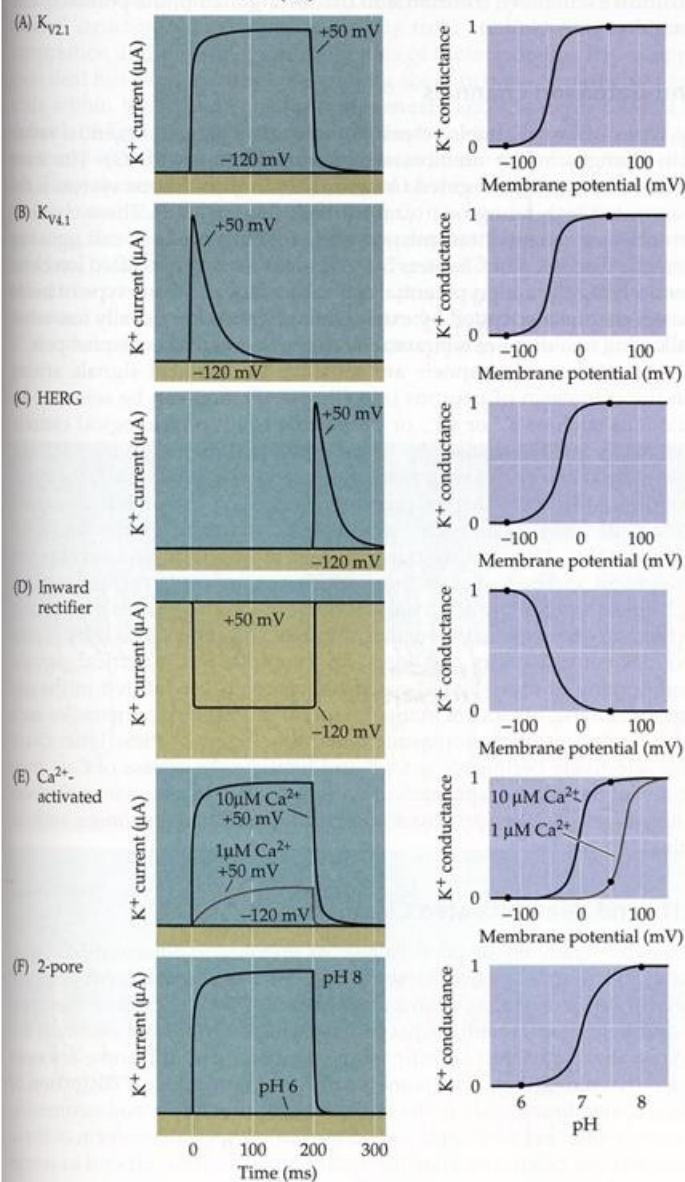
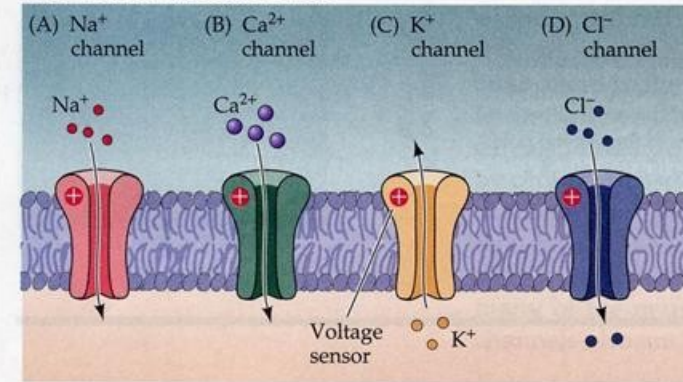


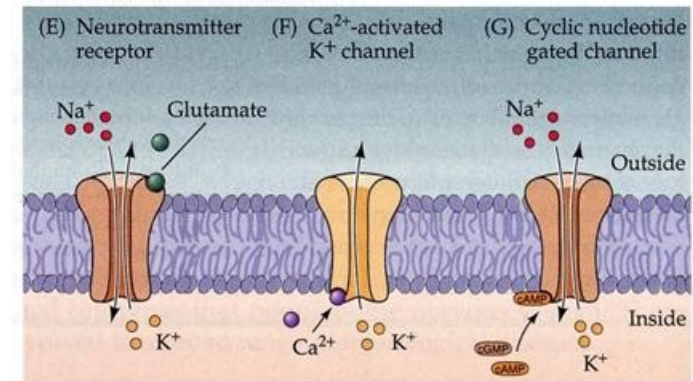
Figure 4.5 Diverse properties of K^+ channels. Different types of K^+ channels were expressed in *Xenopus* oocytes (see Box B), and the voltage clamp method was used to change the membrane potential (top) and measure the resulting currents flowing through each type of channel. These K^+ channels vary markedly in their gating properties, as evident in their currents (left) and conductances (right). (A) K_{V21} channels show little inactivation and are closely related to the delayed rectifier K^+ channels involved in action potential repolarization. (B) K_{V41} channels inactivate during a depolarization. (C) HERG channels inactivate so rapidly that current flows only when inactivation is rapidly removed at the end of a depolarization. (D) Inward rectifying K^+ channels allow more K^+ current to flow at hyperpolarized potentials than at depolarized potentials. (E) Ca^{2+} -activated K^+ channels open in response to intracellular Ca^{2+} ions and, in some cases, membrane depolarization. (F) K^+ channels with two pores usually respond to chemical signals, such as pH, rather than changes in membrane potential.



VOLTAGE-GATED CHANNELS

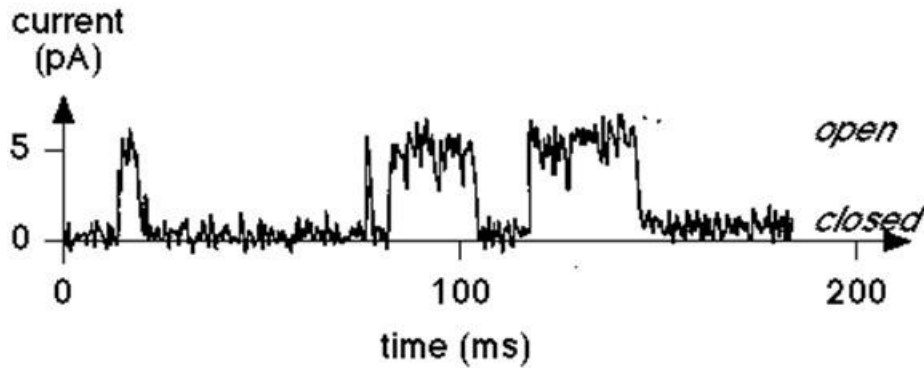


LIGAND-GATED CHANNELS

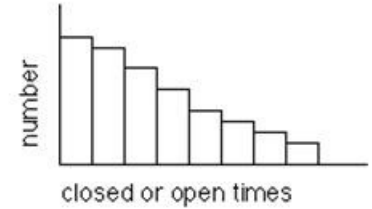


Ion csatornák feszültségfüggése és dinamikája

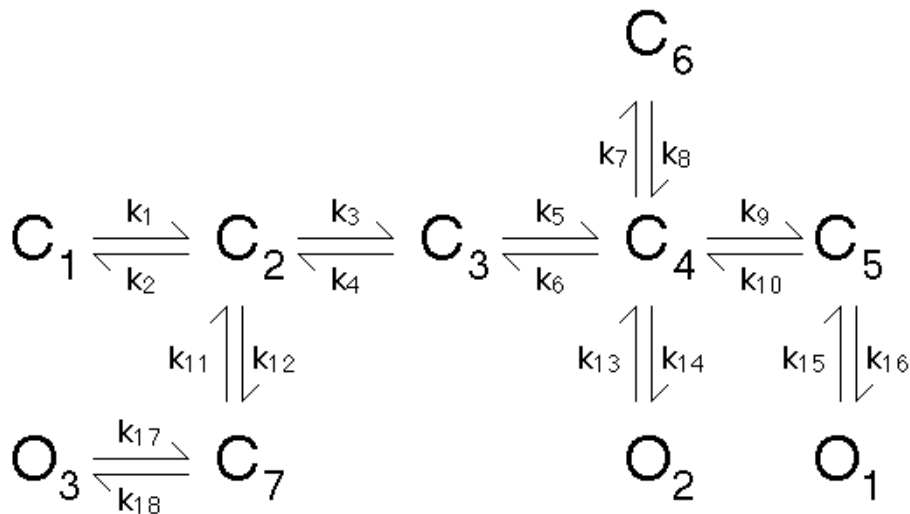
Patch Clamp



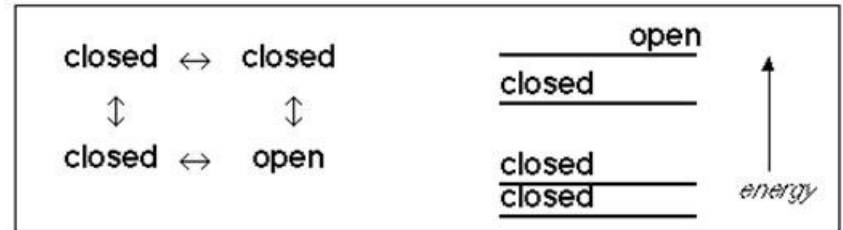
Probability Density Function (PDF) of the Closed and Open Durations



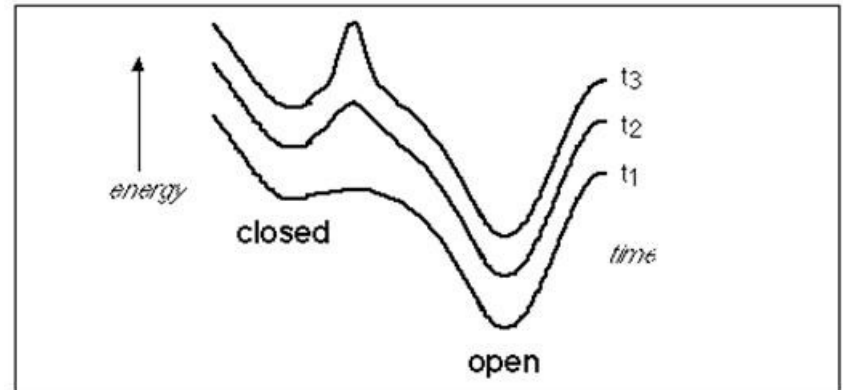
Kinetic Diagram



Energy Level Model:



Dynamical Interpretation:



Ioncsatornák fiziológiai tulajdonságai

Ioncsatornák membránon átívelő fehérjék, amelyek egy vízzel töltött csatornát hoznak létre

Szelektíven áteresztőek a különböző ionokra.

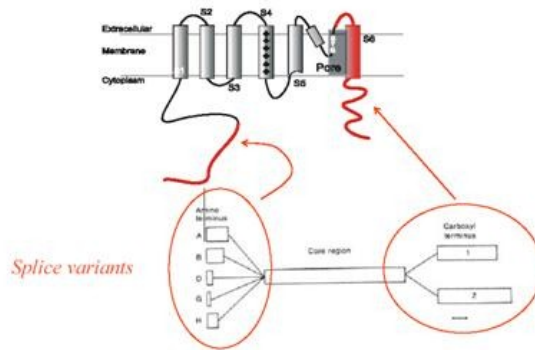
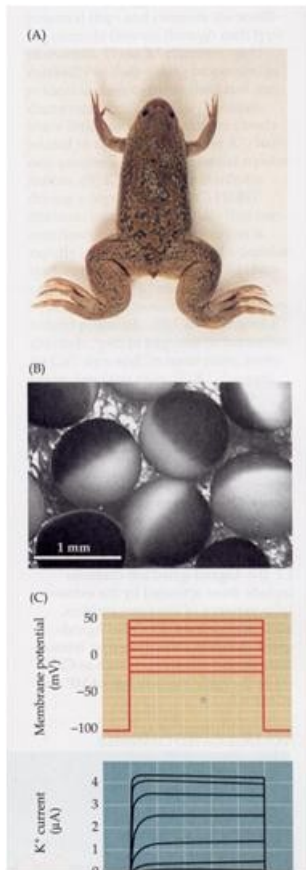
A csatornák nyitási valószínűségét meghatározhatja:

- Membrán potenciál
- Neurotranszmitterek
- Intracelluláris másodlagos hírvivők
- Mechanikus stimulus (fény, pH..)
- Hőmérséklet
- Más hatások (foszforiláció, oxidáció, intracelluláris ionok, etc...)
- Ion csatornák aktivációja és inaktivációja időfüggő dinamikus folyamat
- Ioncsatornák nagy fehérjék számos konformációs állapottal
- Ezeknek az állapotok mérése: single channel patch clamp

Ioncsatornák vizsgálata

1. Expresszáltatás

Xenopus Oocyte or Chinese Hamster Ovary Cell



2. Szekvenálás

<http://www.acsu.buffalo.edu/~moralesm/Discovery%20and%20Methods.pdf>

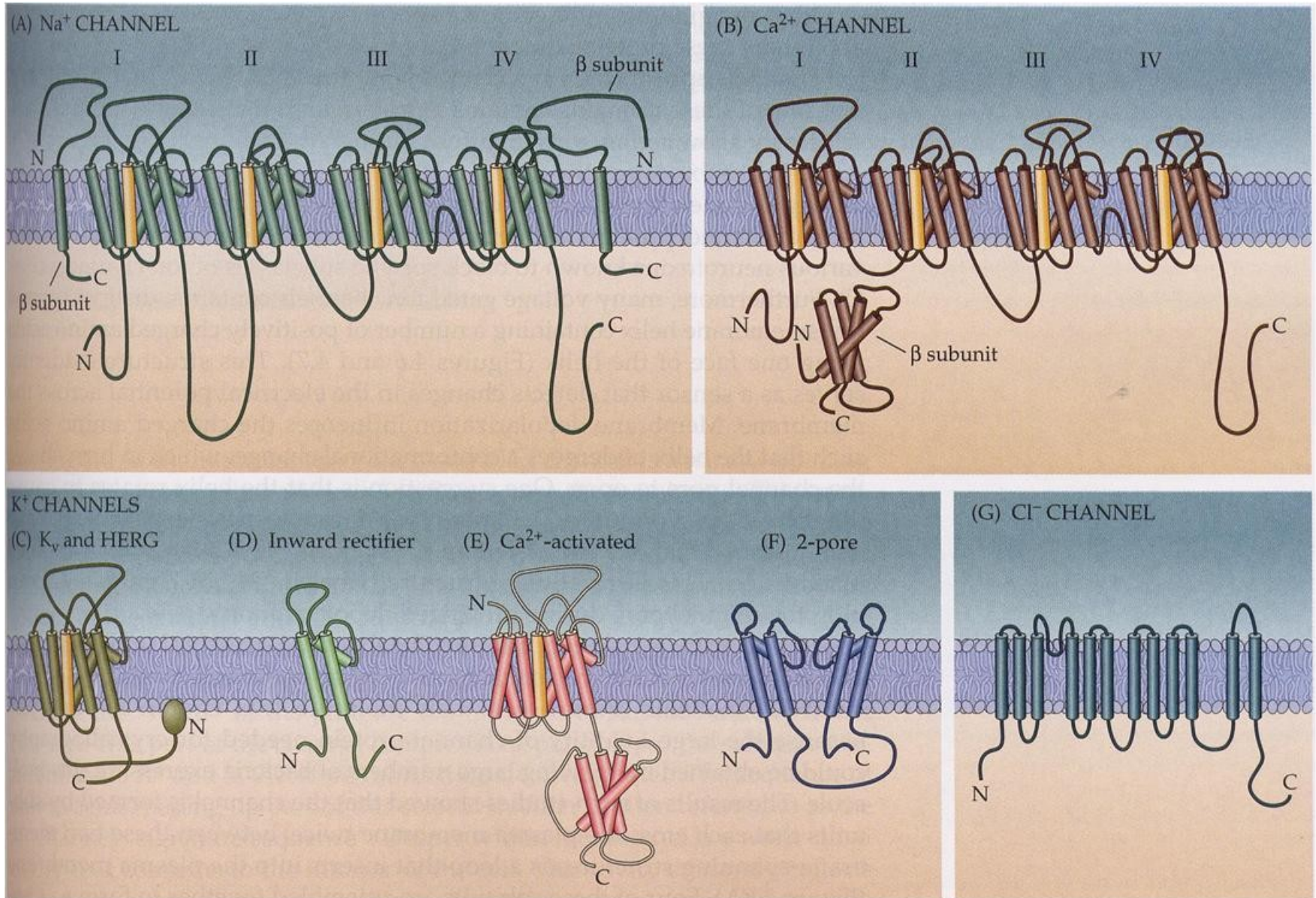
3. Mutációs analízis: Struktúra – Funkció összefüggések

4. Krisztallográfia

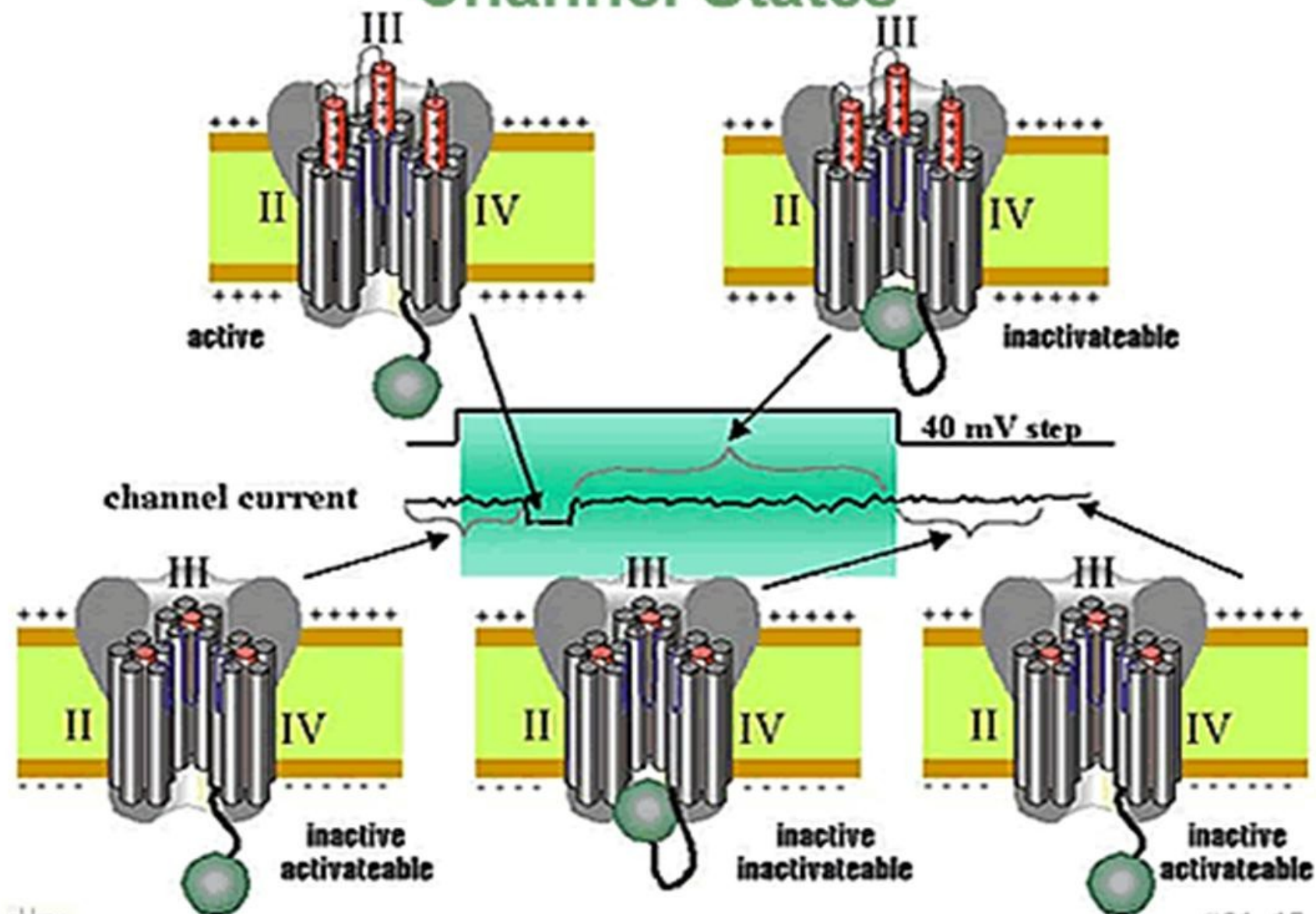
5. Farmakológia

6. Elektrofiziológia

Ioncsatornák struktúrája



Channel States



Crystal structure and mechanism of a calcium-gated potassium channel

Youxing Jiang, Alice Lee, Jayun Chen, Martine Cadene, Brian T. Chait & Roderick MacKinnon

Howard Hughes Medical Institute, Laboratory of Molecular Neurobiology and Biophysics and Laboratory of Mass Spectrometry and Gaseous Ion Chemistry, Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

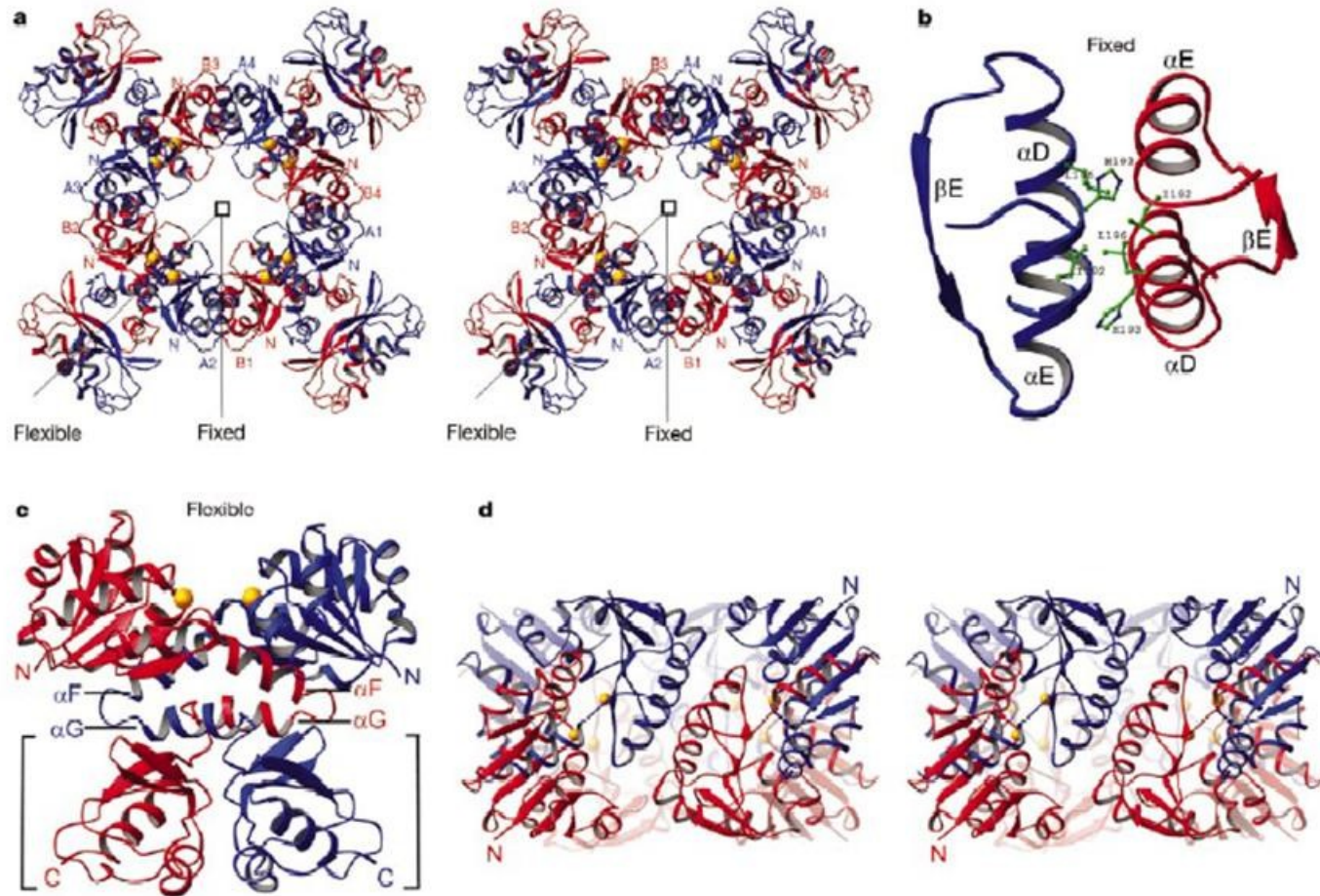


Figure 6 Structure of the gating ring. **a**, Stereo diagram of the gating ring viewed down the four-fold axis (square). Eight RCK domains are divided into two groups, A1–A4 (blue) and B1–B4 (red), with N termini labelled (N). Viewed from the membrane, blue domains would be attached to the pore via a continuous polypeptide chain and red domains assembled from solution. Fixed and flexible dimer interfaces hold the ring together. **b**, Helices αD and αE form the fixed interface. Several amino acids conserved as

hydrophobic or aromatic (Ile 192, His 193 and Leu 196) are shown. **c**, C-terminal subdomains (brackets) and helices αF and αG form the flexible interface. A cleft between two RCK domains creates a ligand-binding site with Ca^{2+} bound at the base (yellow spheres). **d**, Stereo diagram of the gating ring viewed from the side after removing the subdomains.

Ion szelektivitás

The Structure of the Potassium Channel: Molecular Basis of K⁺ Conduction and Selectivity

Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner, Anling Kuo, Jacqueline M. Gulbis, Steven L. Cohen, Brian T. Chait, Roderick MacKinnon*

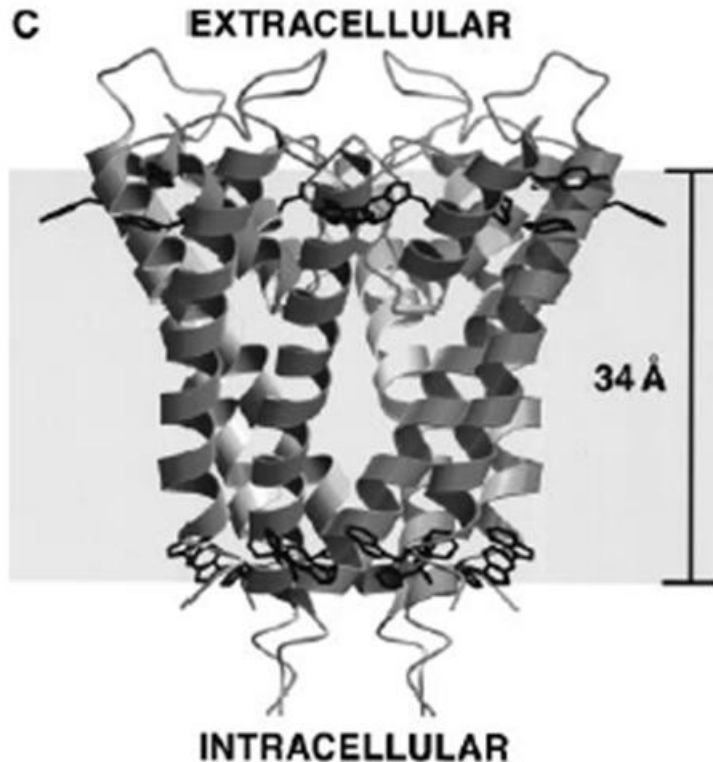
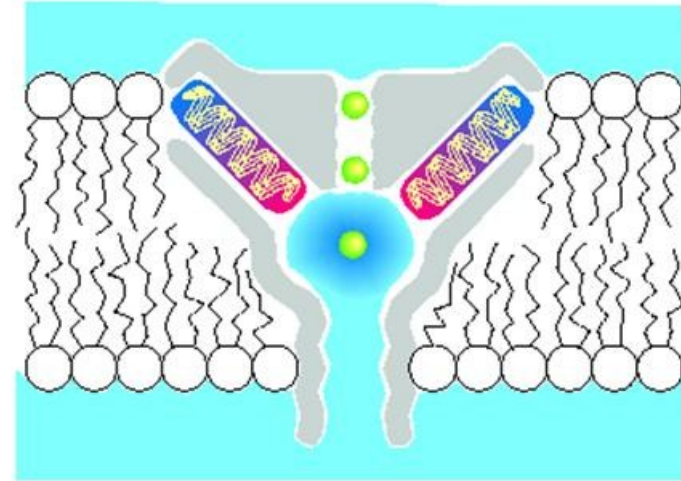


Fig. 7. Two mechanisms by which the K⁺ channel stabilizes a cation in the middle of the membrane. First, a large aqueous cavity stabilizes an ion (green) in the otherwise hydrophobic membrane interior. Second, oriented helices point their partial negative charge (carboxyl end, red) towards the cavity where a cation is located.



- In a series of crystal structures, MacKinnon saw the ions surrounded by water molecules just before they entered the ion filter, became stripped of their water and allowed to pass through the filter, and then met the water on the other side of the filter. MacKinnon also explained why the filters are selective: for each ion, the distance to the oxygen atoms in the ion filter is the same as in its water solution, therefore the smaller sodium ion cannot be freed from its water and pass through a larger potassium ion filter.

Mutációs analízis

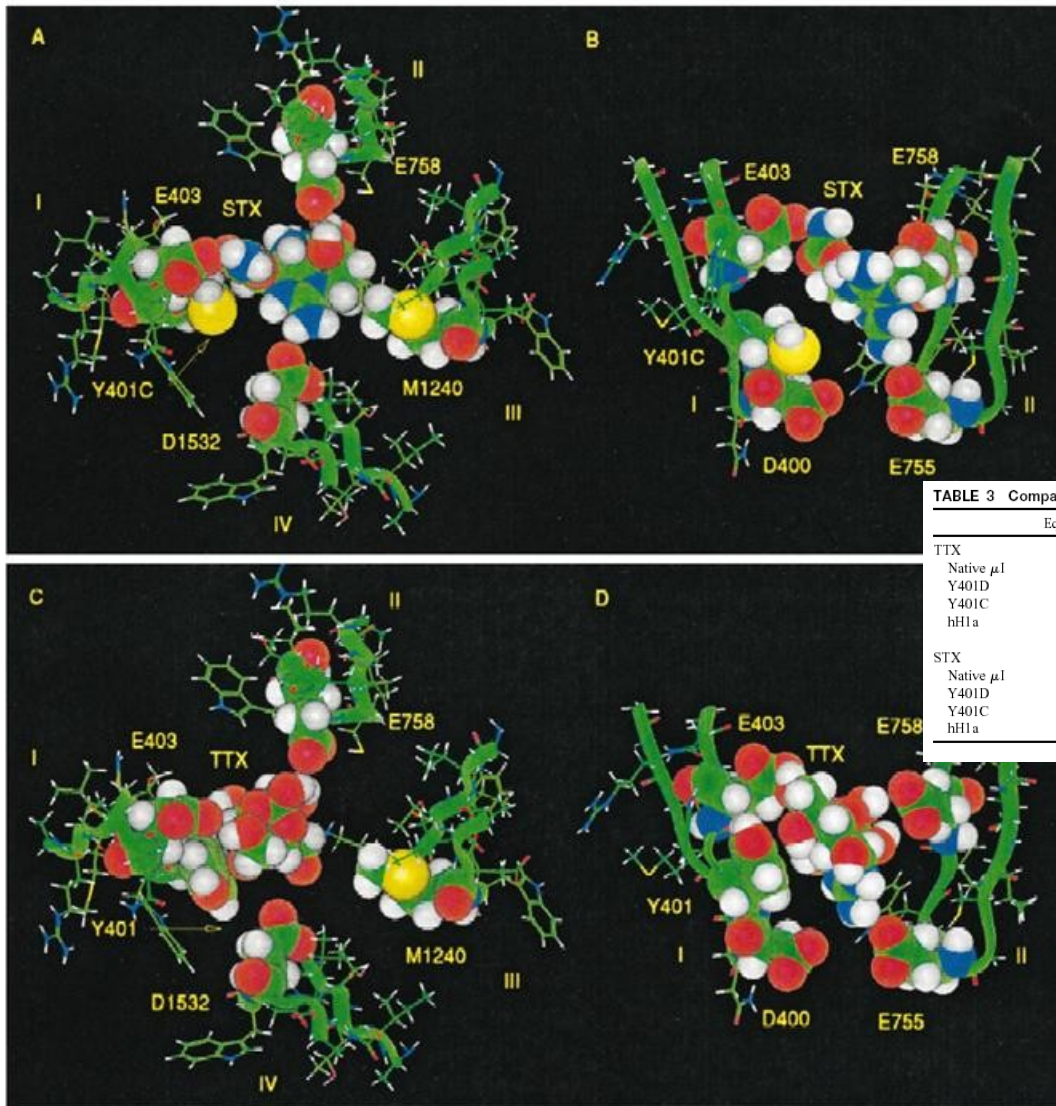


TABLE 3 Comparison of IC_{50} s and kinetic parameters in $\mu 1$, Tyr⁴⁰¹ mutants, and hH1a channels

	Equilibrium IC_{50} (μM)	n	k_{on} ($M^{-1} s^{-1}$)	n	k_{off} (s^{-1})	n	IC_{50} ratio
TTX							
Native $\mu 1$	0.036 ± 0.006	10	$3.53 \times 10^5 \pm 5.66 \times 10^4$	9	$1.02 \times 10^{-2} \pm 1.82 \times 10^{-3}$	9	1
Y401D	171 ± 15	9	$3.03 \times 10^2 \pm 2.49 \times 10^2$	3	$1.42 \times 10^{-2} \pm 5.36 \times 10^{-3}$	3	4800
Y401C	80 ± 15	6	$8.77 \times 10^2 \pm 2.29 \times 10^2$	4	$2.60 \times 10^{-2} \pm 7.54 \times 10^{-4}$	4	2249
hH1a	1.5 ± 0.2	4	$4.41 \times 10^3 \pm 8.61 \times 10^2$	4	$2.11 \times 10^{-2} \pm 7.49 \times 10^{-4}$	4	41
STX							
Native $\mu 1$	3.1 ± 0.4	10	$5.13 \times 10^6 \pm 3.06 \times 10^6$	4	$1.34 \times 10^{-2} \pm 1.74 \times 10^{-3}$	4	1
Y401D	169 ± 14	10	$2.41 \times 10^4 \pm 6.23 \times 10^3$	6	$7.10 \times 10^{-3} \pm 5.14 \times 10^{-4}$	6	55
Y401C	314 ± 12	5	$6.51 \times 10^4 \pm 1.43 \times 10^4$	4	$2.18 \times 10^{-2} \pm 3.44 \times 10^{-3}$	4	102
hH1a	149 ± 18	6	$9.50 \times 10^4 \pm 4.35 \times 10^4$	5	$9.09 \times 10^{-3} \pm 5.19 \times 10^{-4}$	5	48

FIGURE 2 Proposed orientations of STX and TTX in a model of the $\mu 1$ Na⁺ channel outer vestibule (Lipkind and Fozzard, 1994). The P loops are formed by β -hairpins, and their backbones are indicated by green ribbons. (A) Orientation of STX relative to domains I–IV, as viewed from the extracellular side down the axis of ion permeation, with the mutation Y401C present in domain I. The 1,2,3 guanidinium group is close to Asp¹⁵³² of domain IV, and the C12 diol interacts with Glu⁷⁵⁸ of domain II. In this orientation, the carbamoyl group of STX is near Glu⁴⁰³. (B) Orientation of STX relative to domains I and II, viewed in a plane parallel to the membrane, showing the interaction of the 7,8,9 guanidinium with Glu⁷⁵⁵ and Asp⁴⁰⁰. Because of its interaction with the outer ring, STX is held away from the 401 site, leaving room for sulfhydryl reagents to react with Cys in this position in the heart isoform. (C) Top view of the orientation of TTX with domains I–IV, showing the close packing of TTX with the domain I P loop. This packing would tend to prevent access of sulfhydryl reagents to the 401 site. (D) Side view of the orientation of TTX relative to domains I and II. The C4-C5-C7-C8 surface of TTX is closely packed with Tyr⁴⁰¹. Carbon, nitrogen, oxygen, and hydrogen are green, blue, red, and white, respectively.

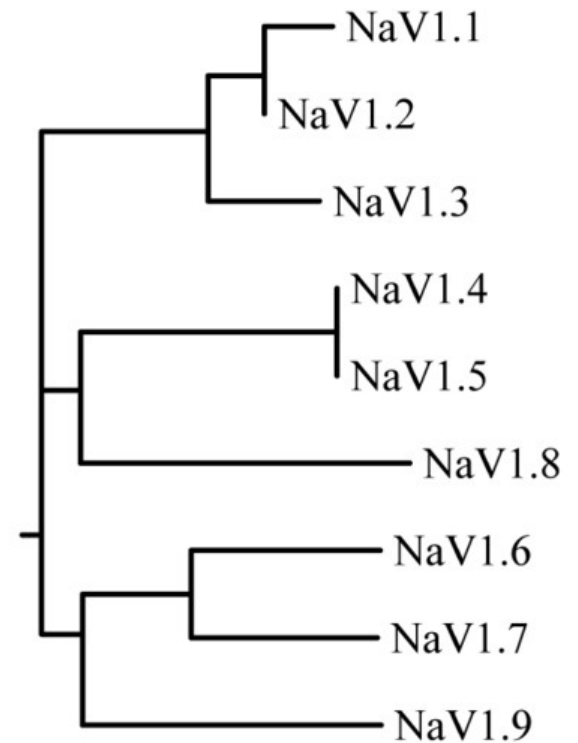
Ioncsatornák diverzitása

- Nátrium csatorna: 9 alfa subunit subtypes $\text{Na}_v1.1 - 1.9$ plus Na_x . Alternative splicing, 4 beta subunits
- Kálium csatorna: Most diverse class of ion channels. Consists of 4 subunits (homomers or heteromers). $\text{K}_v1.1 - 1.9$; $\text{K}_v2.1 - 2.2$; $\text{K}_v3.1 - 3.4$; Alternative splicing.

Table 5.1 Voltage-gated calcium channel types

Channel Type	Former Nomenclature	Voltage-dependence	
Cav 1.1	α_{1S}	high-threshold (> -10 mV)	
Cav 1.2	α_{1C}		
Cav 1.3	α_{1D}		
Cav 1.4	α_{1F}		
Cav 2.1	α_{1A}	P/Q-type	high-threshold (> -20 mV)
Cav 2.2	α_{1B}	N-type (13pS)	
Cav 2.3	α_{1E}	R-type	
Cav 3.1	α_{1G}		Low-threshold (> -70 mV)
Cav 3.2	α_{1H}	T-type (8pS)	
Cav 3.3	α_{1I}		

Protein name	Gene name	Auxiliary subunits	Expression profile	Associated human channelopathies
Na _v 1.1	SCN1A	β1,β2,β3,β4	Central neurons and cardiac myocytes	Inherited febrile epilepsy , GEFS and myoclonic epilepsy
Na _v 1.2	SCN2A	β1,β2,β3,β4	Central neurons	inherited febrile seizures and epilepsy
Na _v 1.3	SCN3A	β1,β3	Central neurons and cardiac myocytes	none known
Na _v 1.4	SCN4A	β1	Skeletal muscle	hyperkalemic periodic paralysis , Paramyotonia congenita , and potassium-aggravated myotonia
Na _v 1.5	SCN5A	β1,β2,β3,β4	Central neurons	Long QT Syndrome , Brugada syndrome , and idiopathic ventricular fibrillation
Na _v 1.6	SCN8A	β1,β2	Central neurons, dorsal root ganglia, peripheral neurons	none known
Na _v 1.7	SCN9A	β1,β2	Dorsal root ganglia, sympathetic neurons, Schwann cells, and neuroendocrine cells	inherited erythromelalgia
Na _v 1.8	SCN10A	unknown	Dorsal root ganglia	none known
Na _v 1.9	SCN11A	unknown	Dorsal root ganglia	none known



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From Ionic Currents to Molecular Mechanisms: The Structure and Function of Voltage-Gated Sodium Channels

Review

Ioncsatornák farmakológiája

TABLE Examples of channel toxins

Function	Na channel	K channel	Ca channel
Blockers	Tetrodotoxin	Tetraethylammonium	Verapamil
	Saxitoxin	Charybtotoxin	Diltiazem
	Chlorpromazine	4-Aminopyridine	alpha-conotoxin
	local anesthetics	local anesthetics	
Activators	Batrachotoxin	Pinacidil	SDZ(+)-202791
	Veratridine		BayK 8644

Channelopathies / Ion channel related diseases

Ion channel diseases

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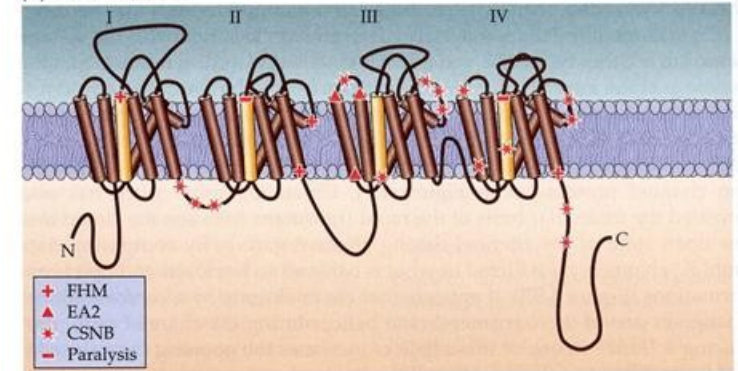
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Table 1. Known ion channel diseases

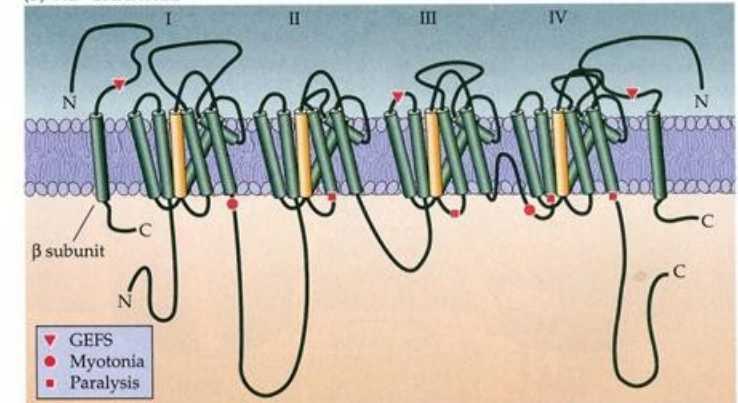
Channel	Gene	Channel-forming unit/ligand	OMIM	Disease
Cation channels:				
CHRNA1/ACHRA	<i>CHRNA1</i>	α , ACh	100690	Myasthenia congenita
CHRNA4	<i>CHRNA4</i>	α , ACh	118504	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	<i>CHRNB2</i>	β , ACh	118507	Autosomal dominant nocturnal frontal lobe epilepsy
Polycystin-2	<i>PKD2</i>	α	173910	Autosomal dominant polycystic kidney disease (ADPKD)
CNGA3	<i>CNGA3</i>	α , cGMP	600053	Achromatopsia 2 (color blindness)
CNGB1	<i>CNGB1</i>	β , cGMP	600724	Autosomal recessive retinitis pigmentosa
CNGB3	<i>CNGB3</i>	β , cGMP	605080	Achromatopsia 3
Sodium channels:				
Na _v 1.1	<i>SCN1A</i>	α	182389	Generalized epilepsy with febrile seizures (GEFS+)
Na _v 1.2	<i>SCN2A</i>	α	182390	Generalized epilepsy with febrile and afebrile seizures
Na _v 1.4	<i>SCN4A</i>	α	603967	Paramyotonia congenita, potassium aggressive myotonia, hyperkalemic periodic paralysis
Na _v 1.5	<i>SCN5A</i>	α	600163	Long-QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)
SCN1B	<i>SCN1B</i>	β	600235	Generalized epilepsy with febrile seizures (GEFS+)
ENaC α	<i>SCNNA1</i>	α	600228	Pseudohypaldosteronism type 1 (PHA1)
ENaC β	<i>SCNN1B</i>	β	600760	PHA1, Liddle syndrome (dominant hypertension)
ENaC γ	<i>SCNN1G</i>	γ	600761	PHA1, Liddle syndrome
Potassium channels:				
K _v 1.1	<i>KCNA1</i>	α	176260	Episodic ataxia with myokymia
KCNQ1/K _v LQT1	<i>KCNQ1</i>	α	192500	Autosomal dominant long-QT syndrome (Romano-Ward) Autosomal recessive long-QT syndrome with deafness (Jervell-Lange-Nielsen)
KCNQ2	<i>KCNQ2</i>	α	602235	BFNC (epilepsy), also with myokymia
KCNQ3	<i>KCNQ3</i>	α	602232	BFNC (epilepsy)
KCNQ4	<i>KCNQ4</i>	α	603537	DFNA2 (dominant hearing loss)
HERG/KCNH2	<i>KCNH2</i>	α	152427	Long-QT syndrome
Kir1.1/ROMK	<i>KCNJ1</i>	α	600359	Barter syndrome (renal salt loss, hypokalemic alkalosis)
Kir2.1/IRK/KCNJ2	<i>KCNJ2</i>	α	600681	Long-QT syndrome with dysmorphic features (Andersen syndrome)
Kir6.2/K _{ATP}	<i>KCNJ11</i>	α	600937	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
SUR1	<i>SUR1</i>	β	600509	PHHI
KCNE1/MinK/ISK	<i>KCNE1</i>	β	176261	Autosomal dominant long-QT syndrome (Romano-Ward) Autosomal recessive long-QT syndrome with deafness (Jervell-Lange-Nielsen)
KCNE2/MiRP1	<i>KCNE2</i>	β	603796	Long-QT syndrome
KCNE3/MiRP2	<i>KCNE3</i>	β	604433	Periodic paralysis
Calcium channels:				
Ca _v 1.1	<i>CACNA1S</i>	α	114208	Hypokalemic periodic paralysis, malignant hyperthermia
Ca _v 1.4	<i>CACNA1F</i>	α	300110	X-linked congenital stationary night blindness
Ca _v 2.1	<i>CACNA1A</i>	α	601011	Familial hemiplegic migraine, episodic ataxia, spinocerebellar ataxia type 6
RyR1	<i>RYR1</i>	α	180901	Malignant hyperthermia, central core disease
RyR2	<i>RYR2</i>	α	180902	Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia type 2
Chloride channels:				
CFTR	<i>ABCC7</i>	α	602421	Cystic fibrosis, congenital bilateral aplasia of vas deferens
ClC-1	<i>CLCN1</i>	α	118425	Autosomal recessive (Becker) or dominant (Thomsen) myotonia
ClC-5	<i>CLCN5</i>	α	300008	Dent's disease (X-linked proteinuria and kidney stones)
ClC-7	<i>CLCN7</i>	α	602727	Osteopetrosis (recessive or dominant)
ClC-Kb	<i>CLCNKB</i>	α	602023	Barter syndrome type III
Barttin	<i>BSND</i>	β	606412	Barter syndrome type IV (associated with sensorineural deafness)
GLRA1	<i>GLRA1</i>	α , glycine	138491	Hyperekplexia (startle disease)
GABA α 1	<i>GABRA1</i>	α , GABA	137160	Juvenile myoclonus epilepsy
GABA γ 2	<i>GABRG2</i>	γ , GABA	137164	Epilepsy
Gap junction channels:				
Cx26	<i>GJB2</i>		121011	DFNA3 (autosomal dominant hearing loss) DFNB1 (autosomal recessive hearing loss)
Cx30	<i>GJB4</i>		605425	DFNA3
Cx31	<i>GJB3</i>		603324	DFNA2
Cx32	<i>GJB1</i>		304040	CMTX (X-linked Charcot-Marie-Tooth neuropathy)

The third column classifies channel proteins into α , β , and γ subunits, where α subunits are always directly involved in pore formation. Several β subunits are only accessory (i.e. do not form pores), as is the case, for example, with SCN1B and barttin. Others (e.g. of ENaC and GABA receptors) participate in pore formation. For ligand-gated channels, the ligand is given. Note that GABA and glycine act from the extracellular side, whereas cGMP is an intracellular messenger.

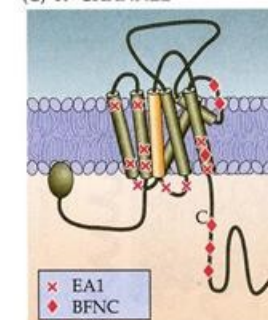
(A) Ca²⁺ CHANNEL



(B) Na⁺ CHANNEL



(C) K⁺ CHANNEL



(D) Cl⁻ CHANNEL

