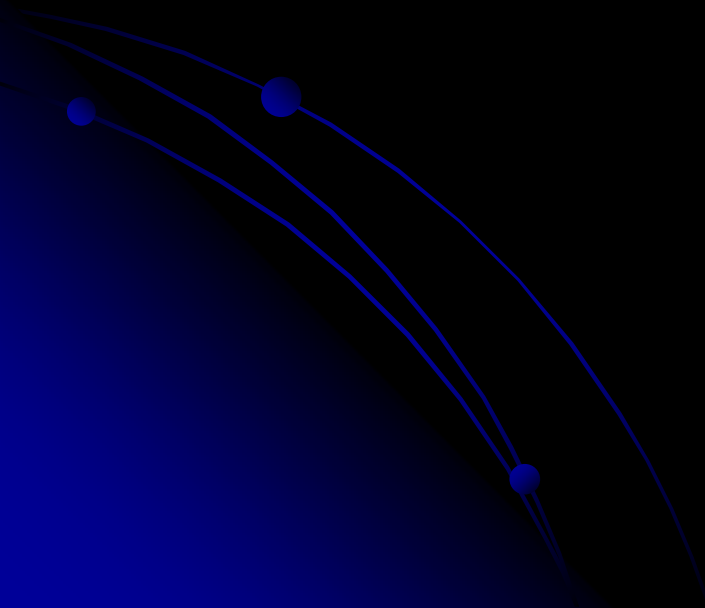


Kapitoly z neurofyziologie smyslů



Neurofyzologie

Ambice: Pochopení psychiky
člověka a jejích poruch.

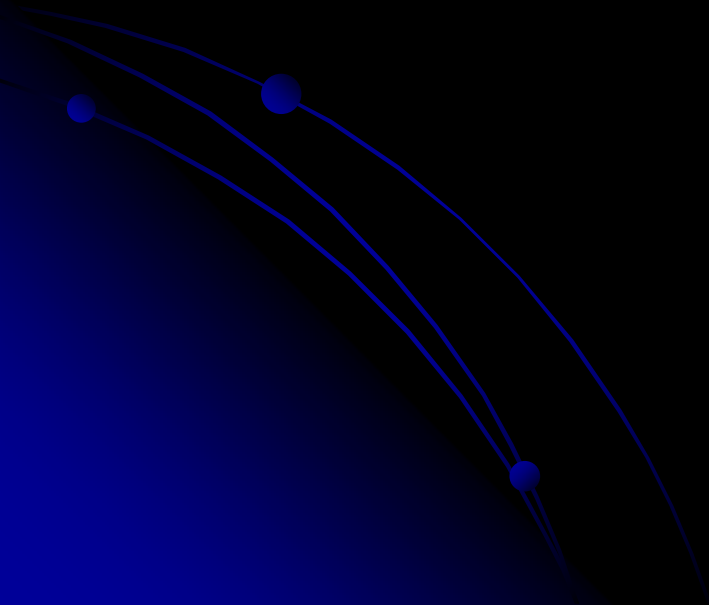


Bouřlivý rozvoj:

Molekulární neurovědy

Neurofarmakologie

Zobrazovací metody



Nobel prices related to neuroscience

1901 Wilhelm Conrad Röntgen (Germany) "in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him"

1904 Ivan Petrovich Pavlov (Russia) "in recognition of his work on the physiology of digestion, through which knowledge on vital aspects of the subject has been transformed and enlarged"

1906 Camillo Golgi (Italy) and Santiago Ramón y Cajal (Spain) "in recognition of their work on the structure of the nervous system"

1909 Emil Theodor Kocher (Switzerland) "for his work on the physiology, pathology and surgery of the thyroid gland"

1914 Robert Bárány (Vienna) "for his work on the physiology and pathology of the vestibular apparatus"

1920 Chemistry: Walther Hermann Nernst (Germany) "in recognition of his work in thermochemistry"

1932 Sir Charles Scott Sherrington (Great Britain) and Edgar Douglas Adrian (Great Britain) "for their discoveries regarding the functions of neurons"

- 1935 Hans Spemann (Germany) "for his discovery of the organizer effect in embryonic development"
- 1936 Sir Henry Hallett Dale (Great Britain) and Otto Loewi (Great Britain) "for their discoveries relating to chemical transmission of nerve impulses"
- 1944 Joseph Erlanger (USA) Herbert Spencer Gasser (USA) "for their discoveries relating to the highly differentiated functions of single nerve fibres"
- 1949 Walter Rudolf Hess "for his discovery of the functional organization of the interbrain as a coordinator of the activities of the internal organs"
- 1949 Antonio Caetano de Abreu Freire Egas Moniz "for his discovery of the therapeutic value of leucotomy in certain psychoses"
- 1952 Physics: Felix Bloch (USA) and Edward Mills Purcell (USA) "for their development of new methods for nuclear magnetic precision measurements and discoveries in connection therewith"
- 1961 Georg von Békésy (USA/Hungary)"for his discoveries of the physical mechanism of stimulation within the cochlea"

- 1962 Francis Harry Compton Crick (Great Britain), James Dewey Watson (USA) and Maurice Hugh Frederick Wilkins (Great Britain) "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"
- 1963 Sir John Carew Eccles (Australia), Alan Lloyd Hodgkin and Andrew Fielding Huxley (Great Britain) "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"
- 1967 Ragnar Granit (Sweden/Finland), Haldan Keffer Hartline (USA) and George Wald (USA) "for their discoveries concerning the primary physiological and chemical visual processes in the eye"
- Robert W. Holley (USA), Har Gobind Khorana (USA) and Marshall W. Nirenberg (USA) "for their interpretation of the genetic code and its function in protein synthesis"
- 1970 Sir Bernard Katz (Great Britain), Ulf von Euler (Sweden) and Julius Axelrod (USA) "for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation"

1972 Physics: John Bardeen (USA), Leon Neil Cooper (USA) and John Robert Schrieffer (USA) "for their jointly developed theory of superconductivity, usually called the BCS-theory" [Professor Cooper was Director of Brown University's Center for Neural Science.]

1973 Karl von Frisch (Germany), Konrad Lorenz (Austria) and Nikolaas Tinbergen (Great Britain) "for their discoveries concerning organization and elicitation of individual and social behaviour patterns"

1973 Physics: Brian David Josephson (Great Britain) "for his theoretical predictions of the properties of a supercurrent through a barrier, in particular those phenomena which are generally known as the Josephson effects"

1976 Baruch S. Blumberg (USA) and D. Carleton Gajdusek (USA) "for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases"

1977 Roger Guillemin and Andrew Schally for their discoveries concerning "the peptide hormone production of the brain"

1977 Rosalyn Yalow for "the development of radioimmunoassays of peptid hormones"

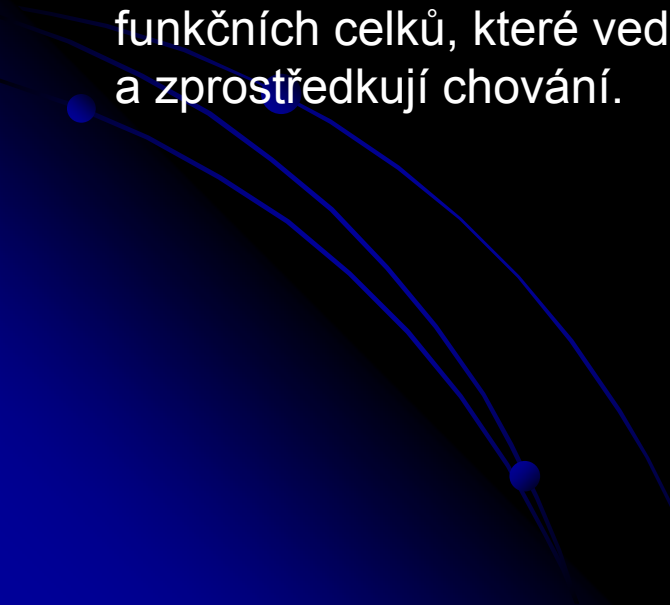
- 1979 Allan M Cormack and Godfrey Newbold Hounsfield for the "development of computer assisted tomography"
- 1981 Roger W. Sperry, for his discoveries concerning "the functional specialization of the cerebral hemispheres"
- 1981 David H. Hubel and Torsten N. Wiesel, for their discoveries concerning "visual system".
- 1986 Stanley Cohen (USA) Rita Levi-Montalcini (Italy/USA)"for their discoveries of growth factors"
- 1991 Erwin Neher (Germany) Bert Sakmann (Germany) "for their discoveries concerning the function of single ion channels in cells"
- 1991 Chemistry: Richard R. Ernst (Switzerland) "for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy"
- 1994 Alfred G. Gilman (USA) Martin Rodbell (USA) "for their discovery of G-proteins and the role of these proteins in signal transduction in cells"
- 1997 Stanley B. Prusiner, in Physiology or Medicine for his discovery of "prions - a new biological principle of infection"

<http://nobelprize.org/medicine/laureates/1981/>

- 1997 Chemistry: Paul D. Boyer (USA) and John E. Walker (Great Britain) "for their elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)"
- 1997 Jens C. Skou (Denmark) "for the first discovery of an ion-transporting enzyme, Na⁺, K⁺-ATPase"
- 1998 Robert F. Furchgott (USA) Louis J. Ignarro (USA) and Ferid Murad (USA) "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system"
- 2000 Arvid Carlsson, Paul Greengard and Eric Kandel for their discoveries concerning "signal transduction in the nervous system"
- 2003 Paul C. Lauterbur Sir Peter Mansfield for their discoveries concerning magnetic resonance imaging
- 2004 Richard Axel, Linda Buck for their discoveries of odorant receptors and the organization of the olfactory system

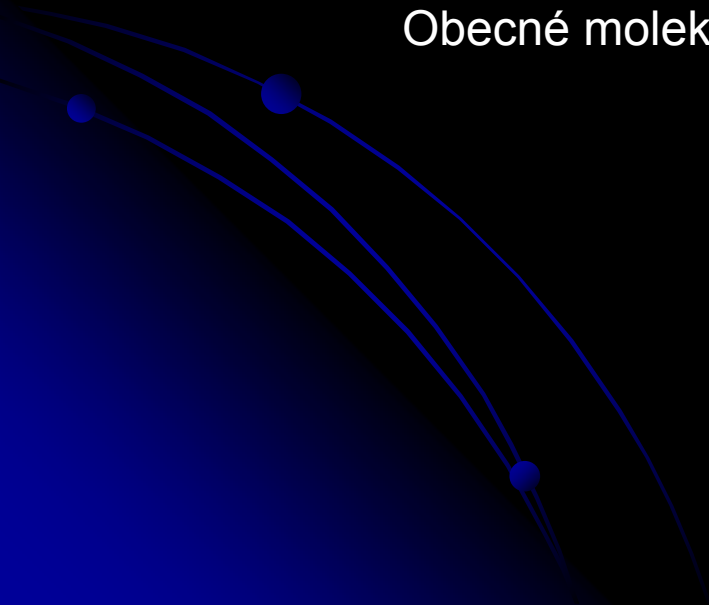
Neurofyzologie

Studium nervových a doprovodných buněk, způsobu jak jsou sestaveny do funkčních celků, které vedou, zpracovávají, ukládají informaci a zprostředkují chování.



Smyslová neurofyzologie

Vrátka do vědomí, kontakt s vnějším světem.
Obecné molekulární principy signalizace.



Internet a něco z jeho neomezené nabídky:

<http://www.physpharm.fmd.uwo.ca/undergrad/medsweb/>

<http://entochem.tamu.edu/index.html>

<http://web.neurobio.arizona.edu/gronenberg/nrsc581/index.html>

<http://www.biol.sc.edu/~vogt/courses/neuro/neurobehavior.html>

<http://instruct1.cit.cornell.edu/courses/bionb424/links.htm>

<http://nelson.beckman.uiuc.edu/courses/neuroethol/>

<http://www.blackwellpublishing.com/matthews/default.html>

<http://www.hhmi.org/biointeractive/vlabs/neurophysiology/index.html>

Kapitoly z neurofyzologie smyslů – výběr kapitol

Fyziologie membrán:

- klidový potenciál
- akční potenciál
- iontové kanály
- šíření signálů a synapse

Fyziologie smyslů:

- obecné principy
- čich a chuť
- hmat a sluch
- zrak a další smysly

Psychofyzologie:

- zpracování zrakové informace
- učení a paměť
- chování, neuroetologie

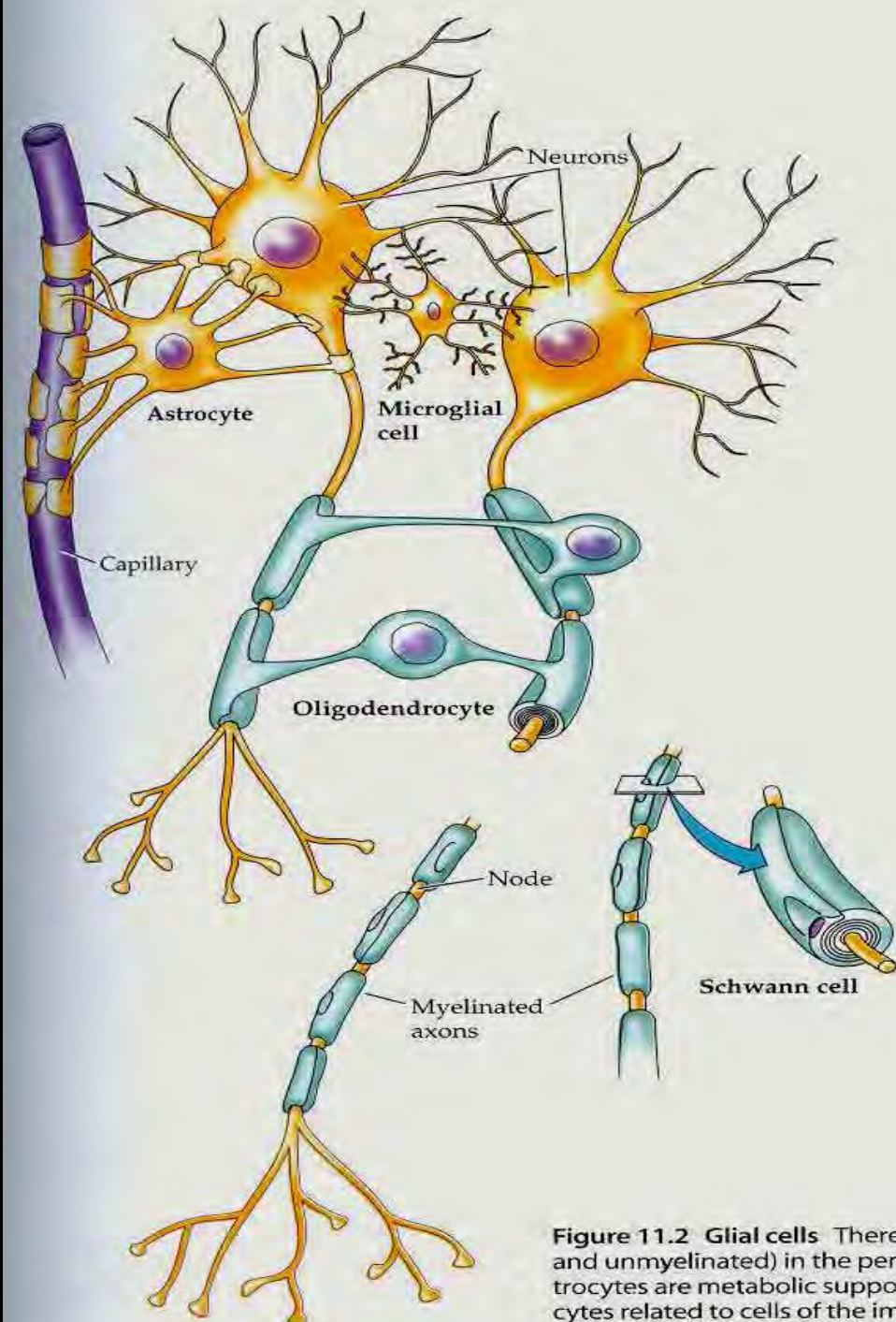
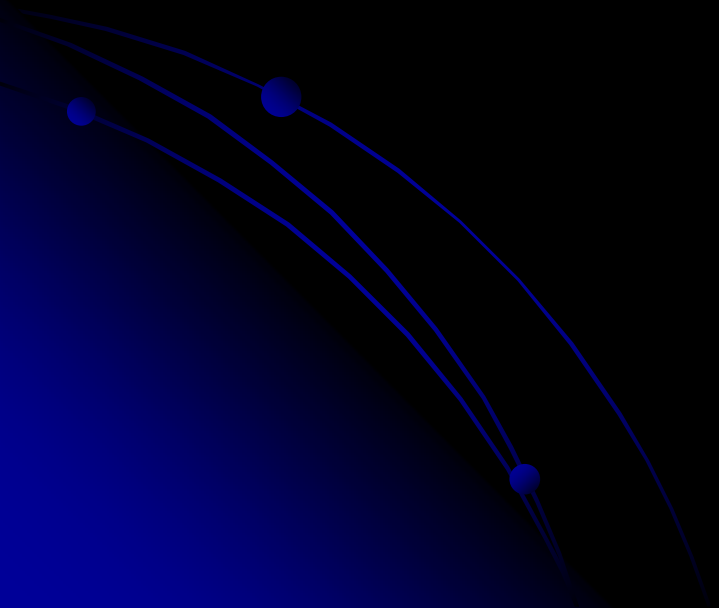
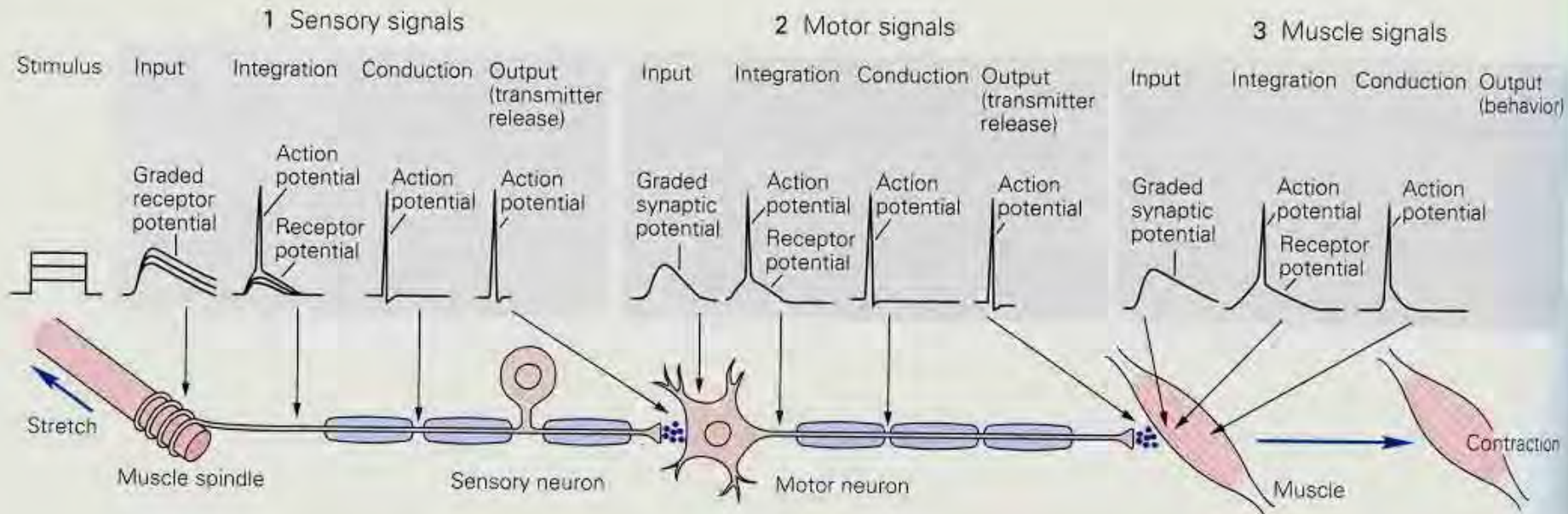


Figure 11.2 Glial cells There are (myelinated and unmyelinated) in the peripheral nervous system. Astrocytes are metabolic support cells, and microglial cells are related to cells of the immune system.

Materiály, prezentace,
návaznosti na předměty,
hodnocení.



Fyziologie nervových membrán: řeč elektrických potenciálů



Předávání a zpracování informací:

elektro - chemická spolupráce



Klidový potenciál

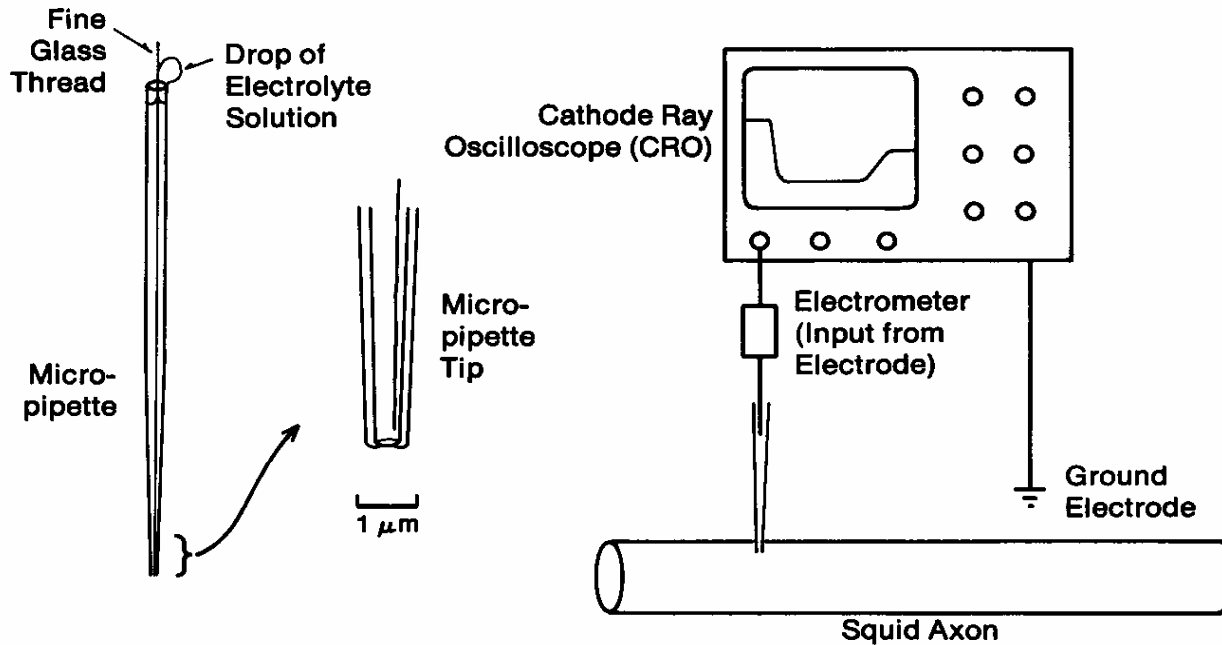


Fig. 4.4 The micropipette is used for electrical recording (extracellular, intracellular, patch), electrical stimulation (current or voltage clamp), or delivery of substances (microionophoresis or pressure ejection). Preparation of an intracellular recording micropipette is shown on the left. The diagram on the right shows the arrangement for recording from a squid axon and observing potentials on a cathode ray oscilloscope (CRO).

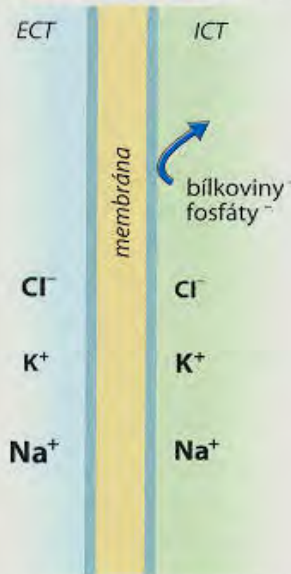
Gibbs-Donnanova rovnováha

Iont	Koncentrace		Gradient Intra/Extra	Rovnovážný potenciál
	Intracelulární	Extracelulární		
Na ⁺	12 mmol/l	145 mmol/l	1:12	+67 mV
K ⁺	155 mmol/l	4 mmol/l	39:1	-98 mV
Cl ⁻	4 mmol/l	123 mmol/l	1:31	-90 mV
volný Ca ²⁺	10 ⁻⁴ mmol/l	1,5 mmol/l	1:15.000	+129 mV
fixní anionty	155 mmol/l			

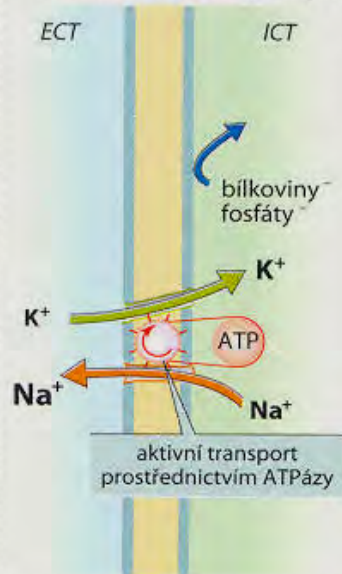
Tab. 2.2. Tabulka rozložení iontových koncentrací na buněčné membráně kosterního svalu savce.

A. Příčiny a důsledky klidového potenciálu membrány

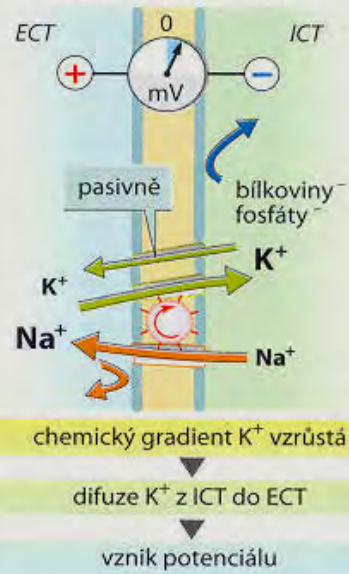
1 pasivní rozložení iontů



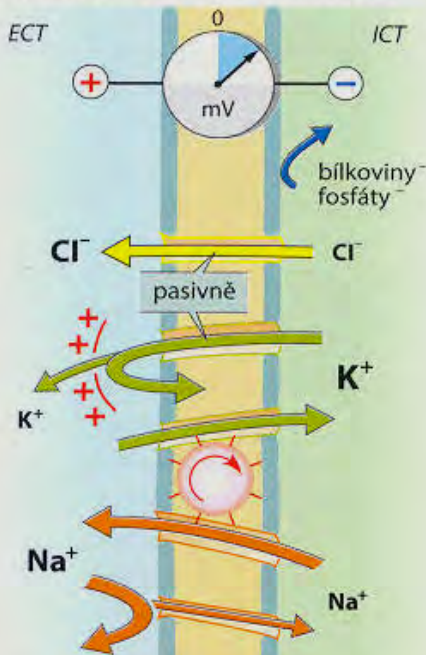
2 aktivní Na⁺-K⁺-pumpa



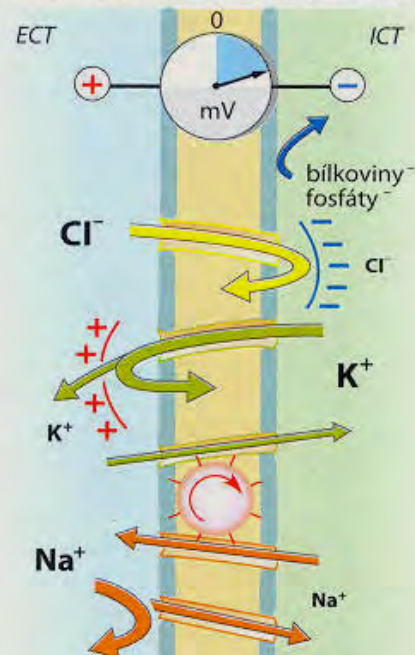
3 difuzní potenciál K⁺



4 potenciál žene Cl⁻ z ICT do ECT



5 konečný stav: klidový membránový potenciál



K⁺:



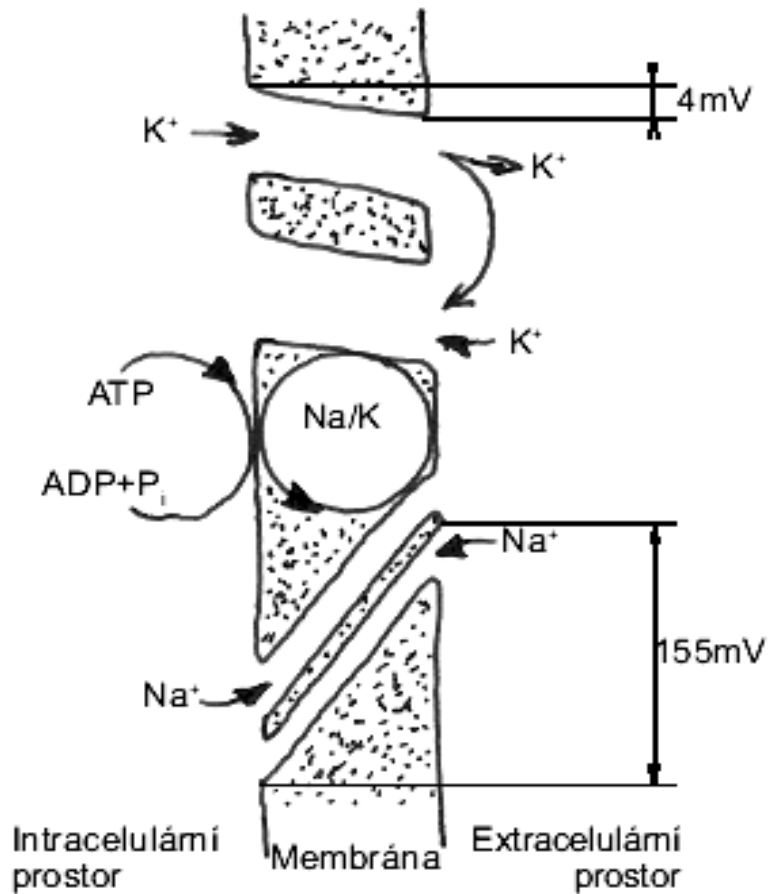
Na⁺:



INTRA

EXTRA





Obr. 2.9. Rozdílné membránové podmínky pro Na⁺ a K⁺. Na/K pumpa stále udržuje na membráně gradient Na⁺ i K⁺. Zatímco K⁺ však může membránou volně procházet, pro Na⁺ je téměř nepropustná. Na⁺ je čerpáno „do strmého kopce“ – proti velké elektrochemické síle.

Rovnovážný potenciál – pro daný iont Nernstova r.

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion]_o}{[ion]_i}$$

$$E_{ion} = 61mV \log \frac{[ion]_o}{[ion]_i}$$

Goldmanova r.

$$E_r = \frac{RT}{F} \ln \frac{PK[K^+]_o + PNa[Na^+]_o + PCl[Cl^-]_i}{PK[K^+]_i + PNa[Na^+]_i + PCl[Cl^-]_o}$$

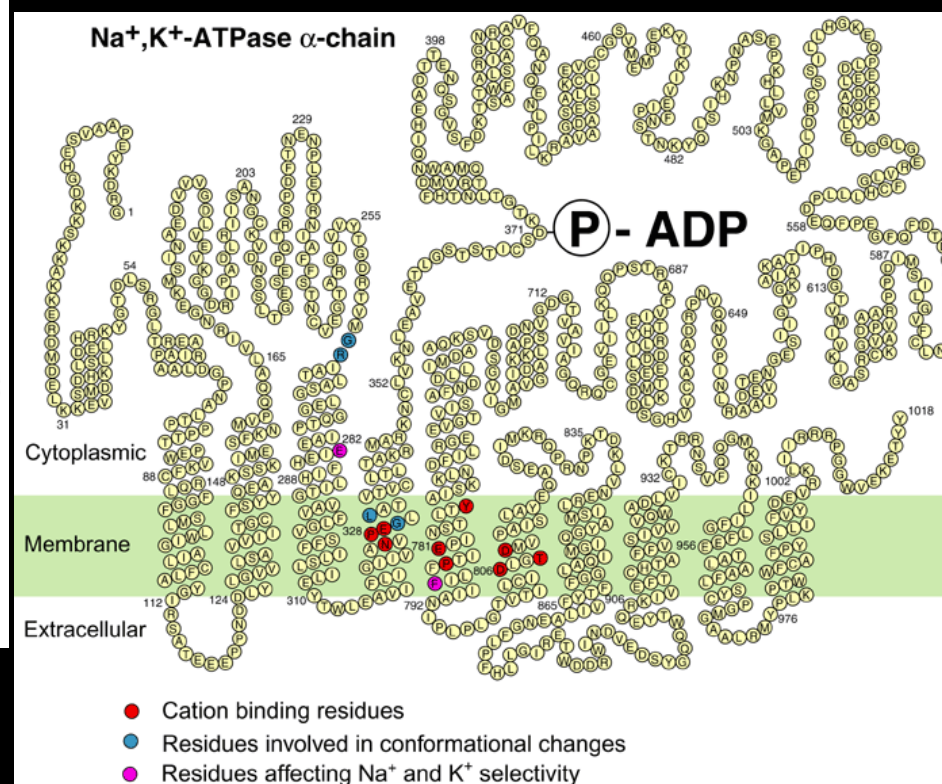
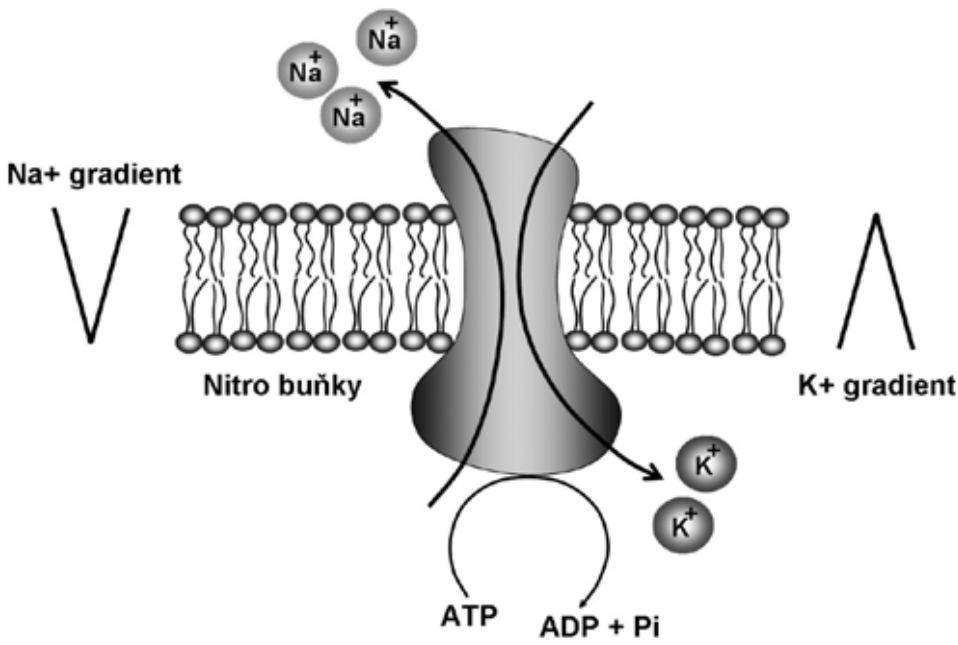
Gradient Intra/Extra	Rovnovážný potenciál
1:12	+67 mV
39:1	-98 mV

Hnací síla = Driving Force
 -90mV – (Rovnovážný potenciál)

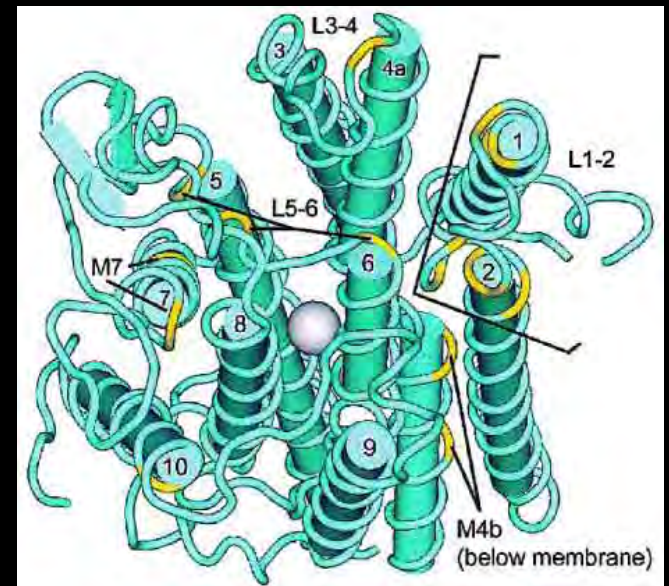
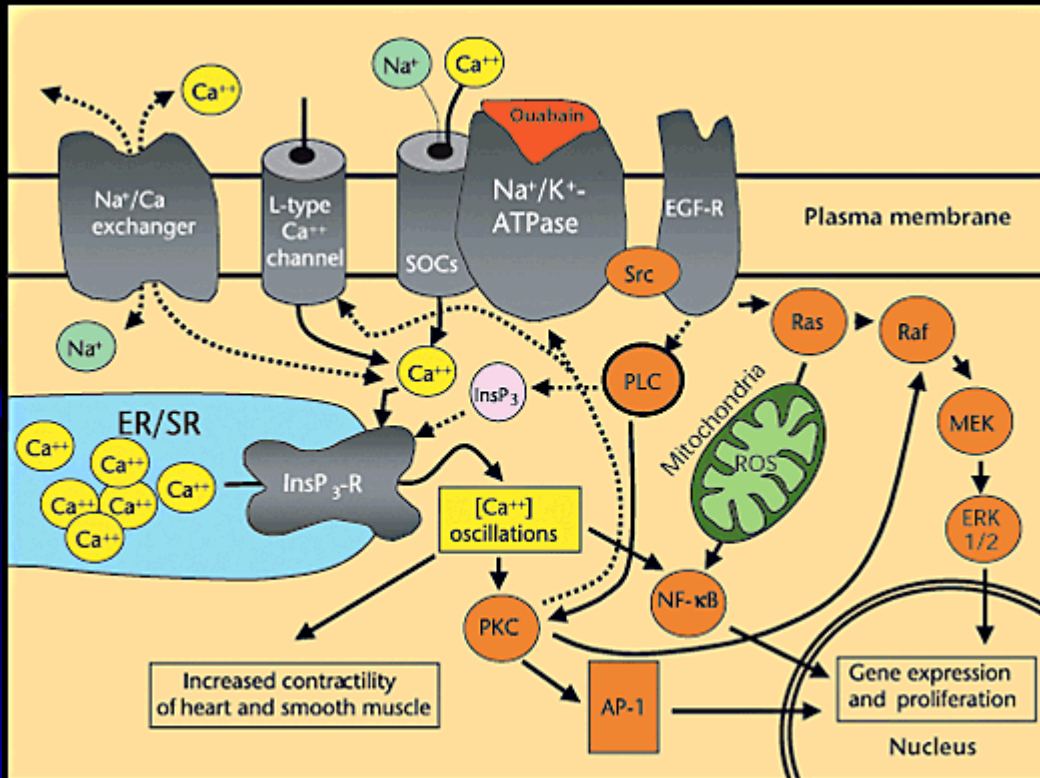
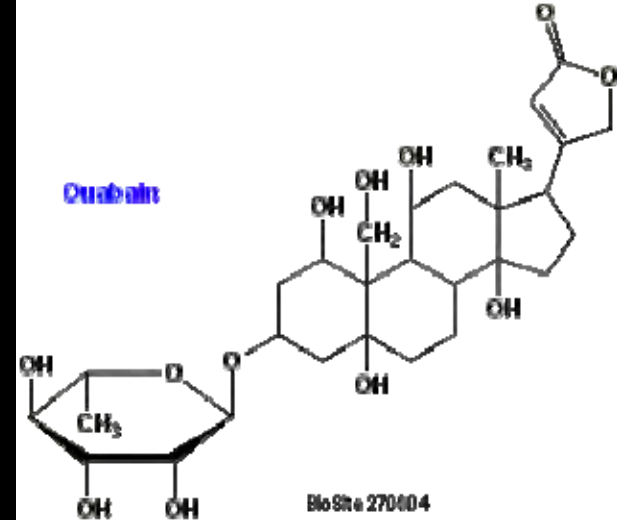
Iont	Koncentrace		Gradient Intra/Extra	Rovnovážný potenciál
	Intracelulární	Extracelulární		
Na ⁺	12 mmol/l	145 mmol/l	1:12	+67 mV
K ⁺	155 mmol/l	4 mmol/l	39:1	-98 mV
Cl ⁻	4 mmol/l	123 mmol/l	1:31	-90 mV
volný Ca ²⁺	10 ⁻⁴ mmol/l	1,5 mmol/l	1:15.000	+129 mV
fixní anionty	155 mmol/l			

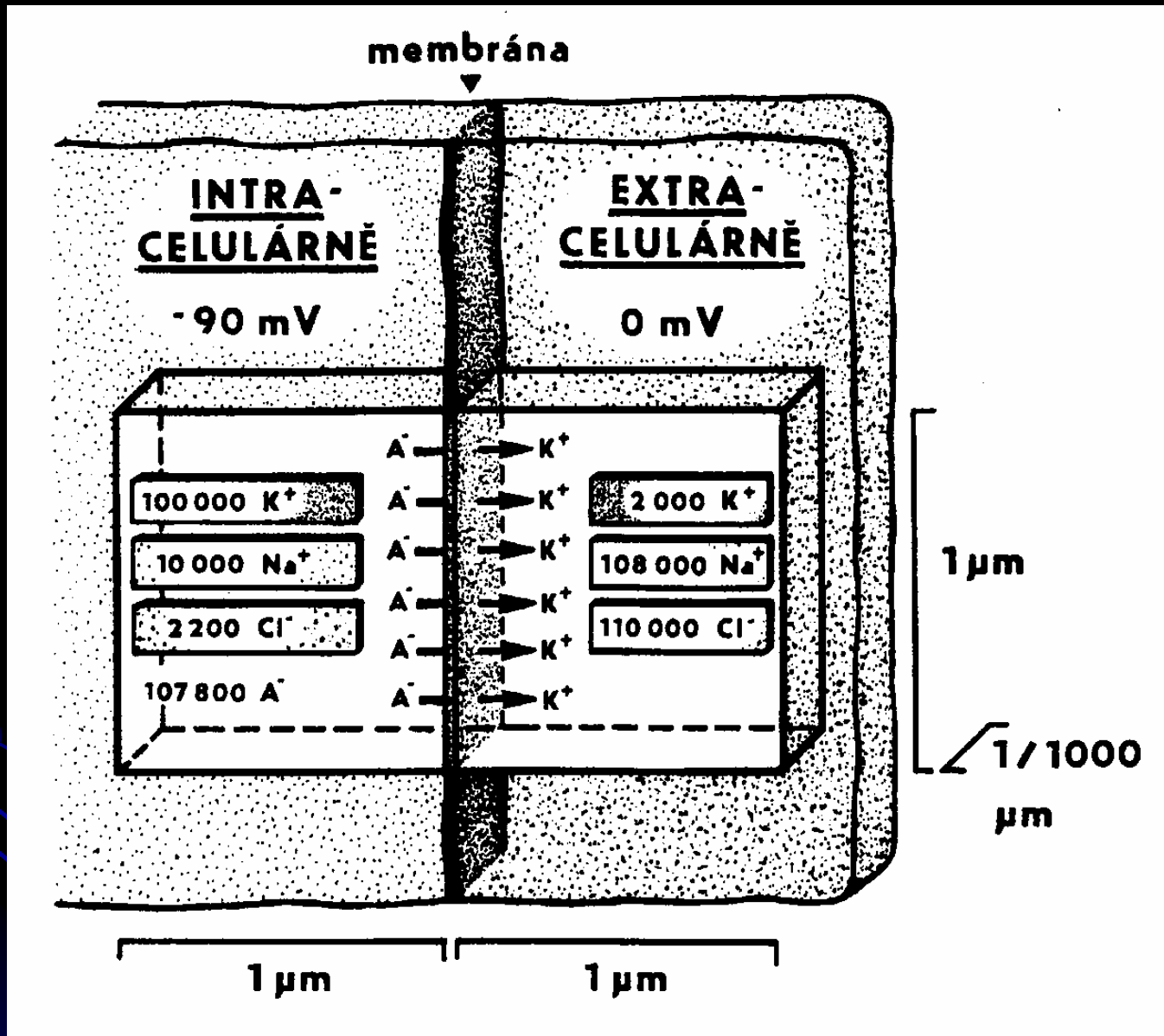
Tab. 2.2. Tabulka rozložení iontových koncentrací na buněčné membráně kosterního svalu savce.

Na/K ATP-áza nabíjí membránu



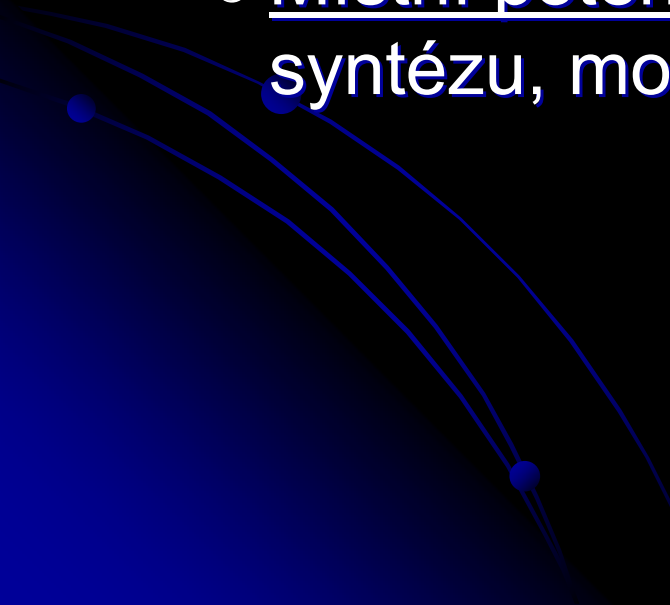
Ouabain – Inhibitor Na/K pumpy



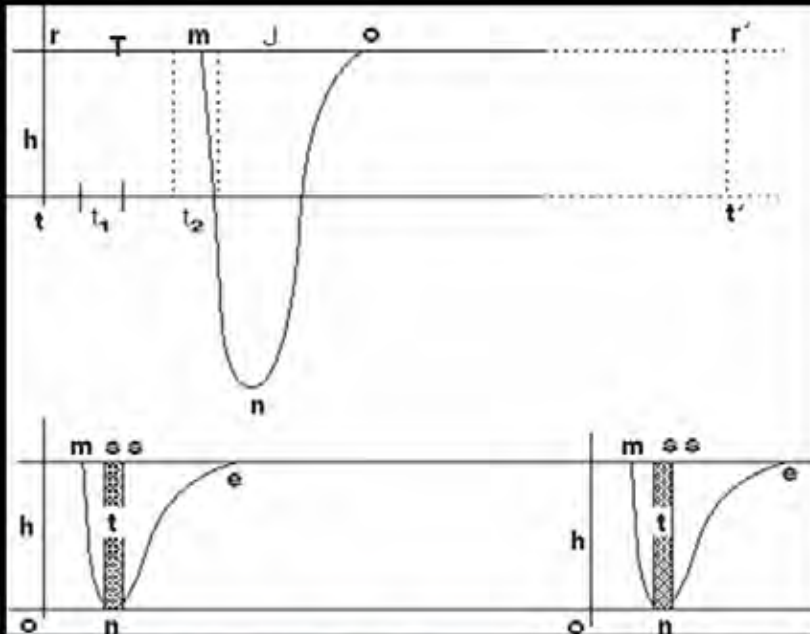


Jen 6 kationtů vně navíc na pozadí 110.000/110.000 je schopno nabít membránu. Stačí tedy přemístit jen nepatrná množství a potenciál se výrazně změní.

Klidový potenciál

- Uložená energie pro generování, šíření a zpracování elektrických signálů:
 - Akční potenciál – vhodný pro dálkový, nezkreslený a rychlý přenos signálů
 - Místní potenciál – vhodný pro zpracování, syntézu, modifikaci informací
- 

Akční potenciál

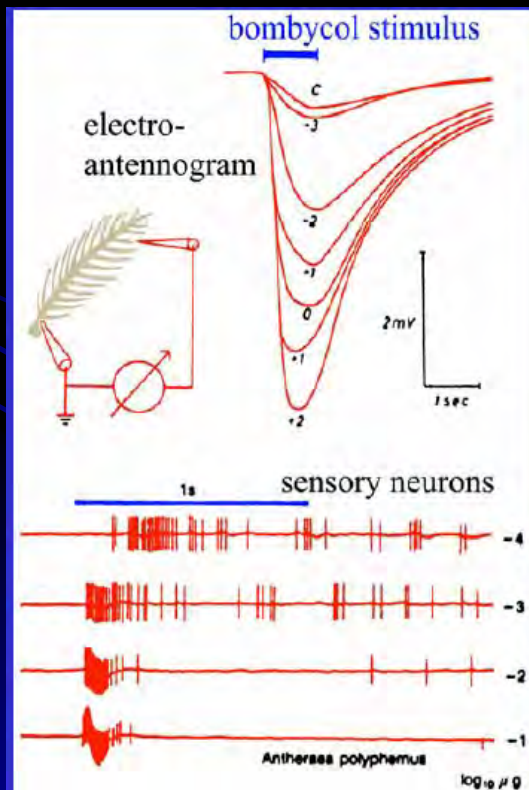


Horní záznam odpovídá průběhu "nervového akčního proudu", tak jak jej Bernstein naměřil r. 1868 a publikoval r. 1871. Na spodním záznamu, který Bernstein publikoval v *Elektrobiologii* r. 1913, chybí překmit "akčního proudu" do kladných hodnot (průběhy jsou zaznamenány s opačnou polaritou, než na jakou jsme dnes zvyklí).



Jak se dnes měří a jak vypadá?

<http://www.hhmi.org/biointeractive/vlabs/neurophysiology/index.html>



Informace, kterou přenáší, je zapsána do frekvence.

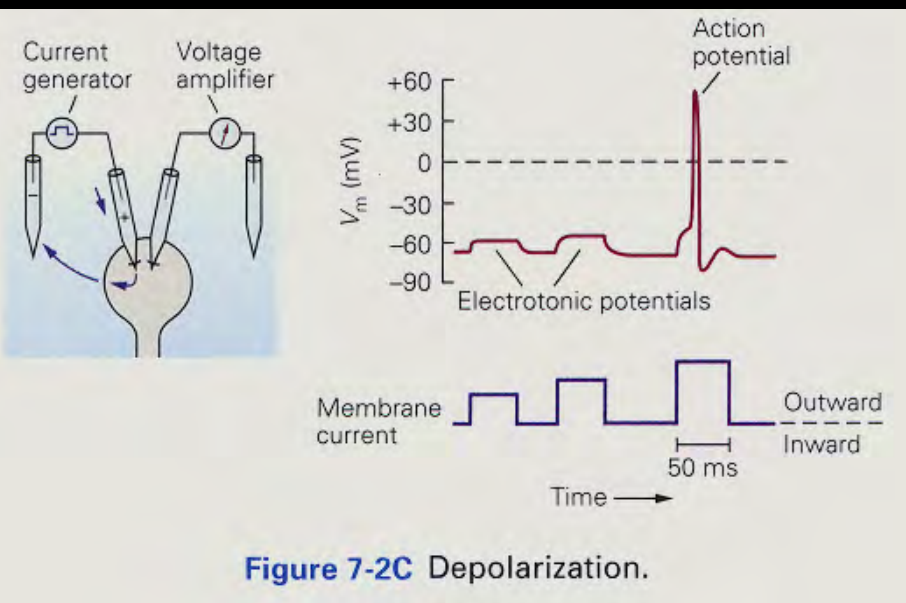
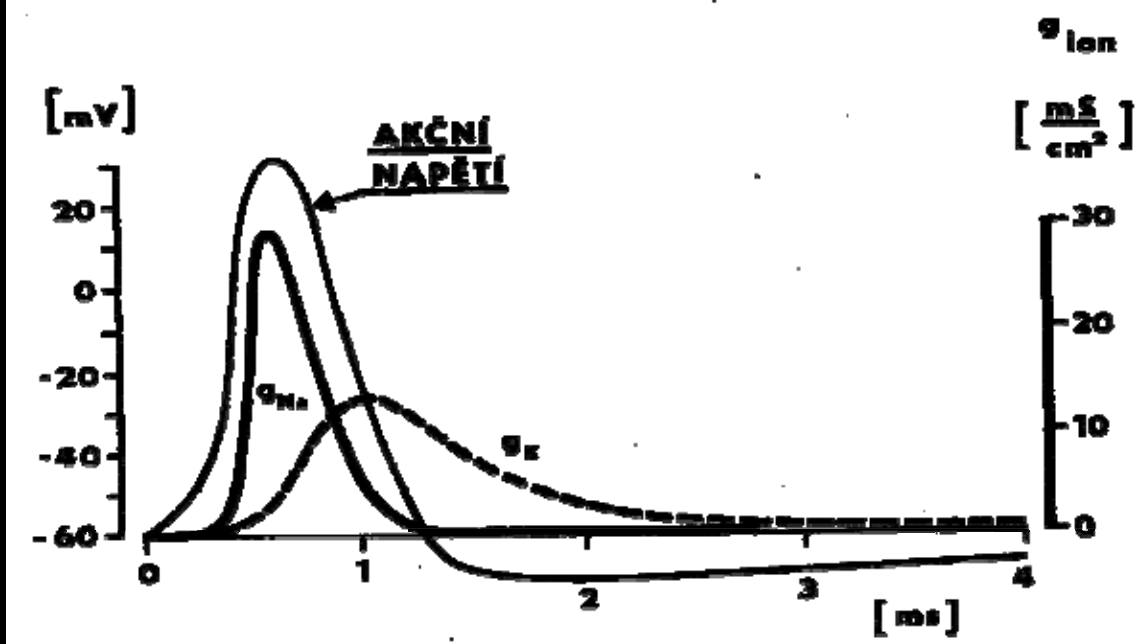


Figure 7-2C Depolarization.

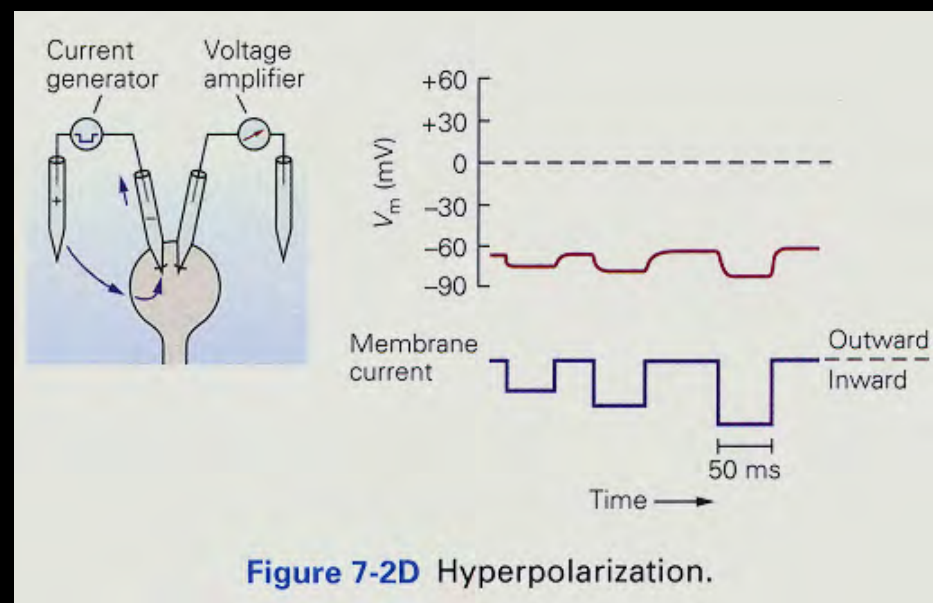


Figure 7-2D Hyperpolarization.

Buď nevznikne vůbec,
nebo vzniká stále stejně velký.

■
The Nobel Prize in Physiology
or Medicine 1963



"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"



**Sir John
Carew
Eccles**
■
1/3 of the
prize
Australia

Australian
National
University
Canberra,
Australia
d. 1997



**Alan Lloyd
Hodgkin**
■
1/3 of the
prize
United
Kingdom
University of
Cambridge
Cambridge,
United
Kingdom
d. 1998

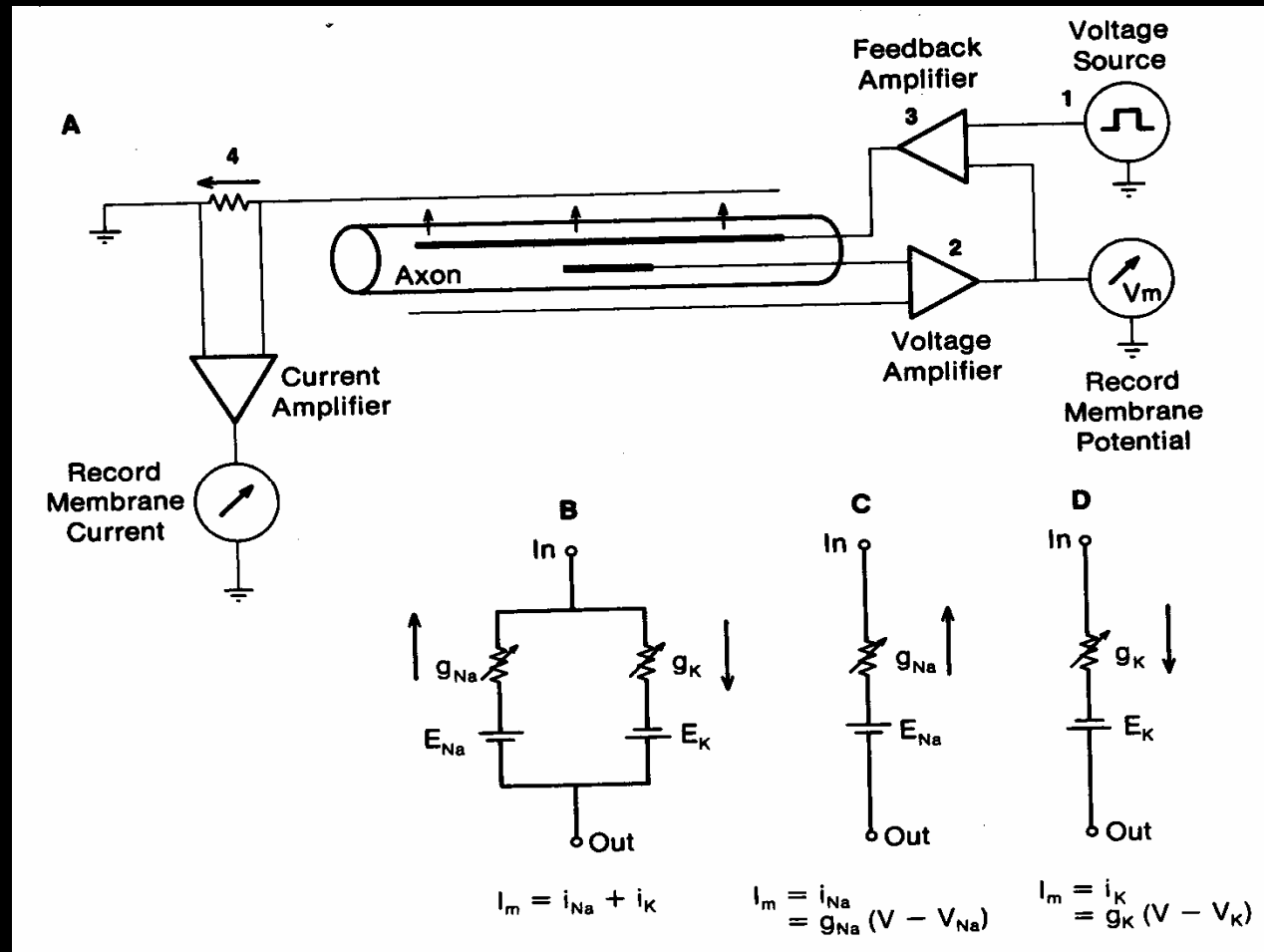


**Andrew
Fielding
Huxley**
■
1/3 of the
prize
United
Kingdom
London
University
London,
United
Kingdom
d. 1987

Voltage clamp

Hodgkin & Huxley
napěťový zámek, 1963.

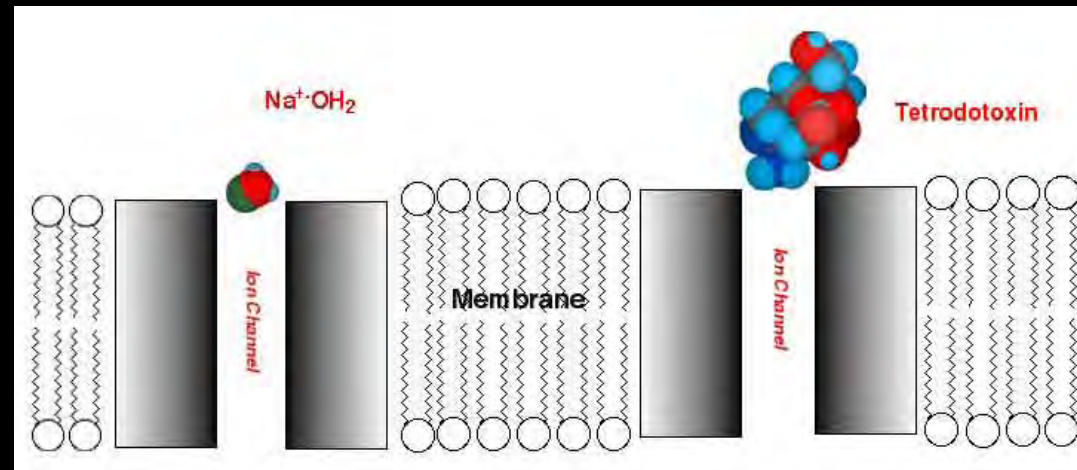
Dodávaný proud kompenzuje
iontové toky tak, aby napětí
zůstalo konstantní. Proud
je registrován.



Blokátory kanálů

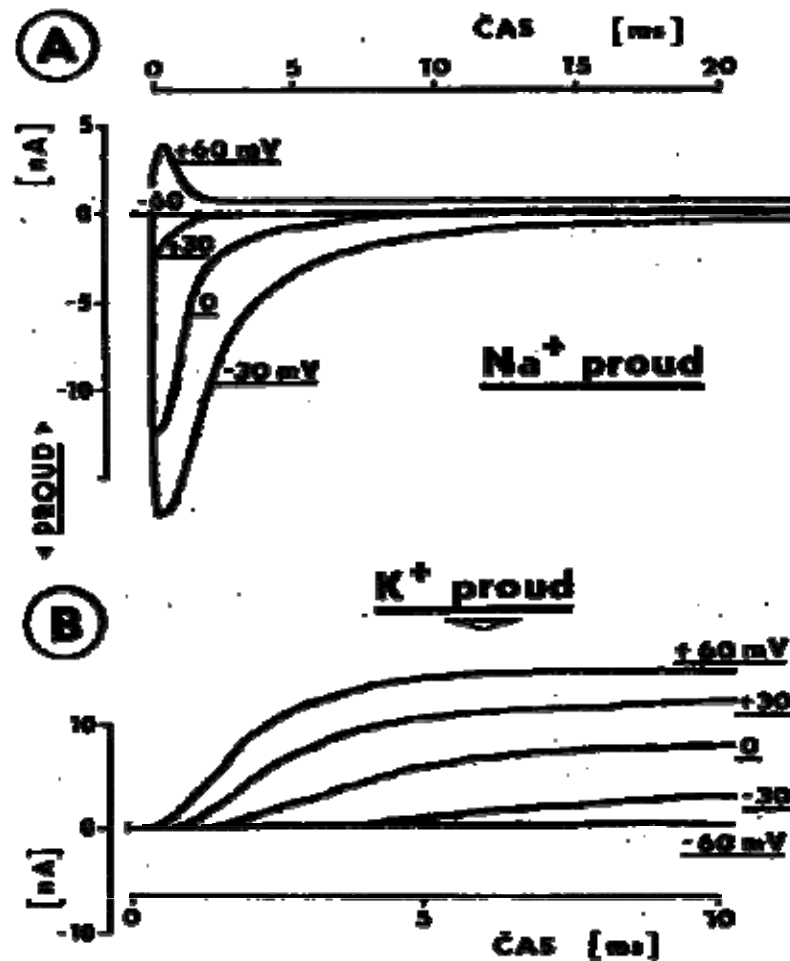
Na – TTX (Tetrodotoxin) – „ucpe“ ústí kanálu

K – TEA (Tetraethyl amonium)

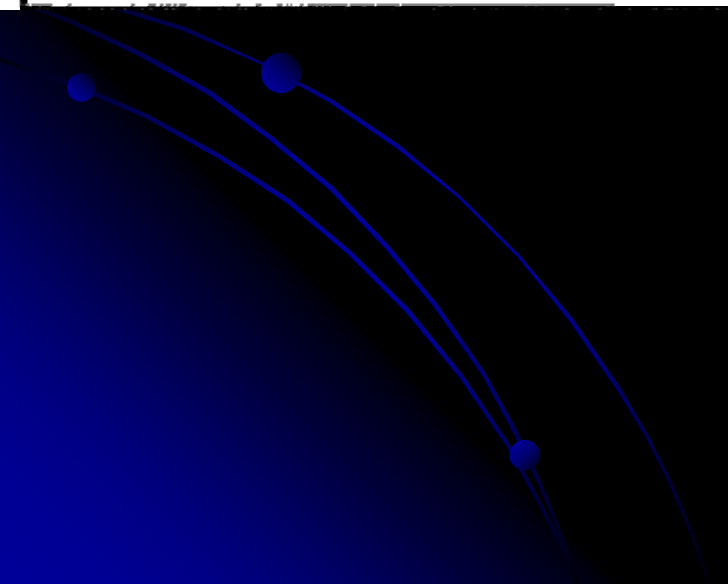
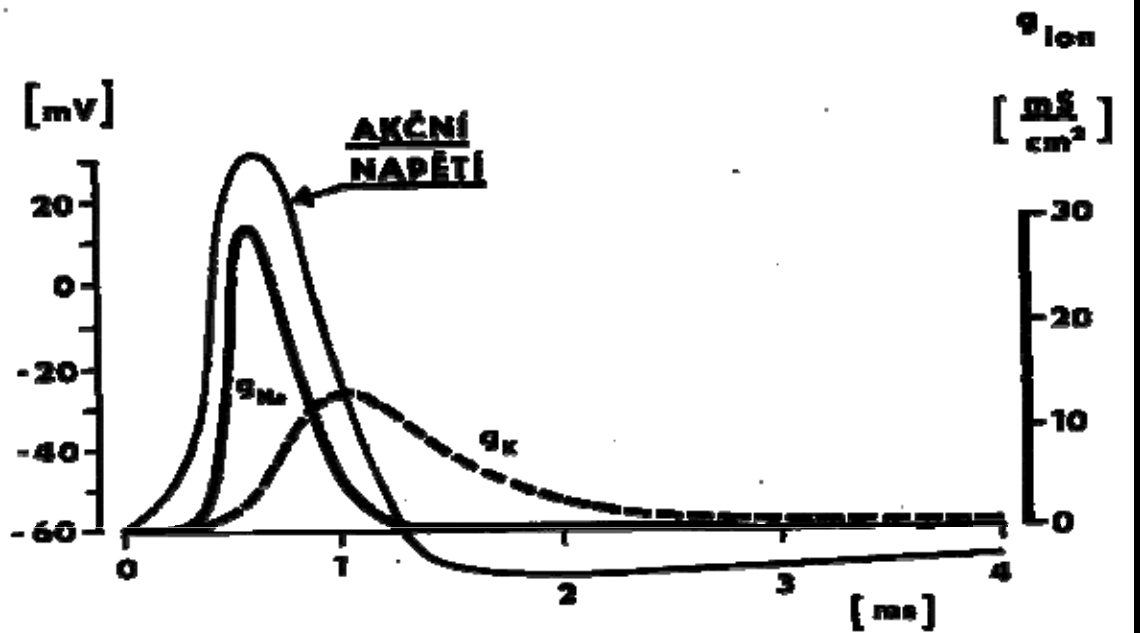
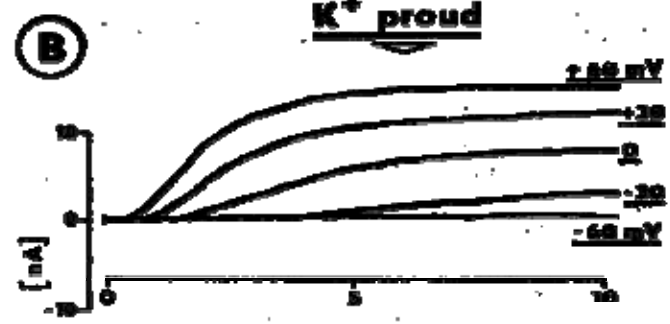
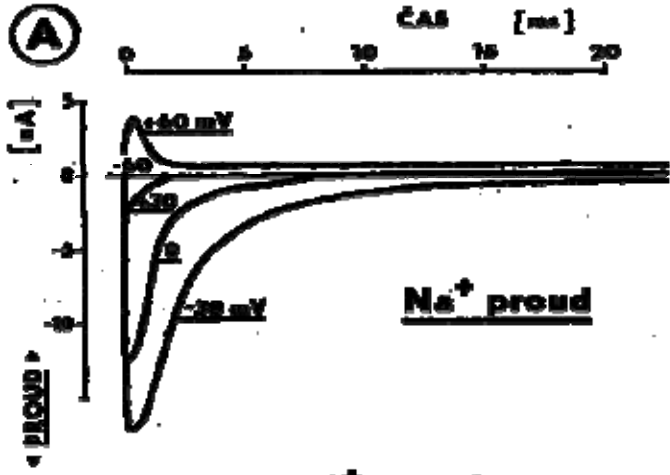


Čtverzubec Tetraodon - fugu





Obr. 14.16 Membránové proudy na myelinisovaných axonech po experimentálně provedené skokové změně membránového napětí. Membránové napětí bylo v čase $t=0$ skokem změněno z -95 mV na hodnoty udané u jednotlivých křivek. Křivky vyjadřují naměřené proudy iontů, nahoře natria, dole kalia. Svislá osa - intenzita proudu, vodorovná osa - čas. Při skoku na -60 mV je skok ještě podprahový a nevyvolává žádný proud. A: Na^+ proud; mezi $+30$ a $+60$ mV mění Na^+ proud polaritu z negativního (směrem do buňky, pod vodorovnou přímkou) na pozitivní (ven z buňky, nad přímkou, pro daný preparát leží totiž hodnota rovnovážného napětí pro Na^+ pod $+60$ mV) a s přibývajícím depolarisací teče stále kratčeji. B: K^+ proud; tento proud stoupá po depolarisaci (do pozitivních hodnot, tj. ven z buňky) mnohem pomaleji než proud Na^+ a drží se na stejné výšce během celé depolarisace. (Z DUDELA 1990b)

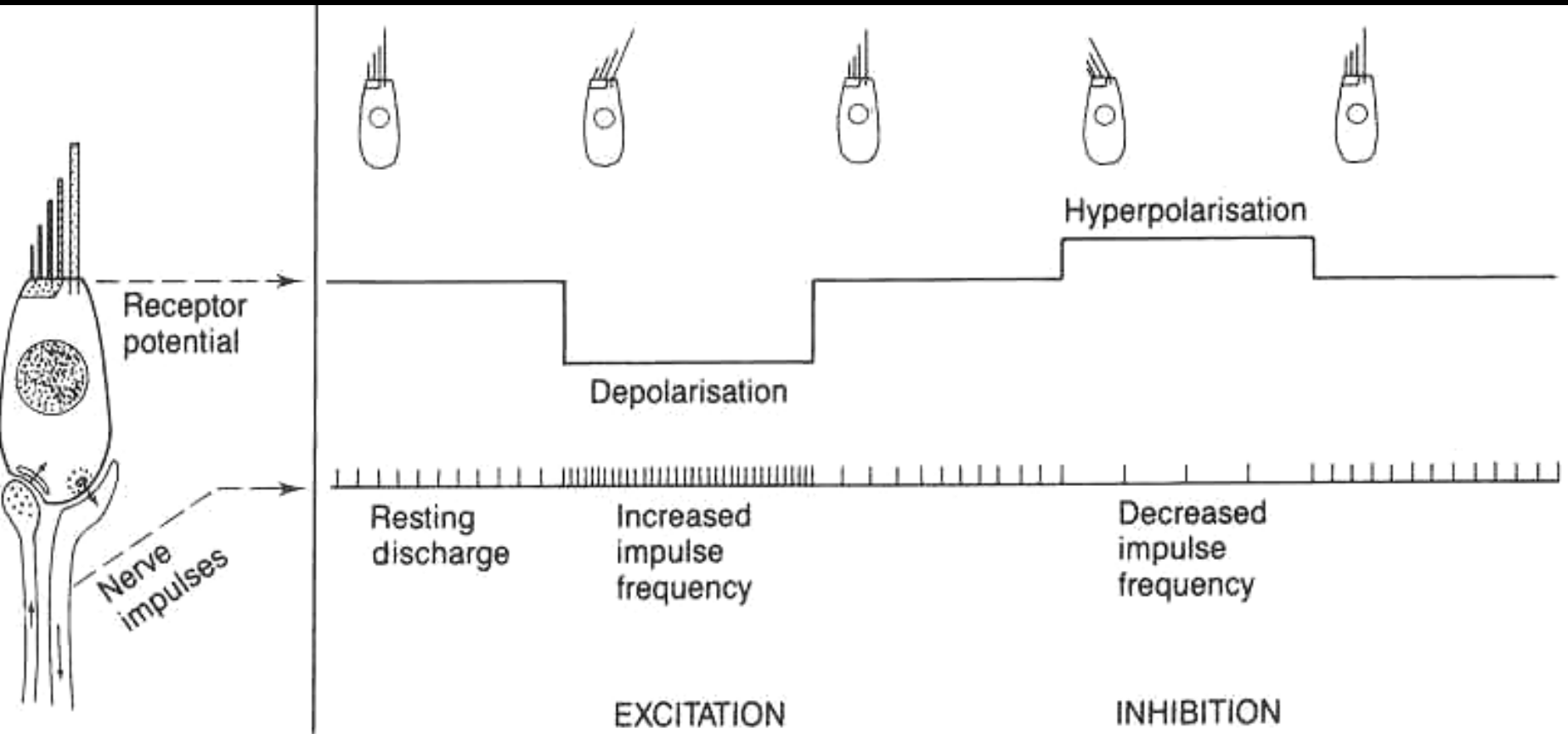


Propagace, Voltage clamp



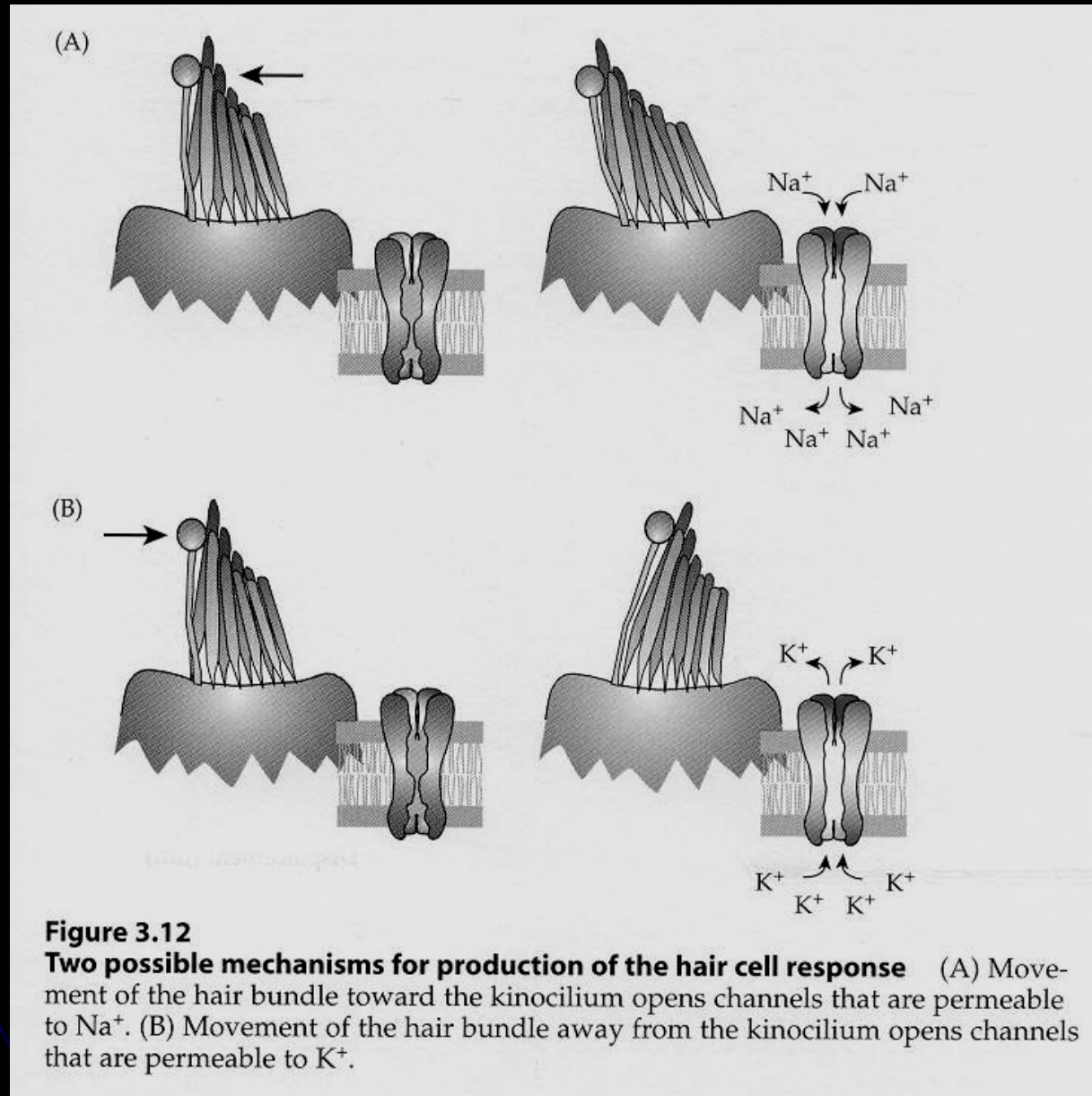
<http://bcs.whfreeman.com/thelifewire/content/chp44/4402s.swf>

K čemu ještě voltage clamp?



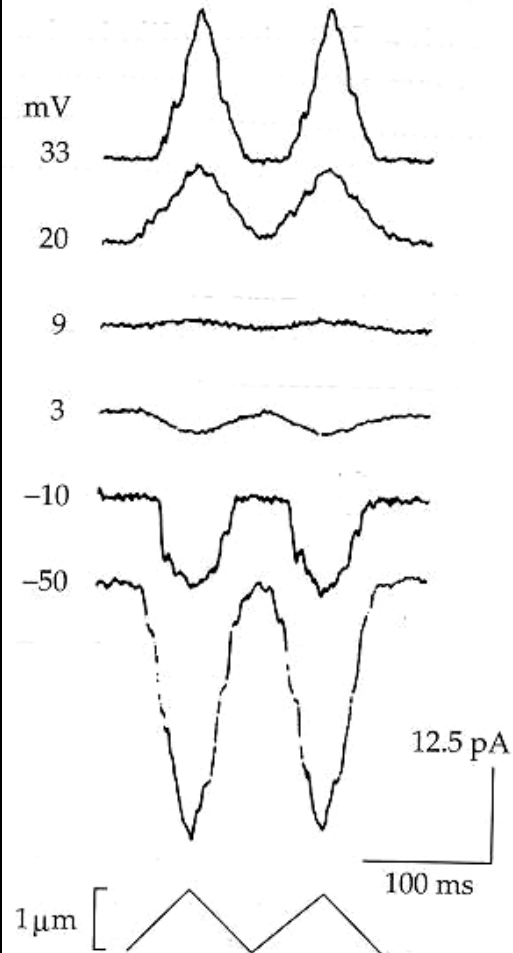
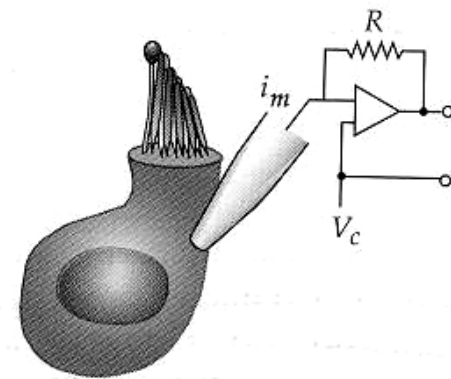
Otvírají se Na nebo zavírají K kanály?

Zamknutí membrány vyšachuje napětově sensitive kanály a iontové toky jsou důsledkem jen mechanické manipulace!



Různé proudy přes membránu po pohybech
cilií u různých hodnot „zamknutého“
napětí.

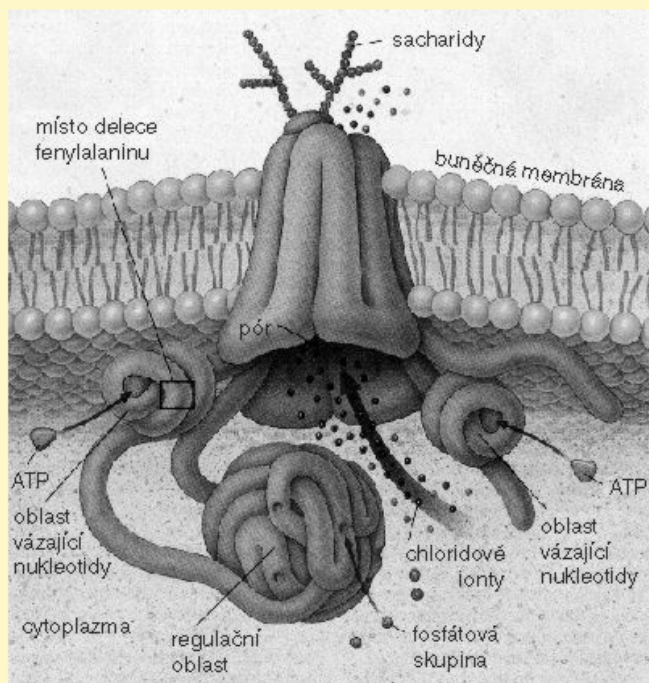
Není to ani K ani jen Na, jsou to neselektivně
kationty.



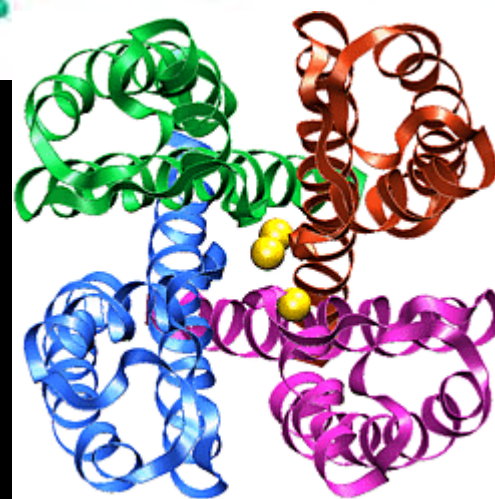
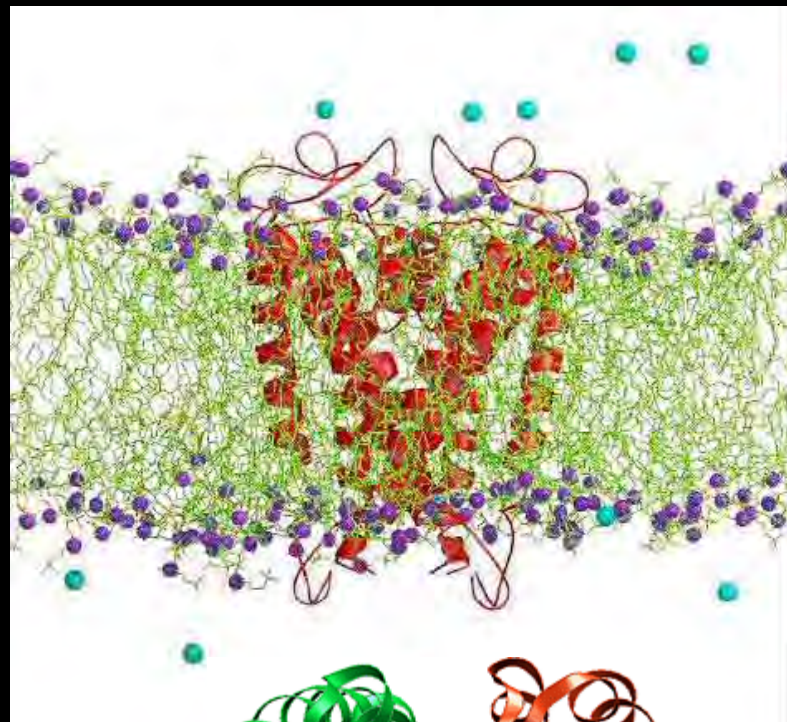
Kanály a patch clamp



Kanály – prostředek udržování integrity buňky a komunikace

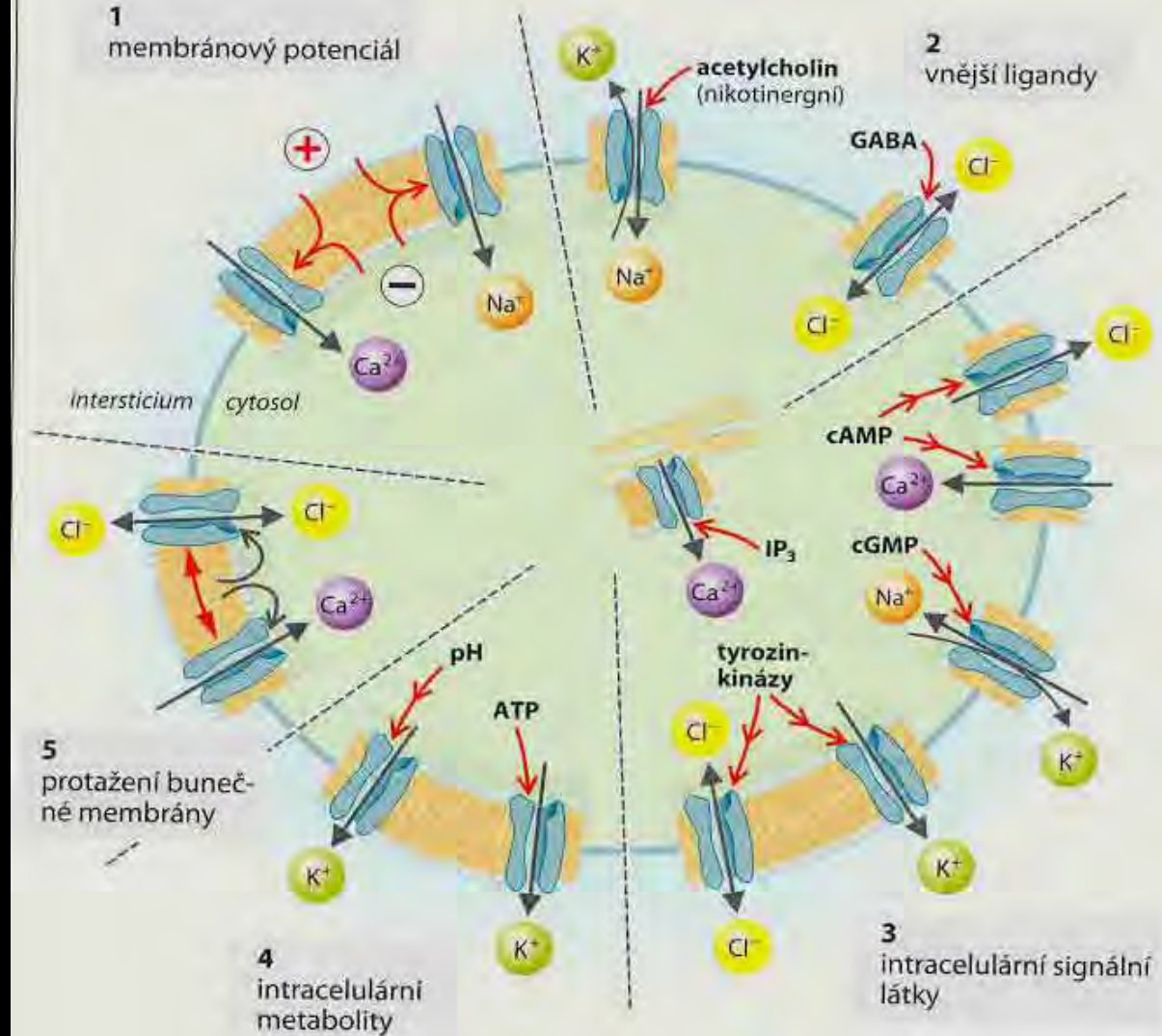
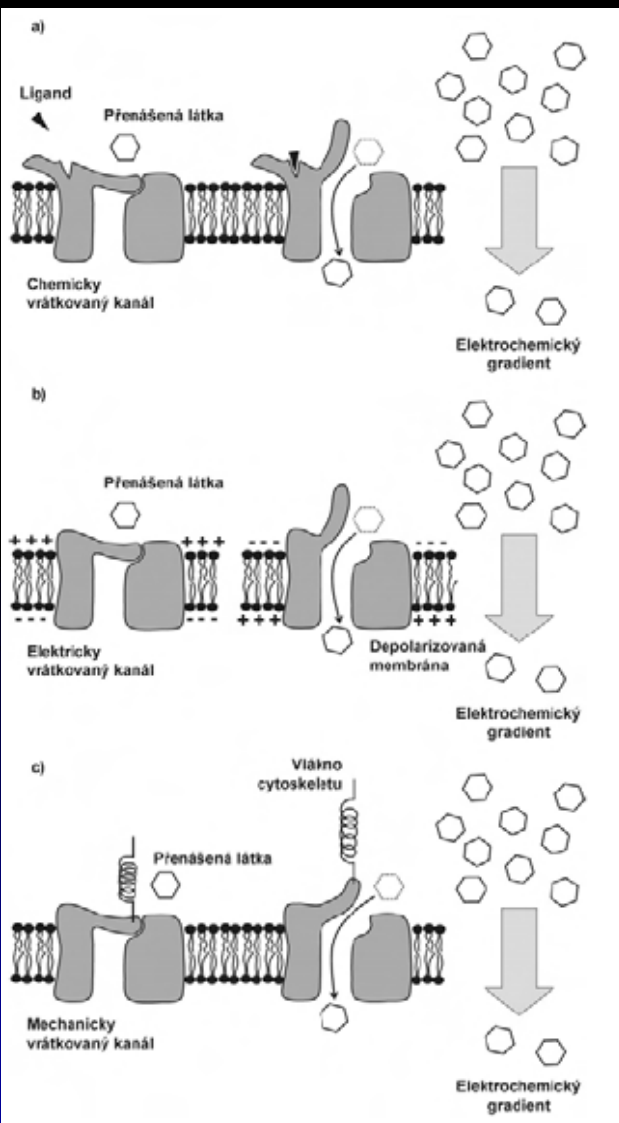


Po ukotvení v membráně se protein CFTR složitě přizpůsobuje – vytváří kanálky, kterými mohou přes membránu proudit chloridové ionty. V cytoplazmatické části proteinu jsou tři regulační oblasti, které se podílejí na uzavírání a otevírání póru. Kanálek se otevře jedině tehdy, když se na CFTR navážou dvě molekuly ATP a zároveň je fosforylována třetí regulační oblast. U mutovaného proteinu je jedna z oblastí vázajících ATP intaktní a membránový kanálek se neotevírá.



Nevrátkované – řídí klidový potenciál
Vrátkované – řídí místní i akční potenciály

Kanály – typy vrátkování



Ionotropní transdukce – receptor přímo na kanálu

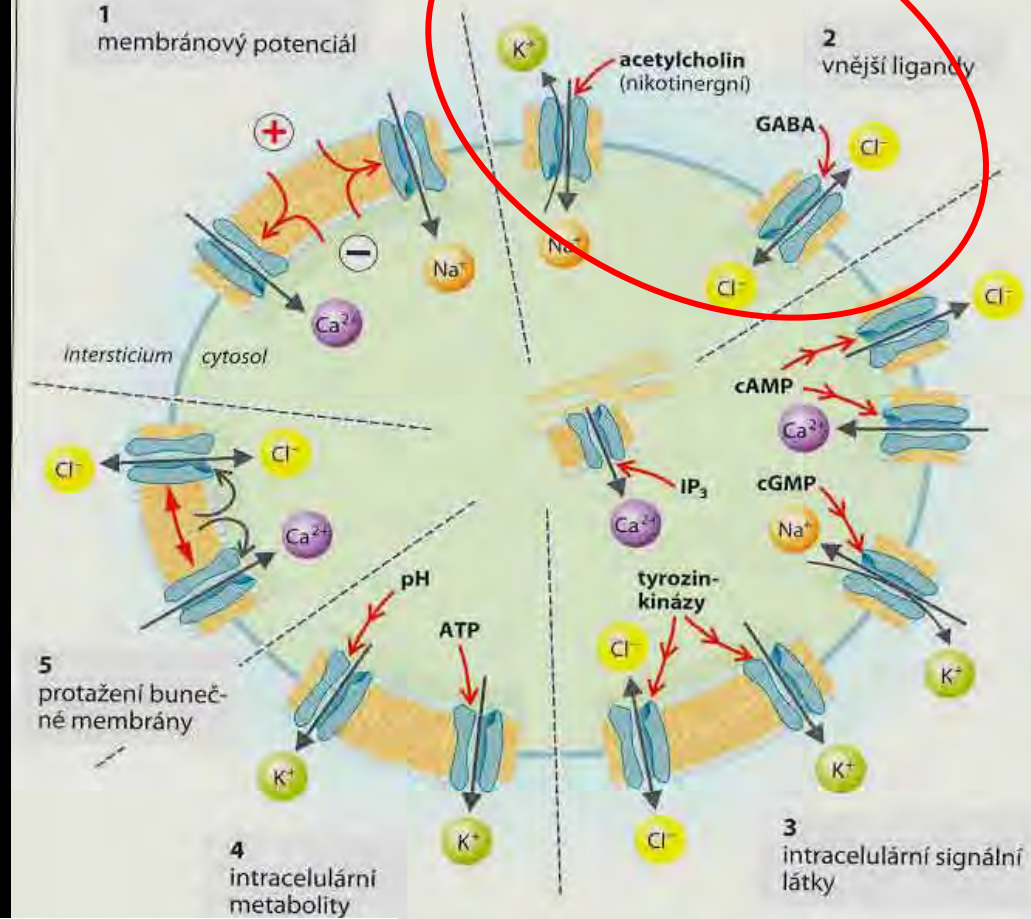


TABLE 12.3 Ionotropic and metabotropic receptors: Structural, functional, and mechanistic differences

Characteristic	Ionotropic receptors	Metabotropic receptors
Receptor molecule	Ligand-gated channel receptor	G protein-coupled receptor
Molecular structure	Five subunits around an ion channel	Protein with seven transmembrane segments; no channel
Molecular action	Open ion channel	Activate G protein; metabolic cascade
Second messenger	No	Yes (usually)
Gating of ion channels	Direct	Indirect (or none)
Type of synaptic effect	Fast EPSP or IPSP	Slow PSPs; modulatory changes (in channel properties, cell metabolism, or gene expression)

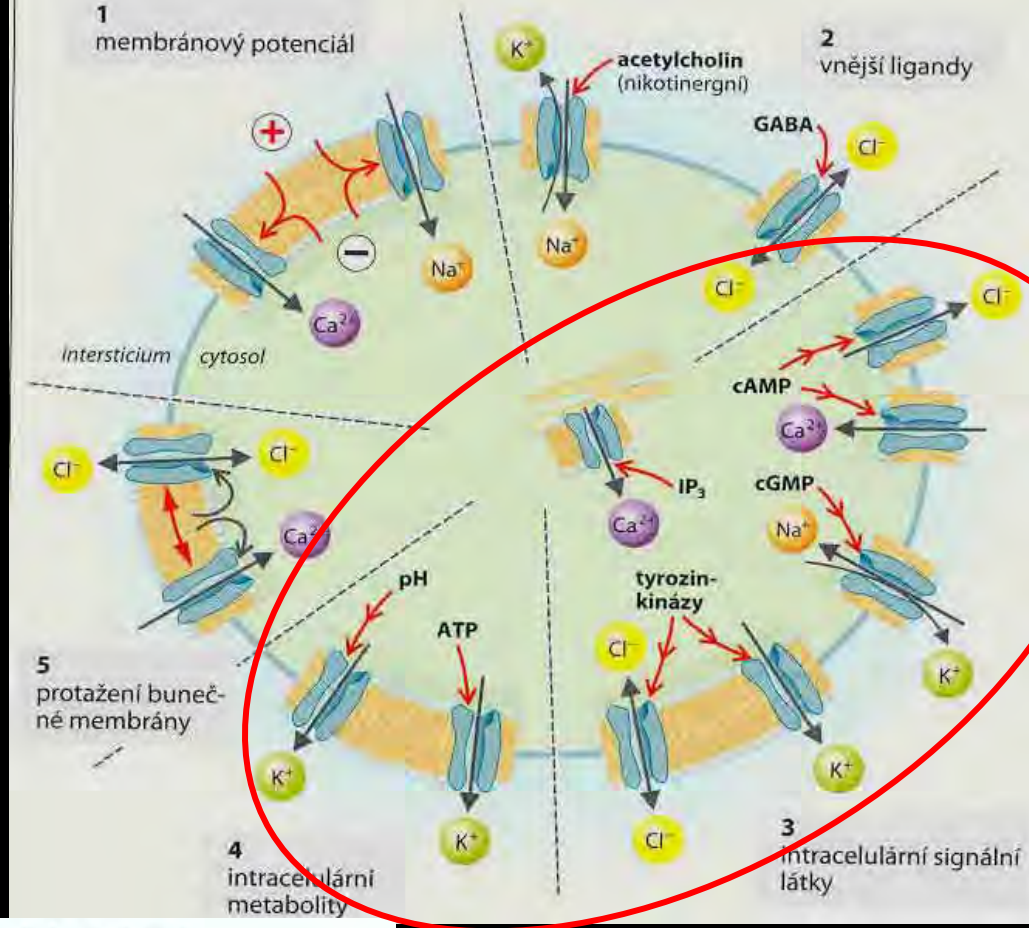
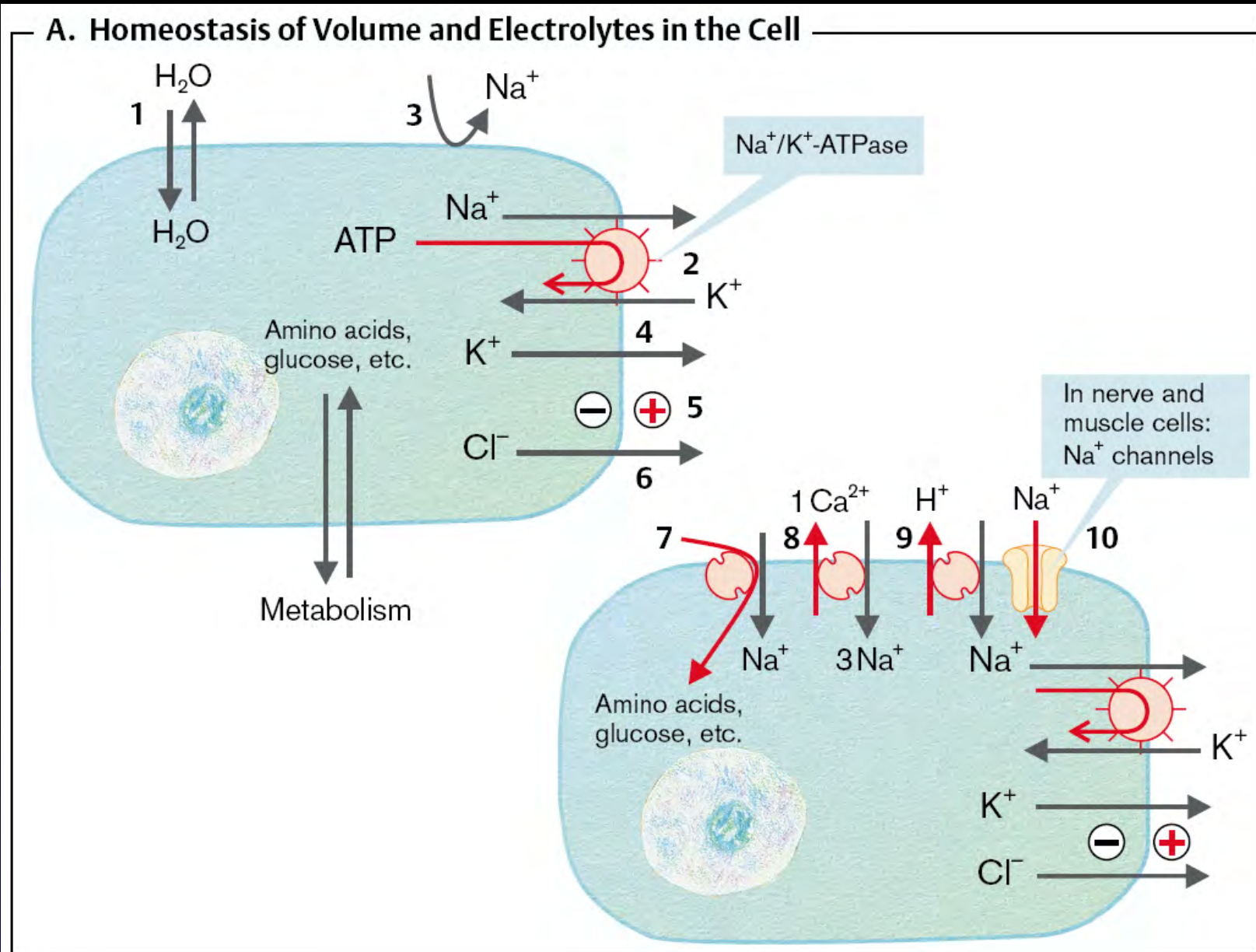


TABLE 12.3 Ionotropic and metabotropic receptors: Structural, functional, and mechanistic differences

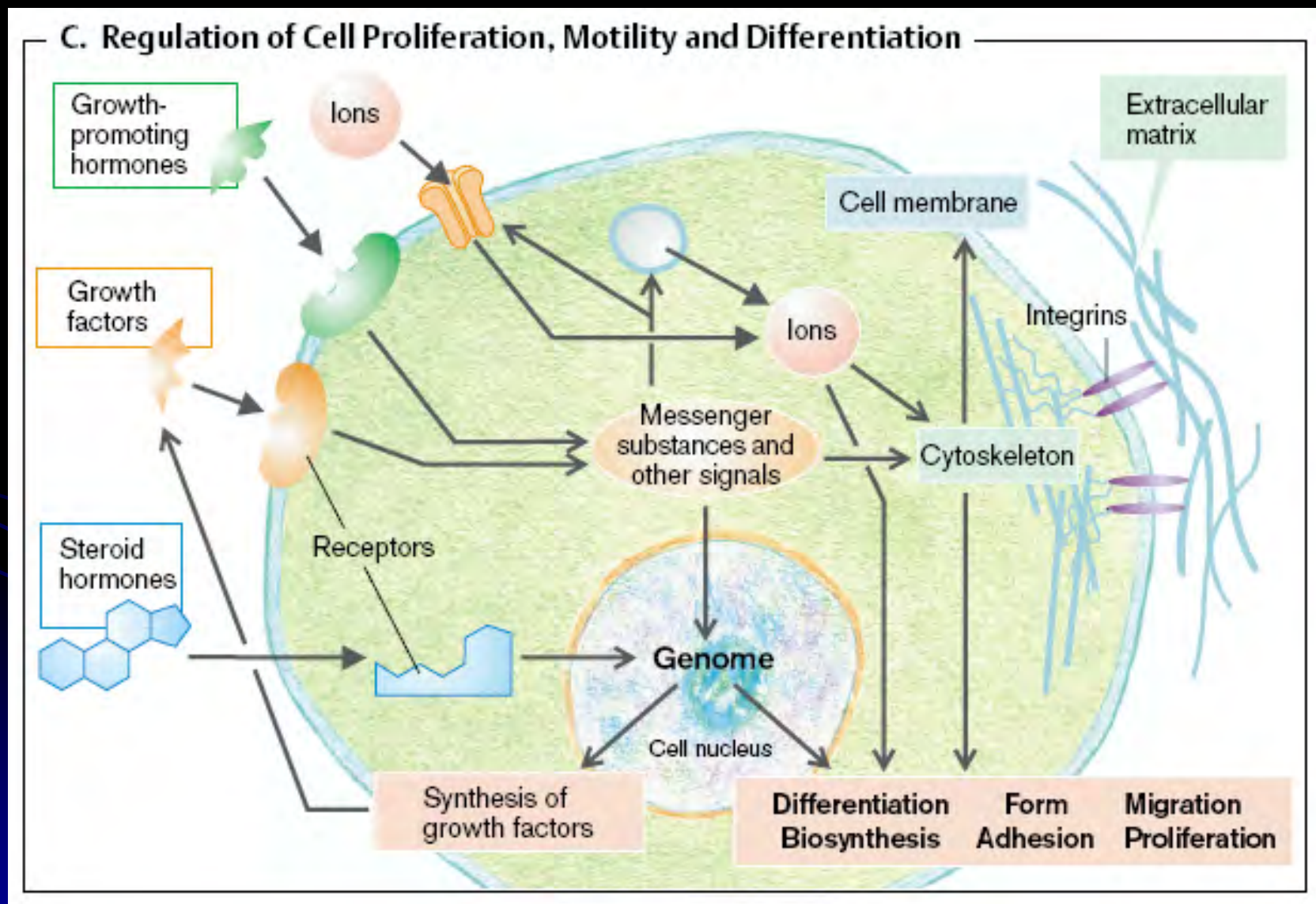
Characteristic	Ionotropic receptors	Metabotropic receptors
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Molecular structure	Five subunits around an ion channel	Protein with seven transmembrane segments; no channel
Molecular action	Open ion channel	Activate G protein; metabolic cascade
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Type of synaptic effect	Fast EPSP or IPSP	Slow PSPs; modulatory changes (in channel properties, cell metabolism, or gene expression)

Metabotropní transdukce

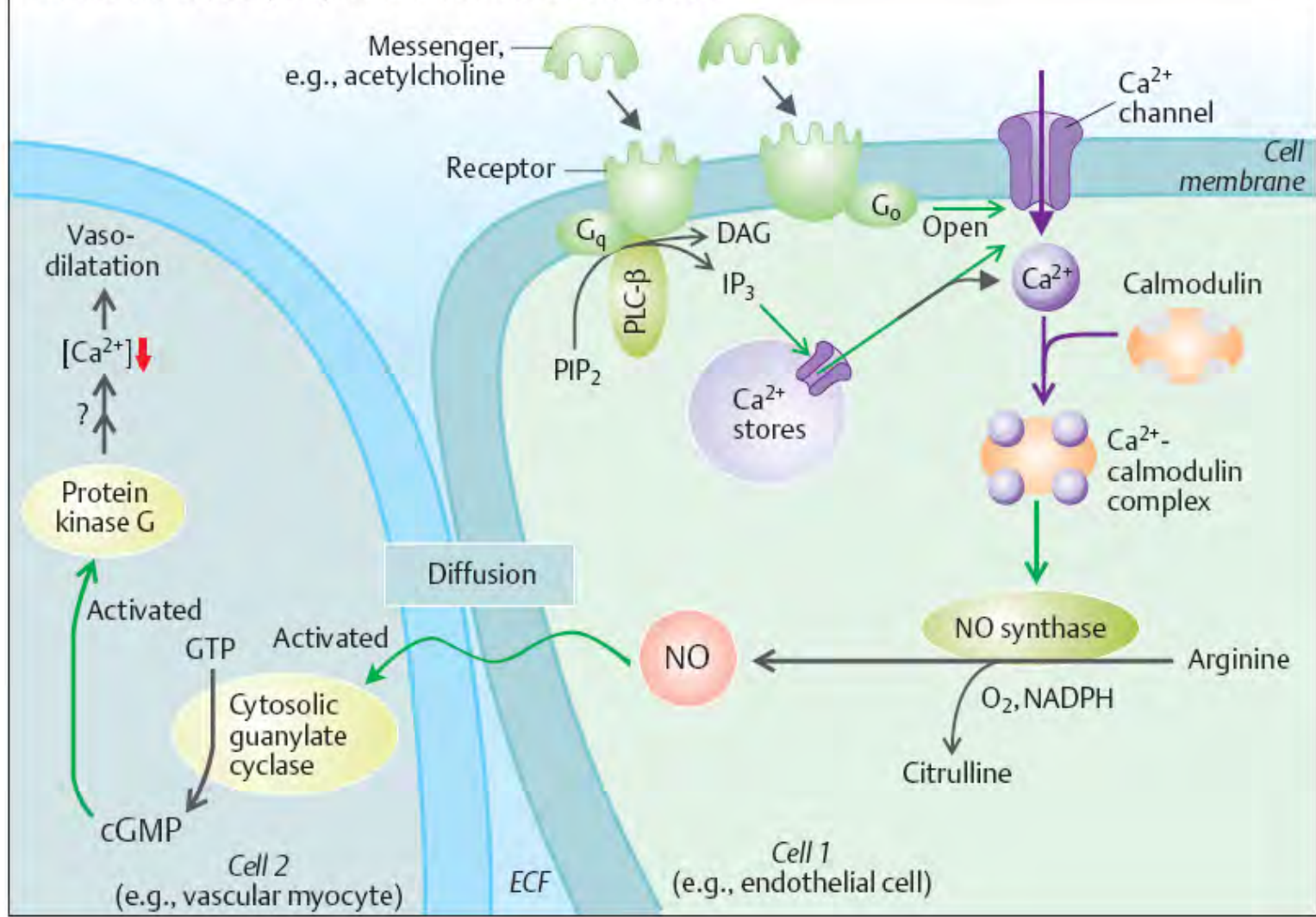
Už jste se potkali s kanály?



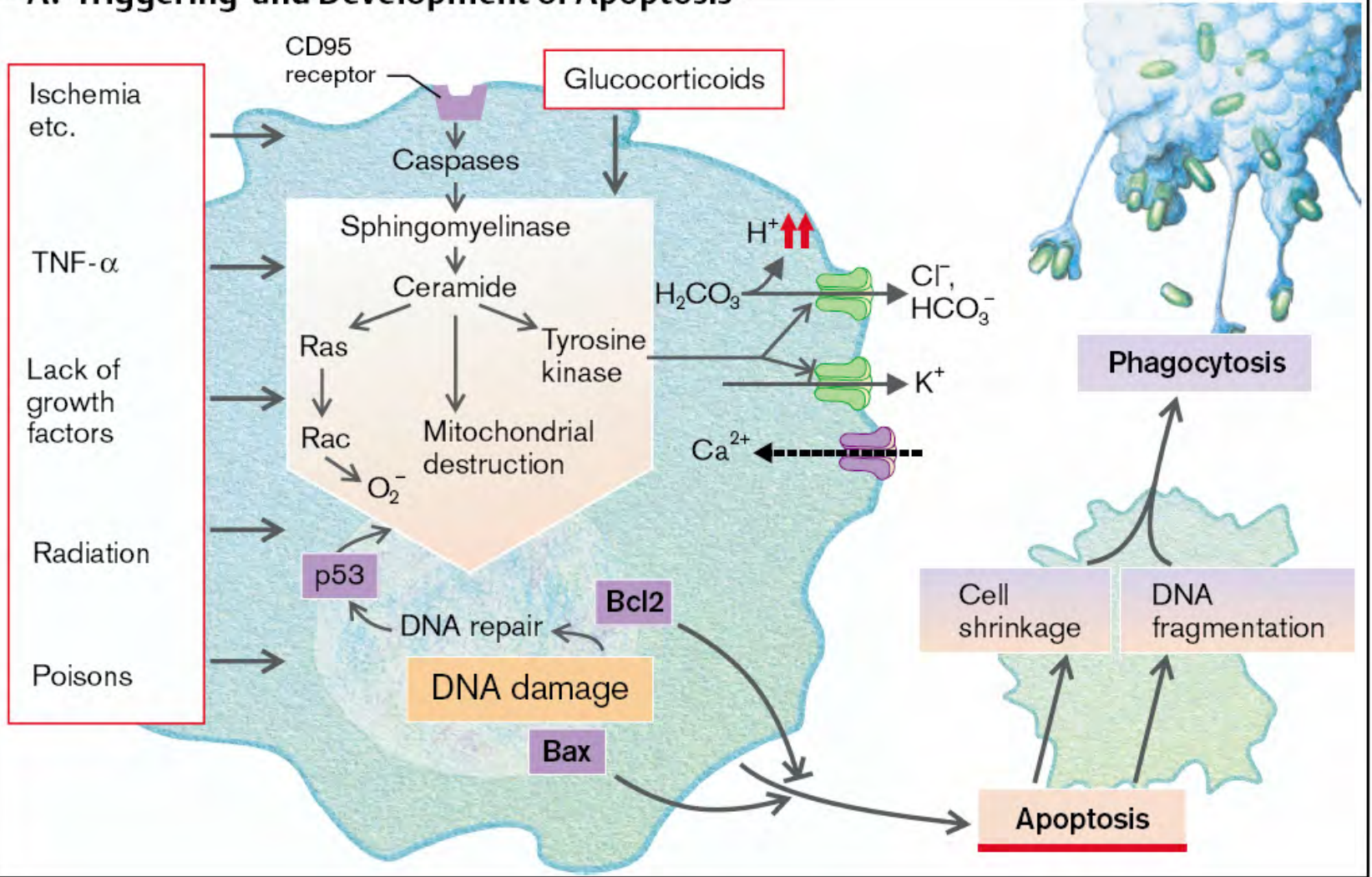
Řídí předávání signálů nesených ionty.



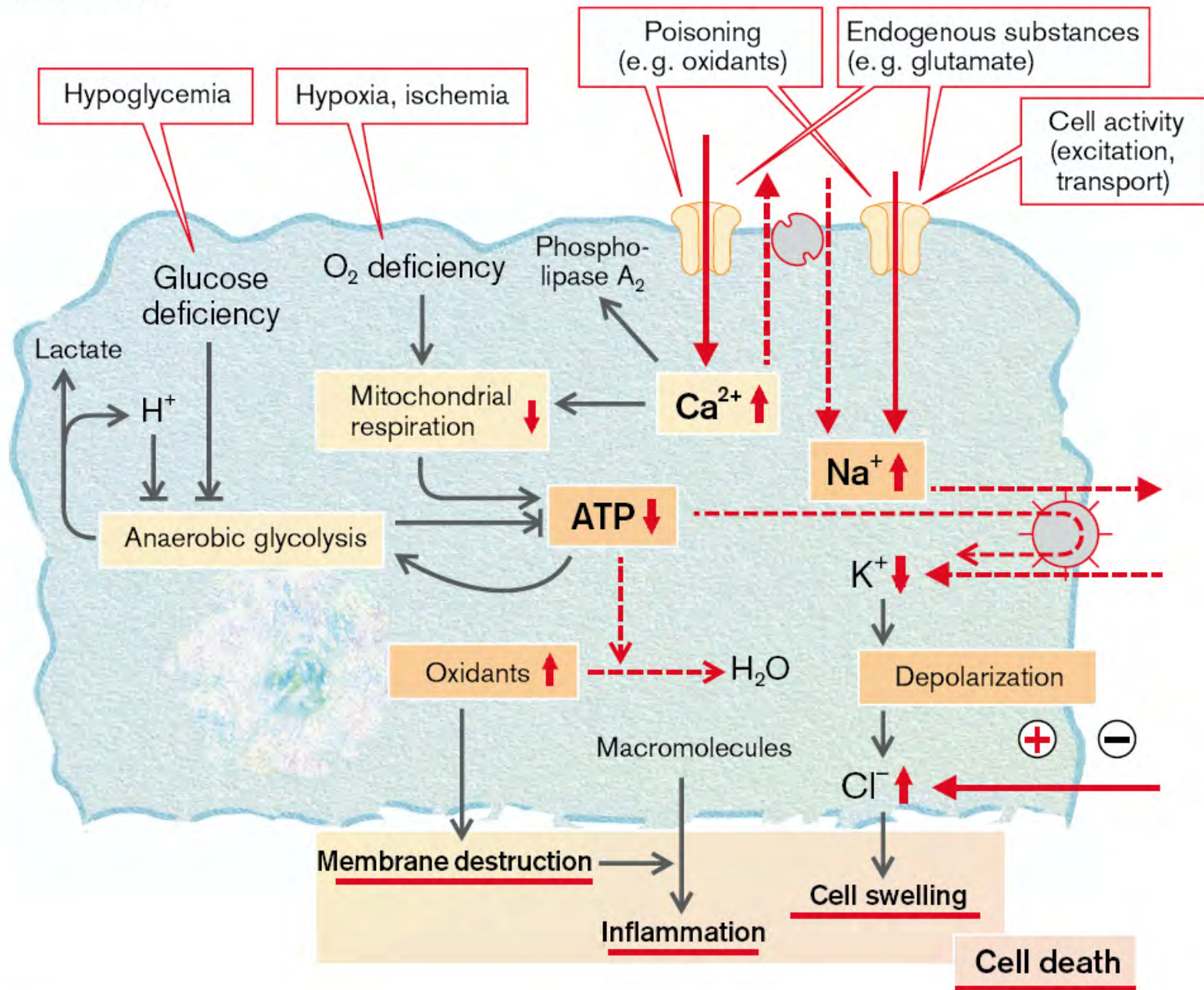
E. Nitric oxide (NO) as a transmitter substance



A. Triggering and Development of Apoptosis



B. Necrosis



Struktura – Transmembránové proteiny Rekonstrukce podle vlastností

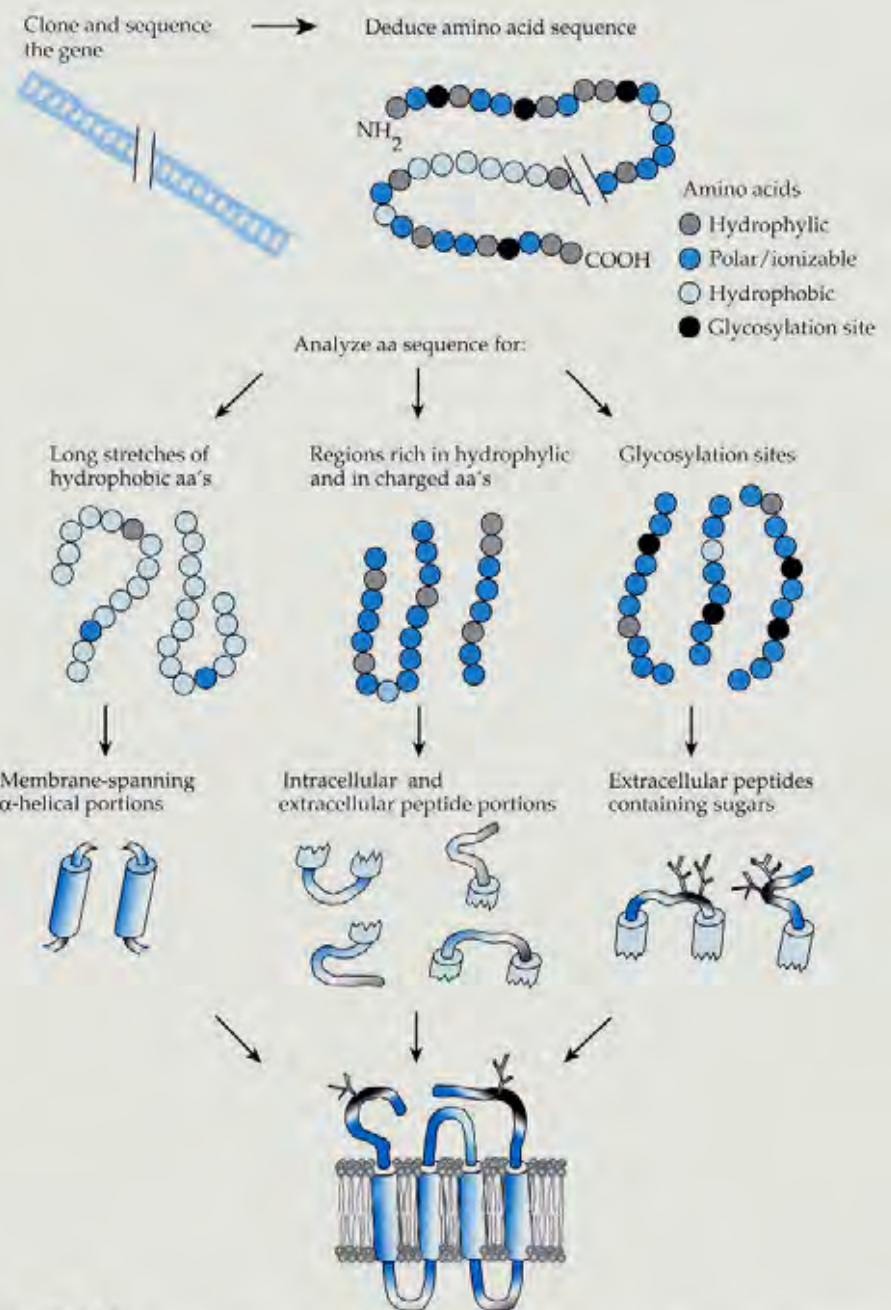
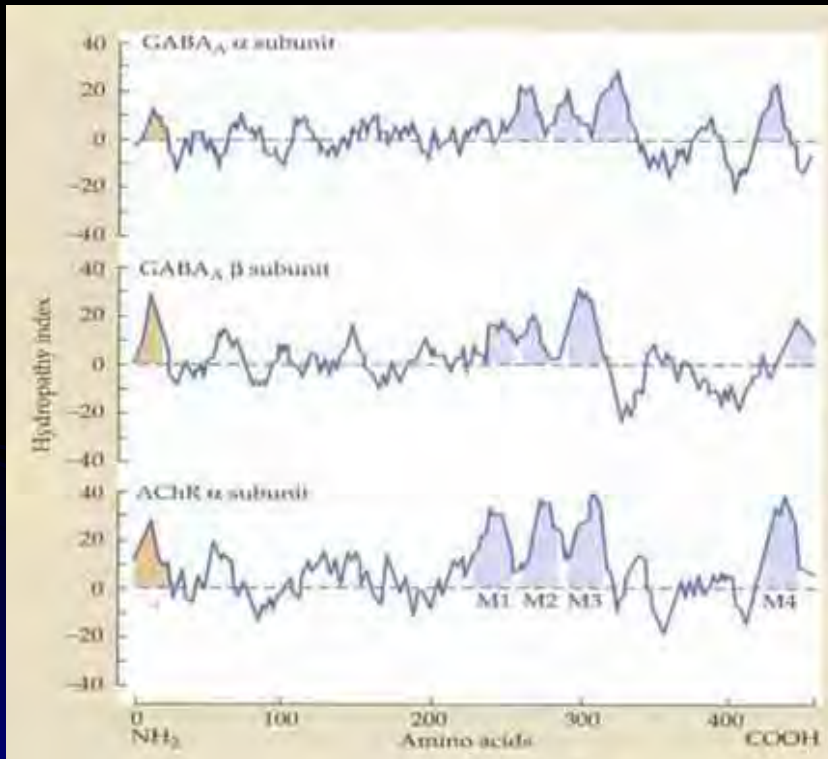
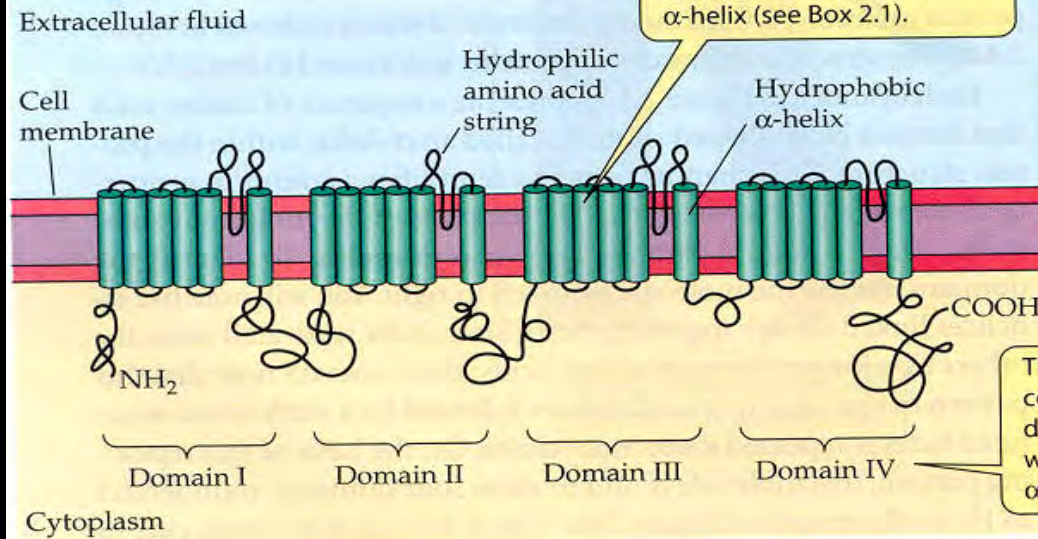


Figure 1.10
Analysis of hydropathy and the folding of membrane proteins The amino acid sequence of a membrane protein can be used to make inferences about protein structure, as described in the text.

(a) Secondary structure (linear presentation)



carbohydrate groups always project from the face, not the inner, cytoplasmic face (see Figure hydrate groups are thought to serve as attachment cellular proteins and as cell recognition sites.

¹ The word fragment *glyco* refers to carbohydrates (after the

Figure 2.4 The structure of a transmembrane pro- gated Na⁺ channel—illustrating several modes of

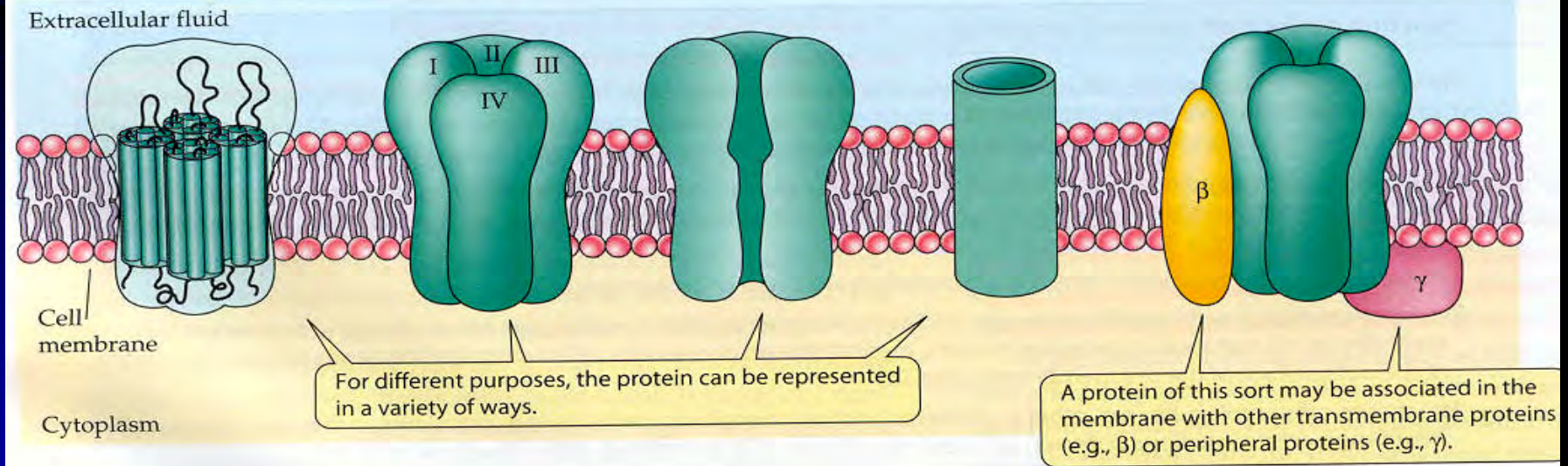
(b) Simplified three-dimensional structure enclosed in a sketch of the envelope of the molecule

(c) Stylized version of chemical structure showing subunits

(d) Semirealistic symbol

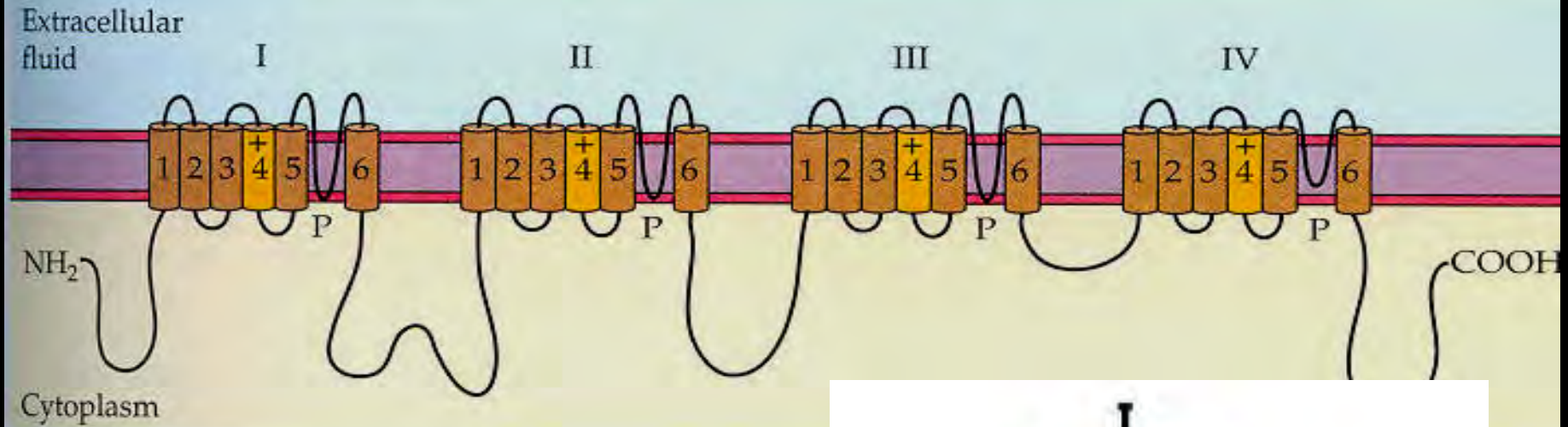
(e) Schematic symbol

(f) Stylized version of chemical structure showing associated protein molecules

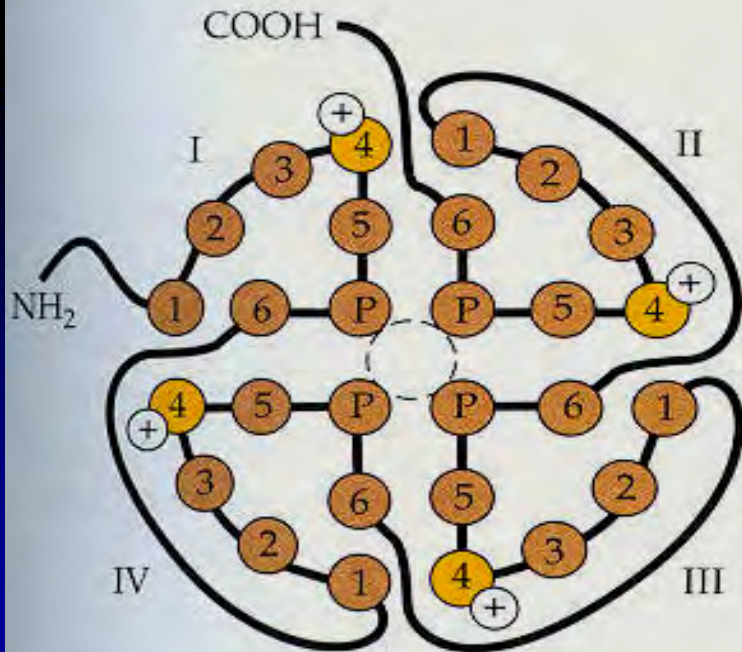


(a) Topology of voltage-gated Na^+ channels

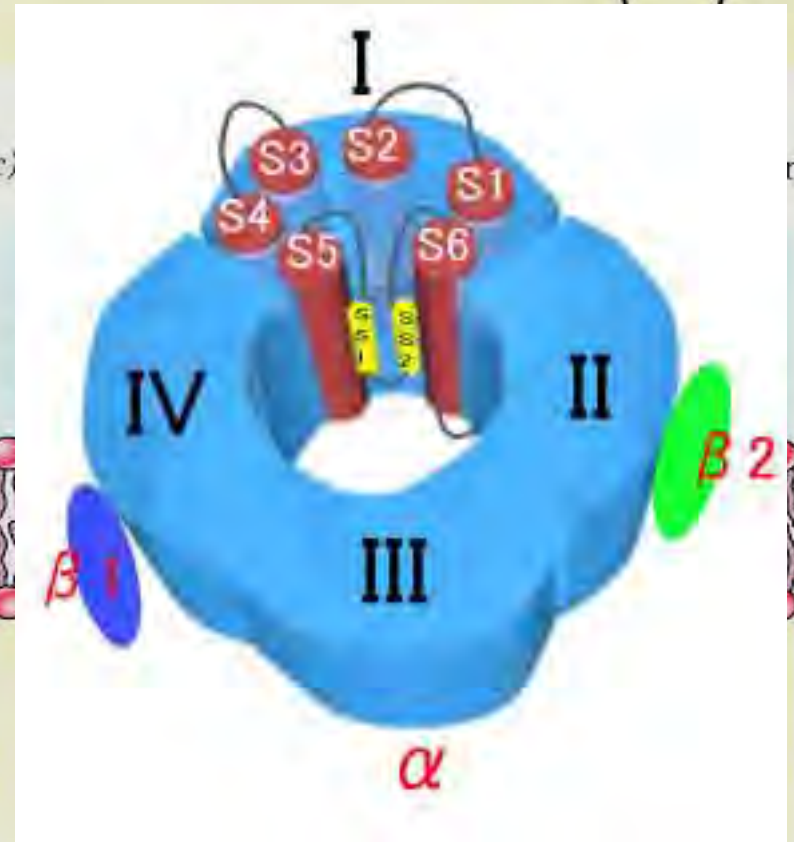
4 domény, 6 segmentů



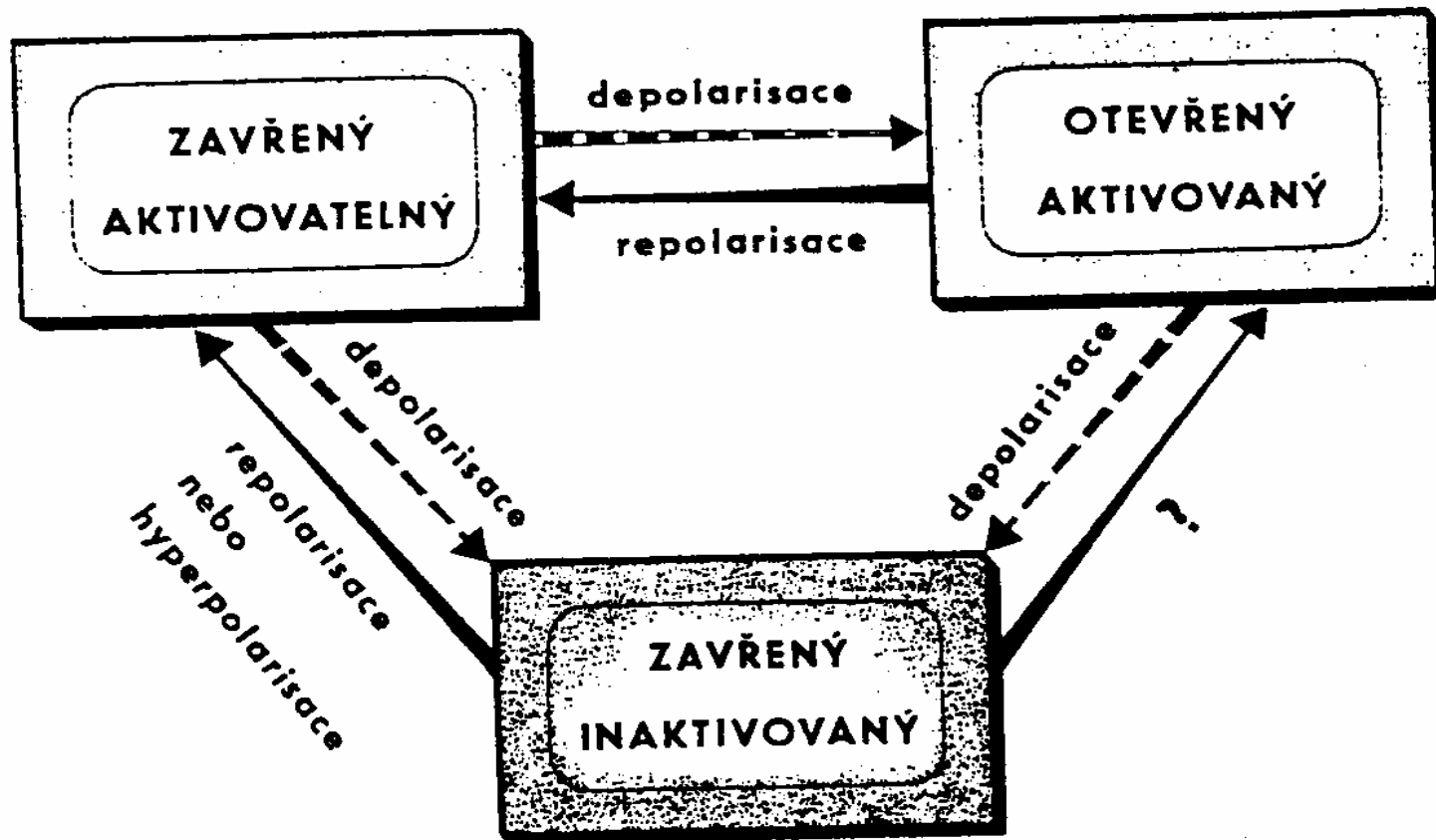
(b) Surface view of a Na^+ channel



(c)

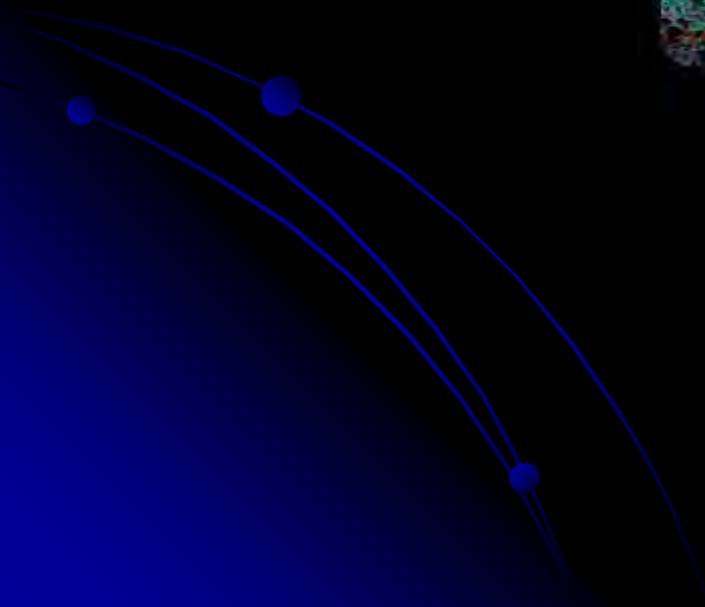
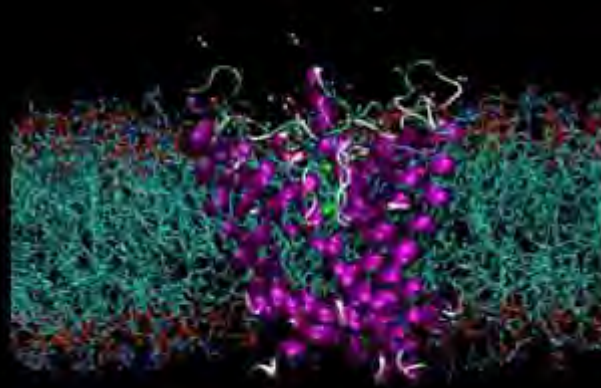


STAVY KANÁLŮ



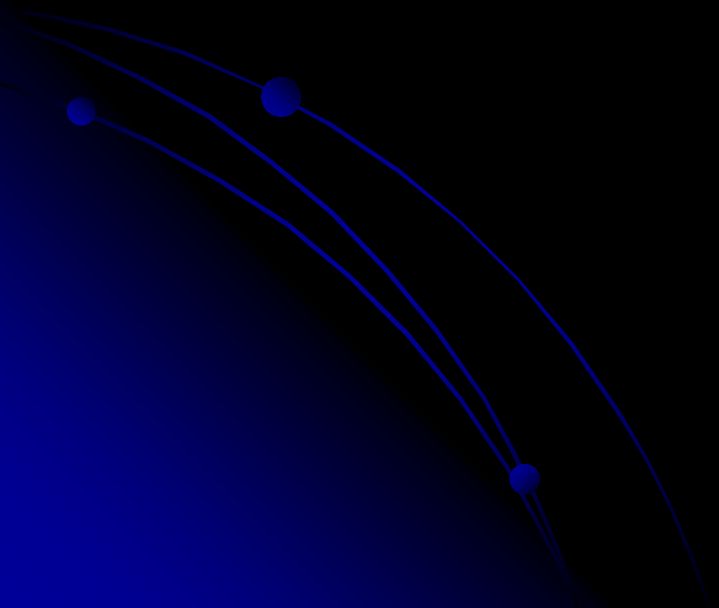
Refrakterní fáze kanálu – omezení frekvence AP

Draslíkový kanál



Na kanál

- Citlivý na napětí
- Selektivní
- Schopný inaktivace



Citlivý na napětí

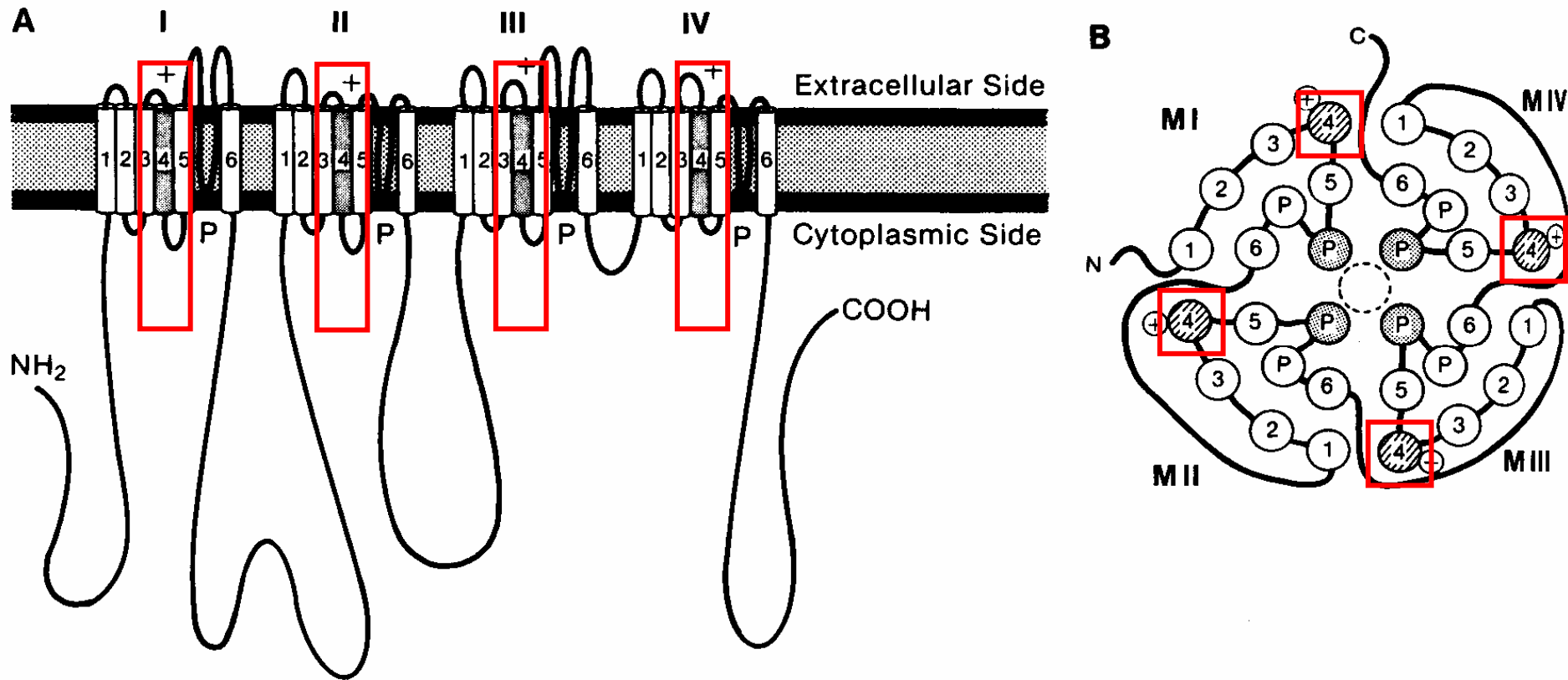
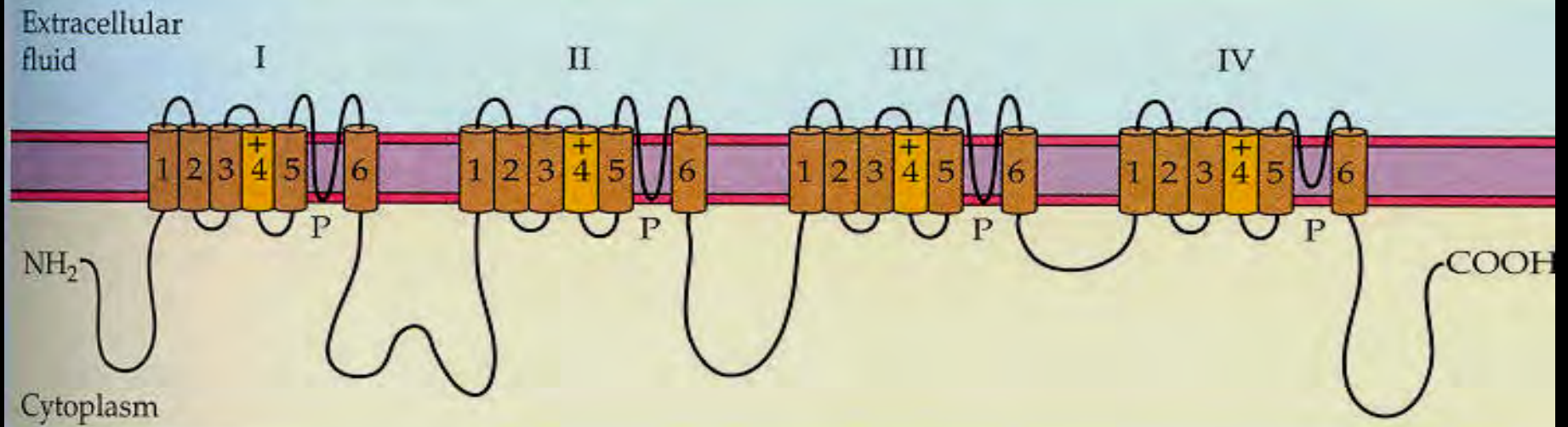
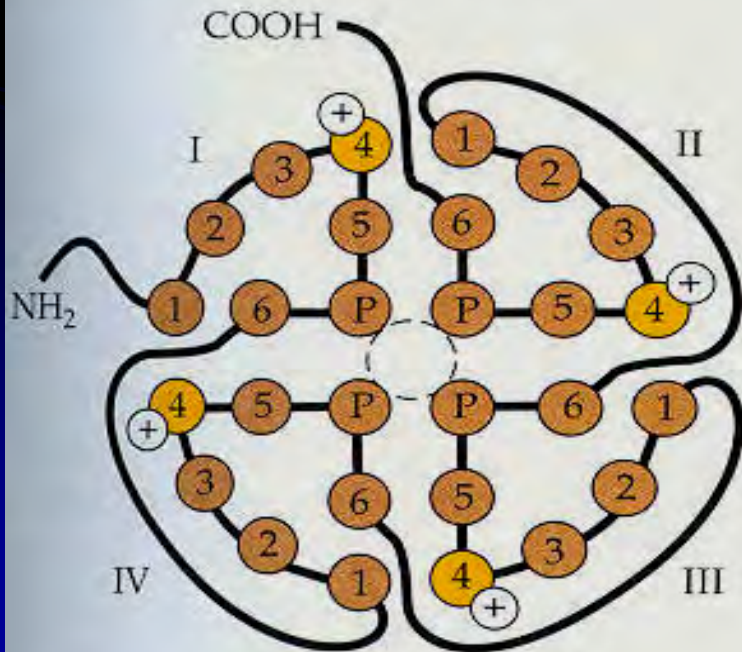


Fig. 5.3 Presumed tertiary structure of the Na⁺ channel protein based on hydropathicity plots of the primary amino acid sequence. **A.** The channel protein consists of four repeating subunits, each containing six presumed transmembrane segments. Segment 4 contains an excess of positively charged residues and is assumed to be the voltage sensor. A long loop between segments 5 and 6 is believed to dip into the membrane and form the face of the pore. A cytoplasmic loop contains the inactivation gate. **B.** View looking down on the membrane to see the arrangement of the four subunits around the central pore. The Ca²⁺ channel protein is similar in its construction. (Modified from Catterall, 1988, and Stevens, 1991, in Kandel et al., 1991)

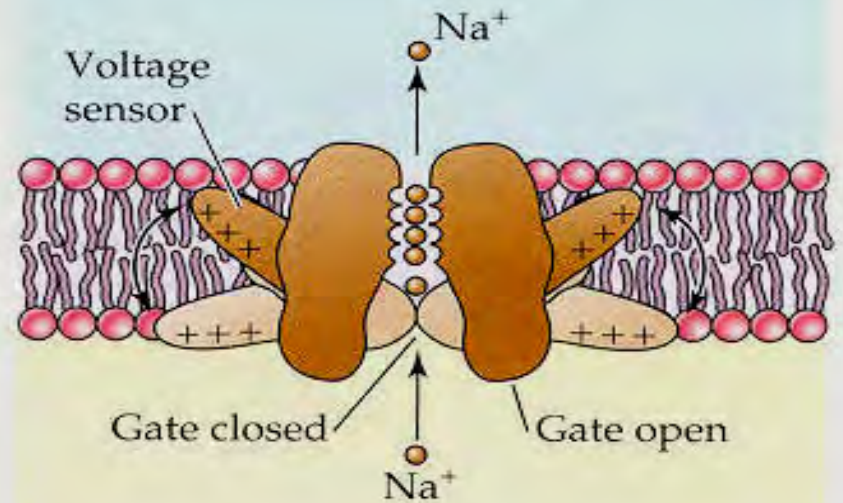
(a) Topology of voltage-gated Na^+ channels



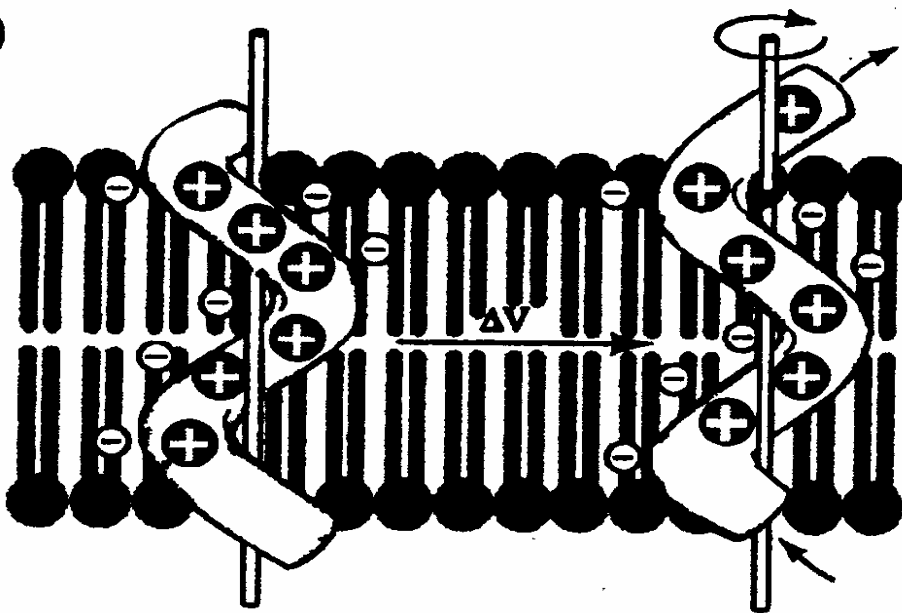
(b) Surface view of a Na^+ channel



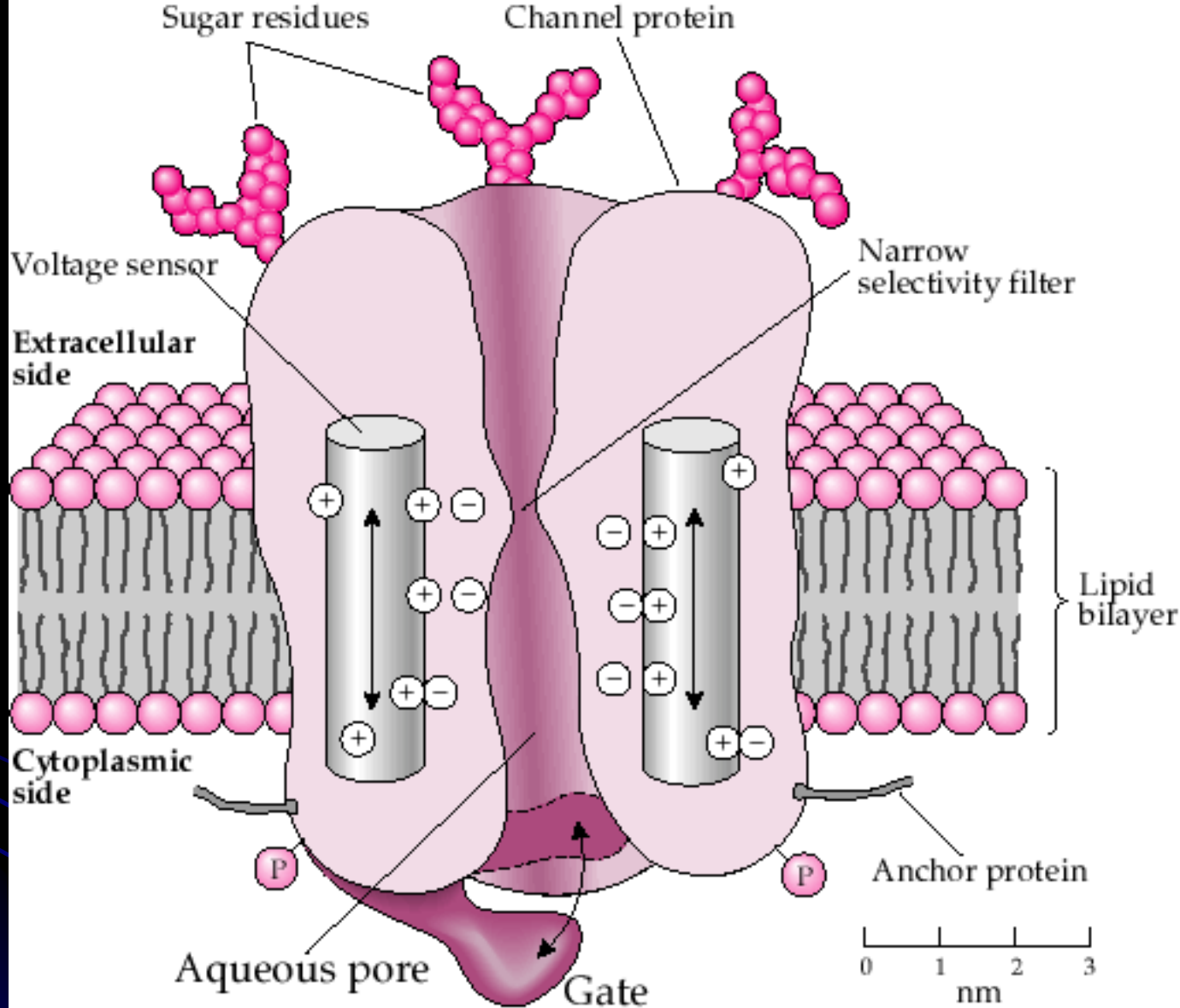
(c) Voltage-dependent conformational change



(B)



Obr. 13 Kluzně šroubový model napěťově závislého vrátkování podle Catteralla. Segment S_4 je zřejmě senzor napětí. Segment S_4 domény III sodíkového kanálu elektrického orgánu parejnoka Torpedo je znázorněn jako transmembránová α šroubovice s řadou pozitivních nábojů, tvořených opakujícími se zbytky "zásadité" aminokyseliny argininu. Každý pozitivní náboj je neutralizován negativním nábojem sousedních transmembránových šroubovic (každá třetí v pořadí sekvence). Vytváří se spirála iontových párů prostupujících membránou. Síla membránového elektrického pole stabilizuje tvorbu iontových párů tím, že táhne pozitivní náboje dovnitř a vytlačuje negativní náboje ven podobně jako jádro v elektromagnetu. Při depolarizaci (ΔV) se tato síla uvolní a šroubovice tvořící segmenty S_4 ve všech 4 homologních doménách se vysunou ven jako uvolněné pružiny ve směru spirály přibližně o 5 Å, přičemž se otočí o 60° tak, že se kladné náboje posunou vzhledem k sousední šroubovici o jedno místo ven z buňky. Dojde tím ke snížení kladného náboje na vnitřní straně membrány. Je zajímavé (A), že velmi podobné uspořádání bazických argininových nebo lysinových kladně nabitých zbytků nacházíme v tomto předpokládaném napěťovém senzoru S_4 jak u sodíkového kanálu z parejnoka či mozku potkana, tak ve vápníkovém kanálu králíčího kosterního svalu a v draslíkovém kanálu mutanta Shaker octomilky *Drosophila melanogaster* (viz obr. 14). (Podle Catterall 1988)



Sinauer Associates, Inc.
 Feldman
*Fundamentals of
 Neuropsychopharmacology*
 Fig. 5-8

Fig 5.8 Basic Model of a Voltage Gated Ion Channel

Selektivní

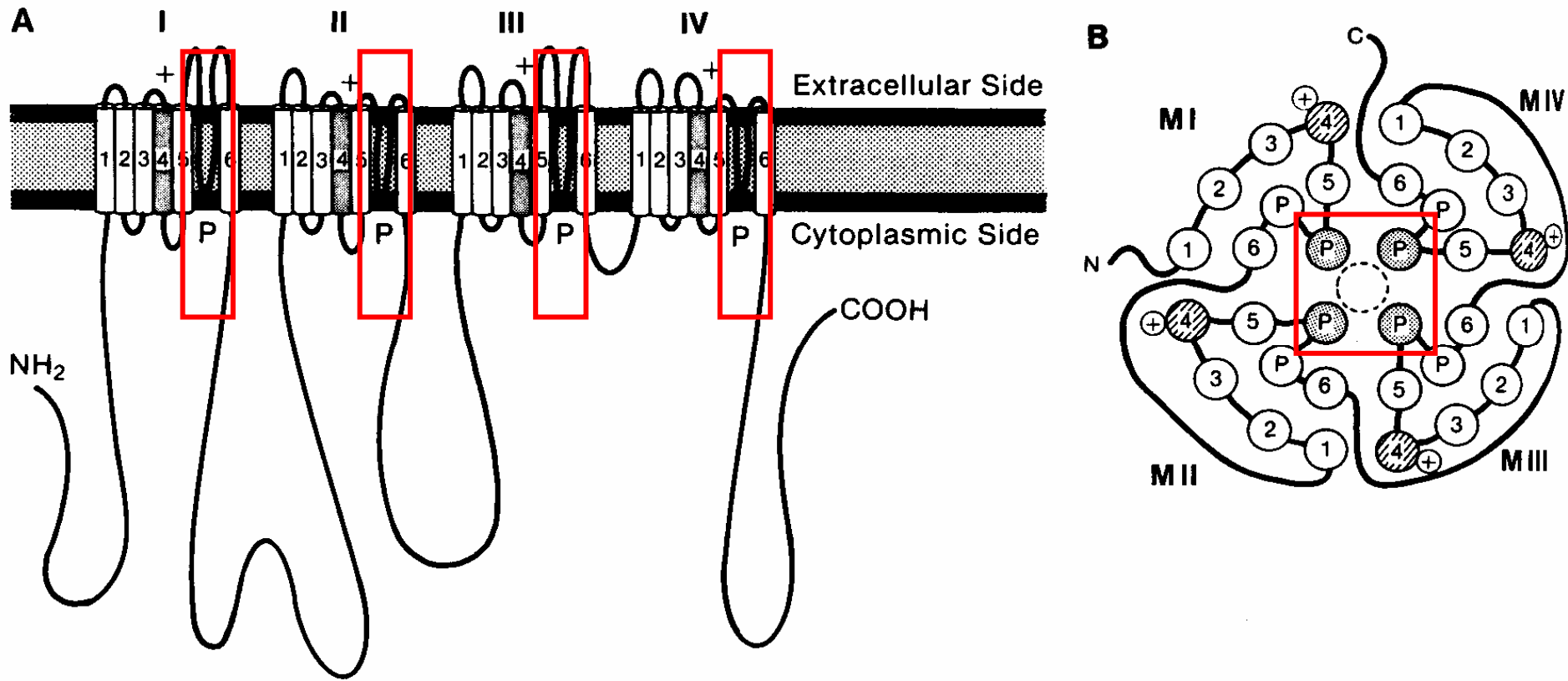


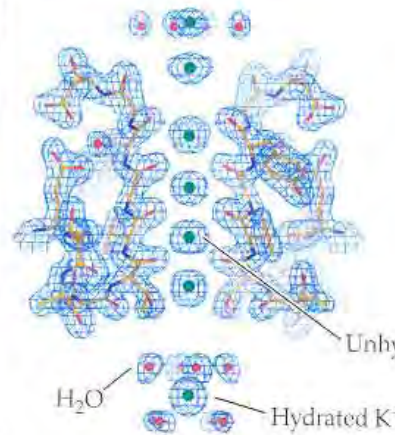
Fig. 5.3 Presumed tertiary structure of the Na⁺ channel protein based on hydropathicity plots of the primary amino acid sequence. **A.** The channel protein consists of four repeating subunits, each containing six presumed transmembrane segments. Segment 4 contains an excess of positively charged residues and is assumed to be the voltage sensor. A long loop between segments 5 and 6 is believed to dip into the membrane and form the face of the pore. A cytoplasmic loop contains the inactivation gate. **B.** View looking down on the membrane to see the arrangement of the four subunits around the central pore. The Ca²⁺ channel protein is similar in its construction. (Modified from Catterall, 1988, and Stevens, 1991, in Kandel et al., 1991)

Selektivita K⁺ kanálu *Streptomyces*

(a) K⁺ channel structure



(b) Ion selectivity filter



(c) Model of ion permeation

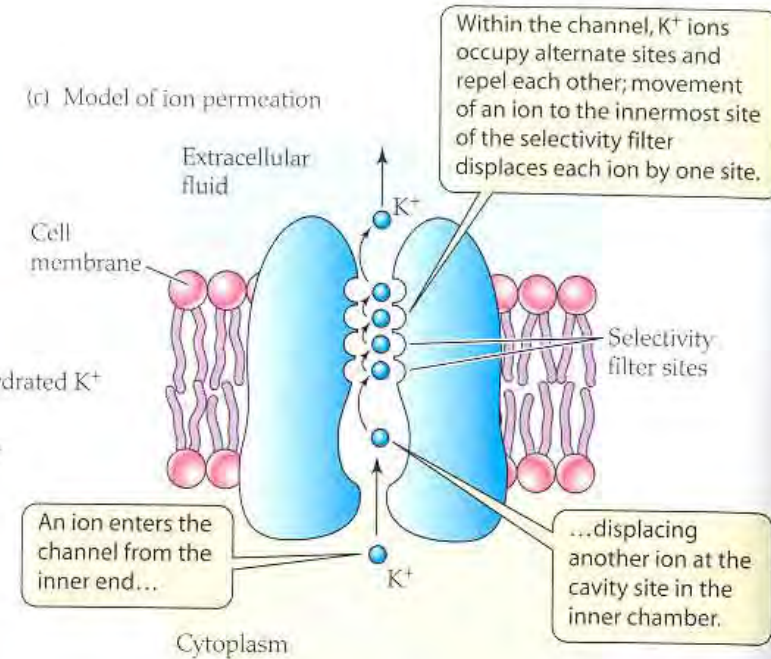
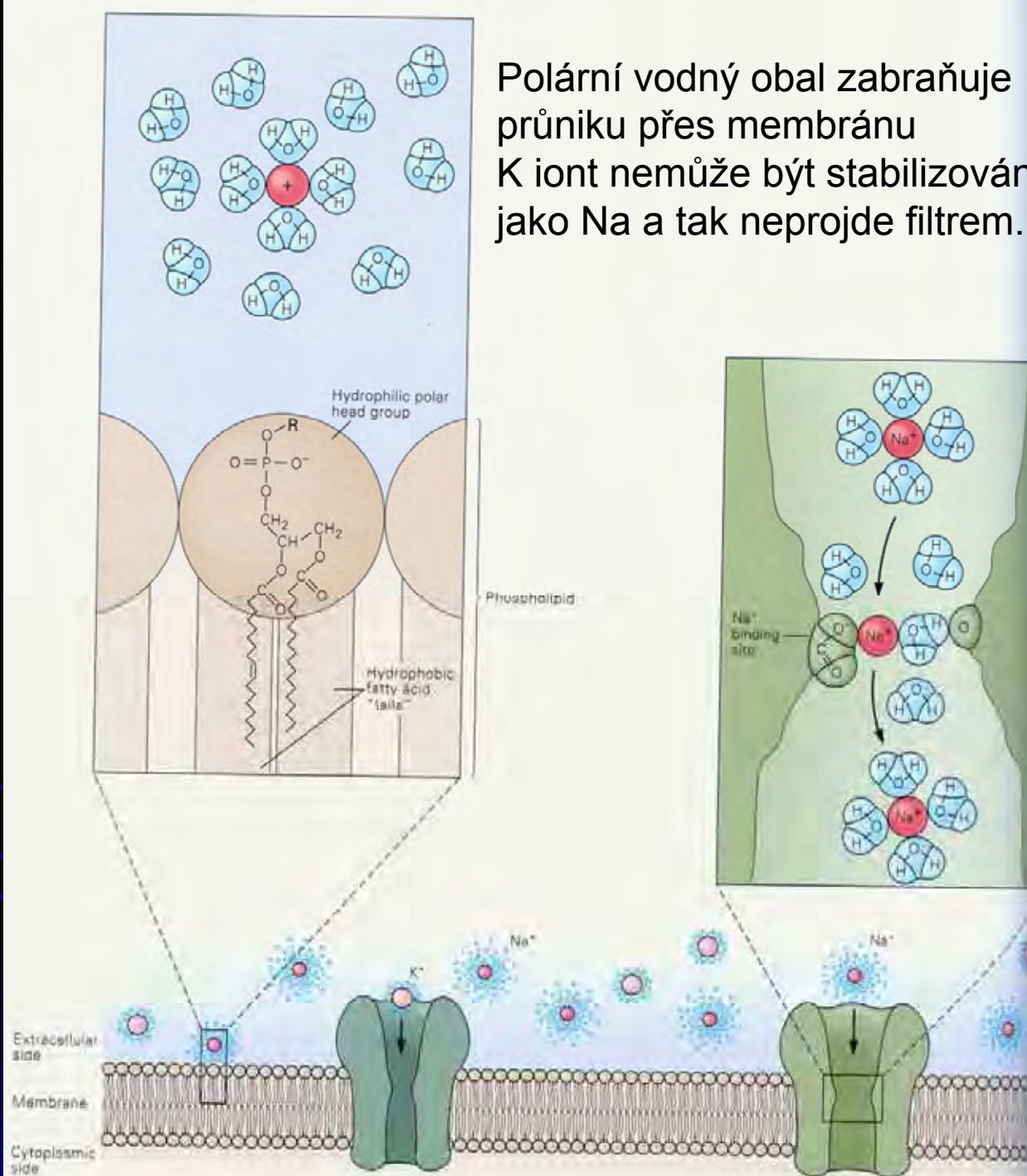


Figure 11.22 Ion permeation through K⁺ channels (a) The structure of a bacterial K⁺ channel as determined by X-ray diffraction. The subunits correspond to membrane-spanning segments 5 and 6 and the P loop of voltage-gated channels (see the figure in Box 11.1). The narrow ion-selective pore is lined by the P loop of each of the four subunits (yellow; only two of the four are visible here), and it has four sites that can be occupied by K⁺ ions (green spheres). An additional K⁺ ion can occupy an inner cavity below the selectivity filter. (b) Sites occupied by K⁺ ions in and near the selectivity filter. K⁺ ions are normally surrounded by polar water molecules, but in the pore of a potassium channel, oxygen atoms lining the pore compete with water molecules to attract the cation. The image shows a K⁺ ion in the inner chamber with eight water molecules around it (bottom), four unhydrated K⁺ ions at the selectivity filter sites, a K⁺ ion at the outer face of the pore, and a K⁺ ion with a partial shell of four water molecules (top). (c) A model of K⁺ ion permeation. This chain reaction allows the channel to be both highly selective and highly permeable to K⁺. (a from Morais-Cabral et al. 2001; b from Zhou et al. 2001; c after Miller 2001.)

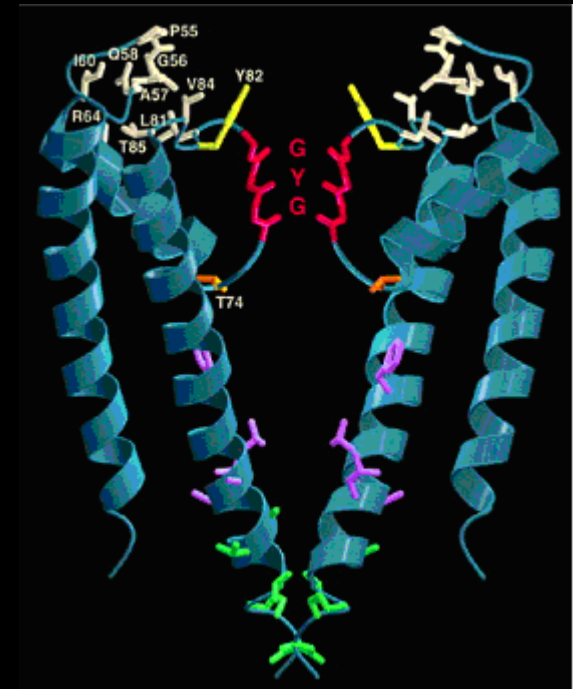
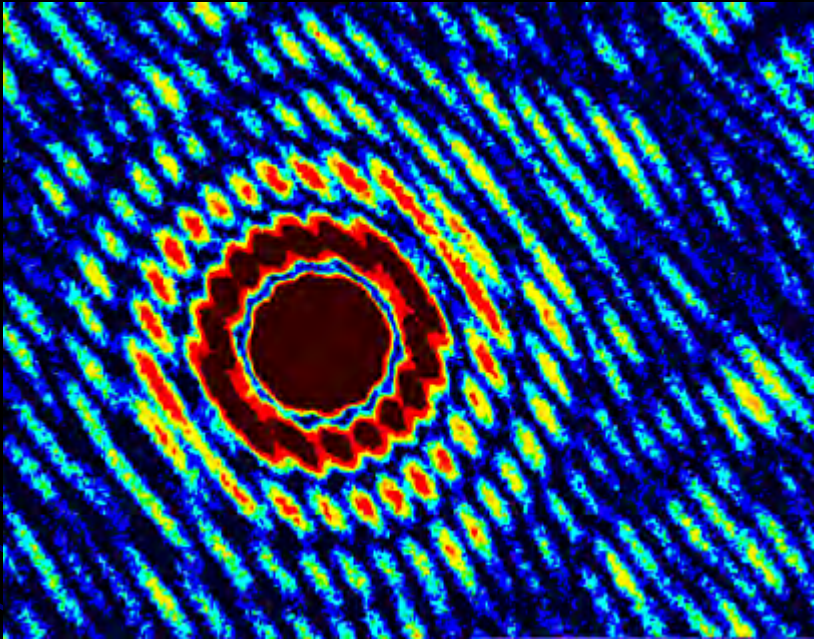
with short axons or no axons, so a graded potential change at one of the cell can spread passively (electrotonically) to the terminal without major decrement.

The inputs and outputs of spiking and nonspiking neurons are the same, but the short-axon nonspiking neuron does not require spiking encoding to carry the signal over large distances. Examples of nonspiking neurons include the photoreceptors, bipolar cells, and horizontal cells of the vertebrate retina (see Chapter 13), granule cells of the olfactory bulb, and many arthropod interneurons.

Polární vodný obal zabraňuje průniku přes membránu
K iont nemůže být stabilizován jako Na a tak neprojde filtrem.

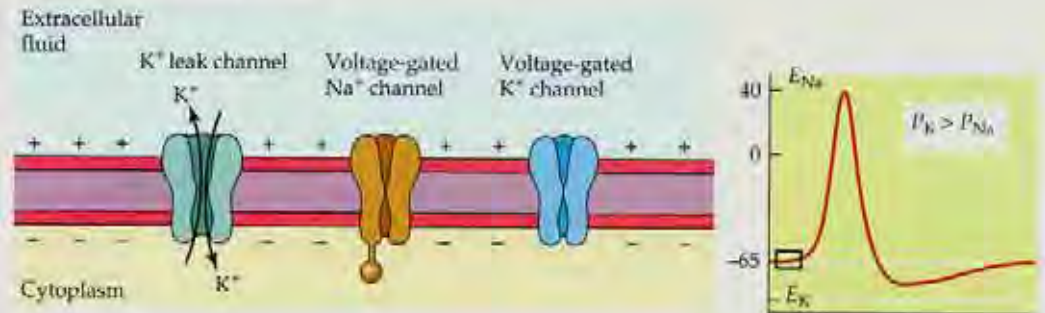


X-ray crystallography

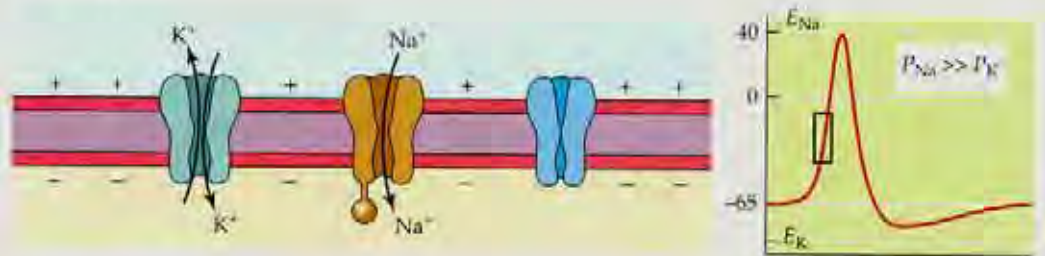


Schopný inaktivace

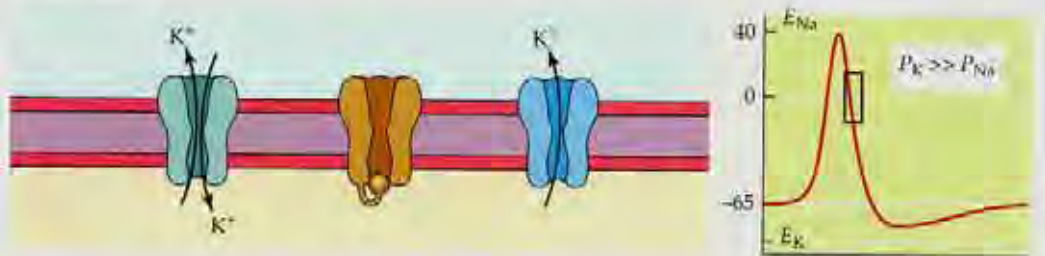
(a) Resting membrane potential



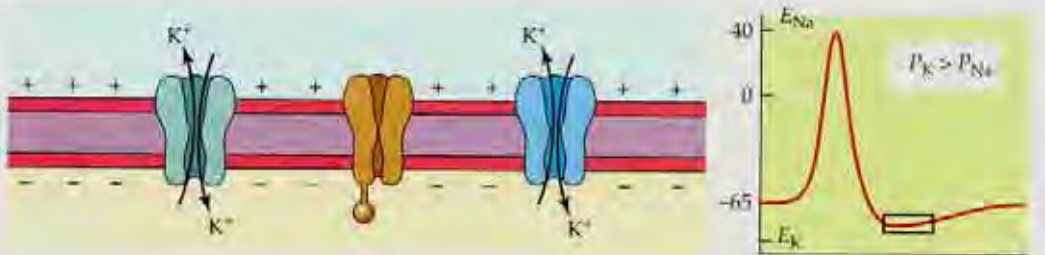
(b) Rising phase



(c) Falling phase



(d) Recovery



Schopný inaktivace

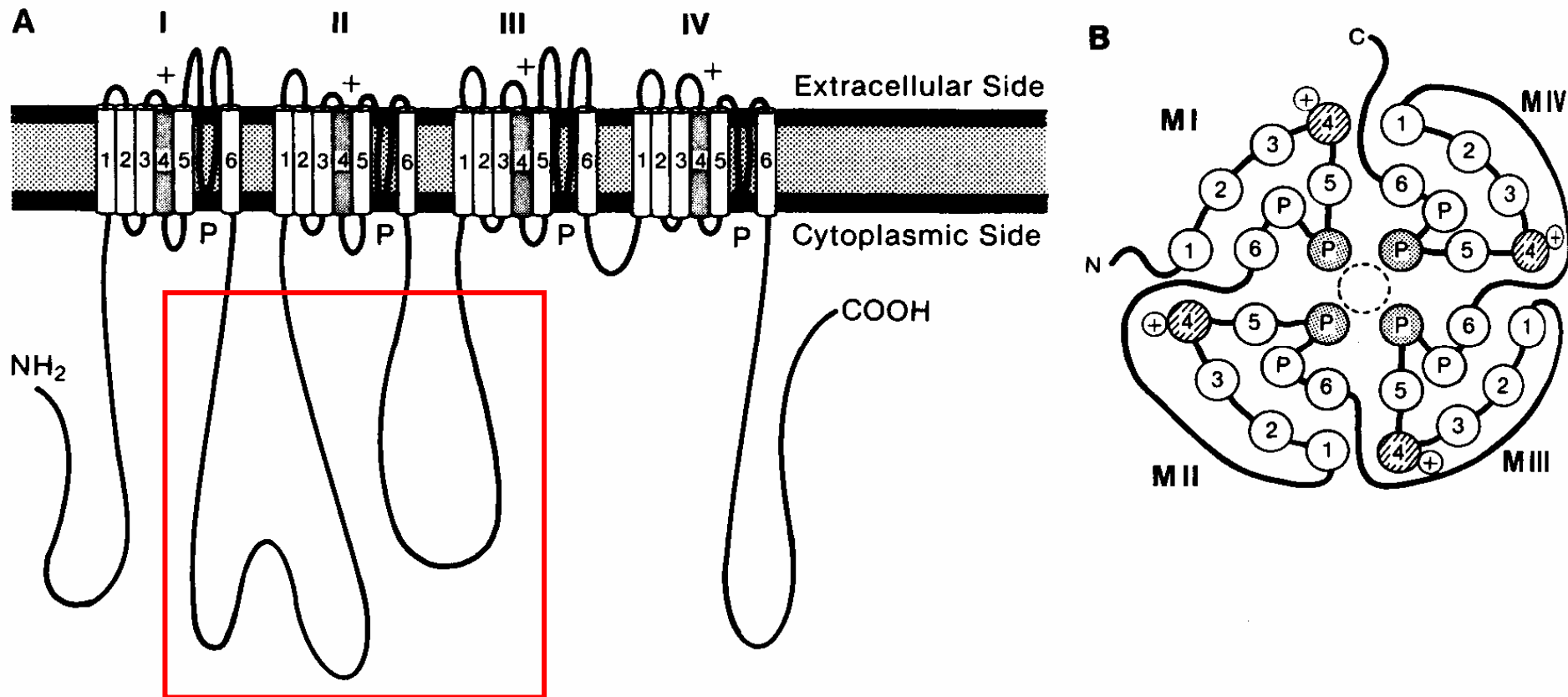


Fig. 5.3 Presumed tertiary structure of the Na⁺ channel protein based on hydropathicity plots of the primary amino acid sequence. **A.** The channel protein consists of four repeating subunits, each containing six presumed transmembrane segments. Segment 4 contains an excess of positively charged residues and is assumed to be the voltage sensor. A long loop between segments 5 and 6 is believed to dip into the membrane and form the face of the pore. A cytoplasmic loop contains the inactivation gate. **B.** View looking down on the membrane to see the arrangement of the four subunits around the central pore. The Ca²⁺ channel protein is similar in its construction. (Modified from Catterall, 1988, and Stevens, 1991, in Kandel et al., 1991)



**The Nobel Prize in Physiology or
Medicine 1991**

Patch Clamp – Technika, která „vidí“ kanály při práci

"for their discoveries concerning the function of single ion
channels in cells"



Erwin Neher

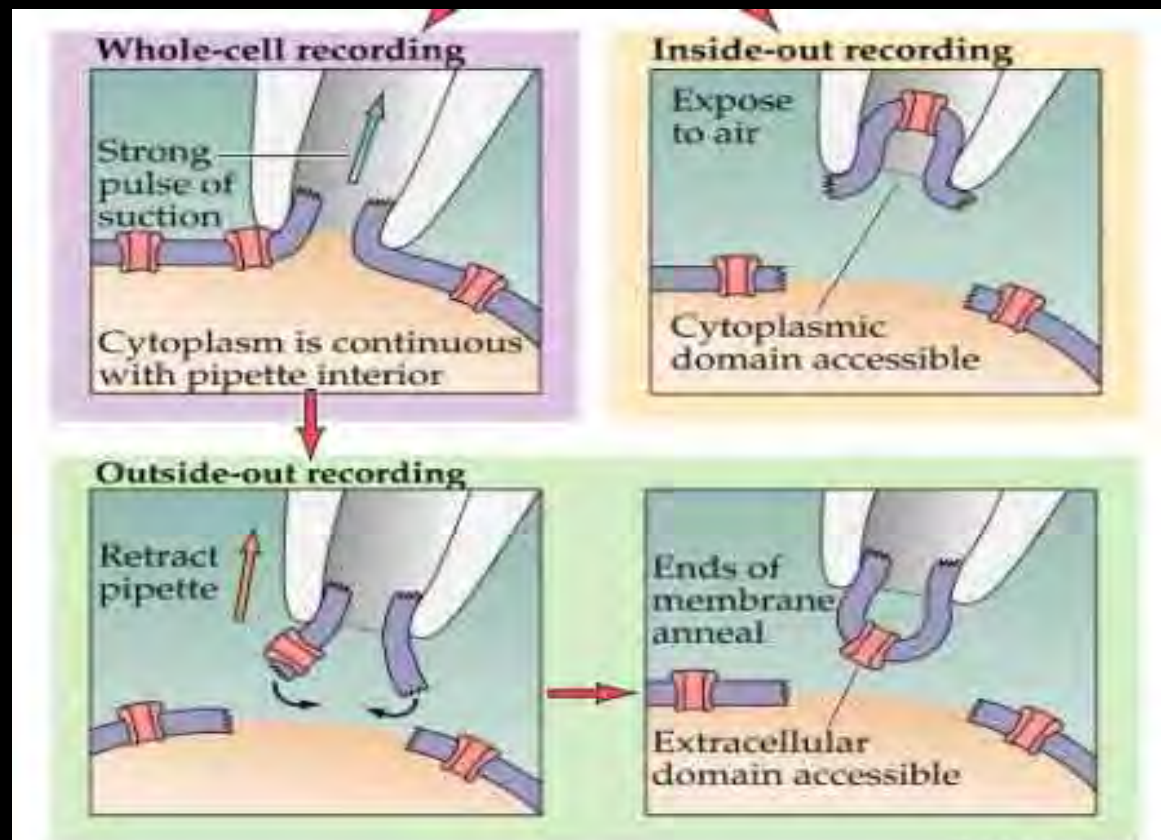
1/2 of the prize
Federal Republic of
Germany
Max-Planck-Institut für
Biophysikalische
Chemie
Goettingen, Federal
Republic of Germany
b. 1944

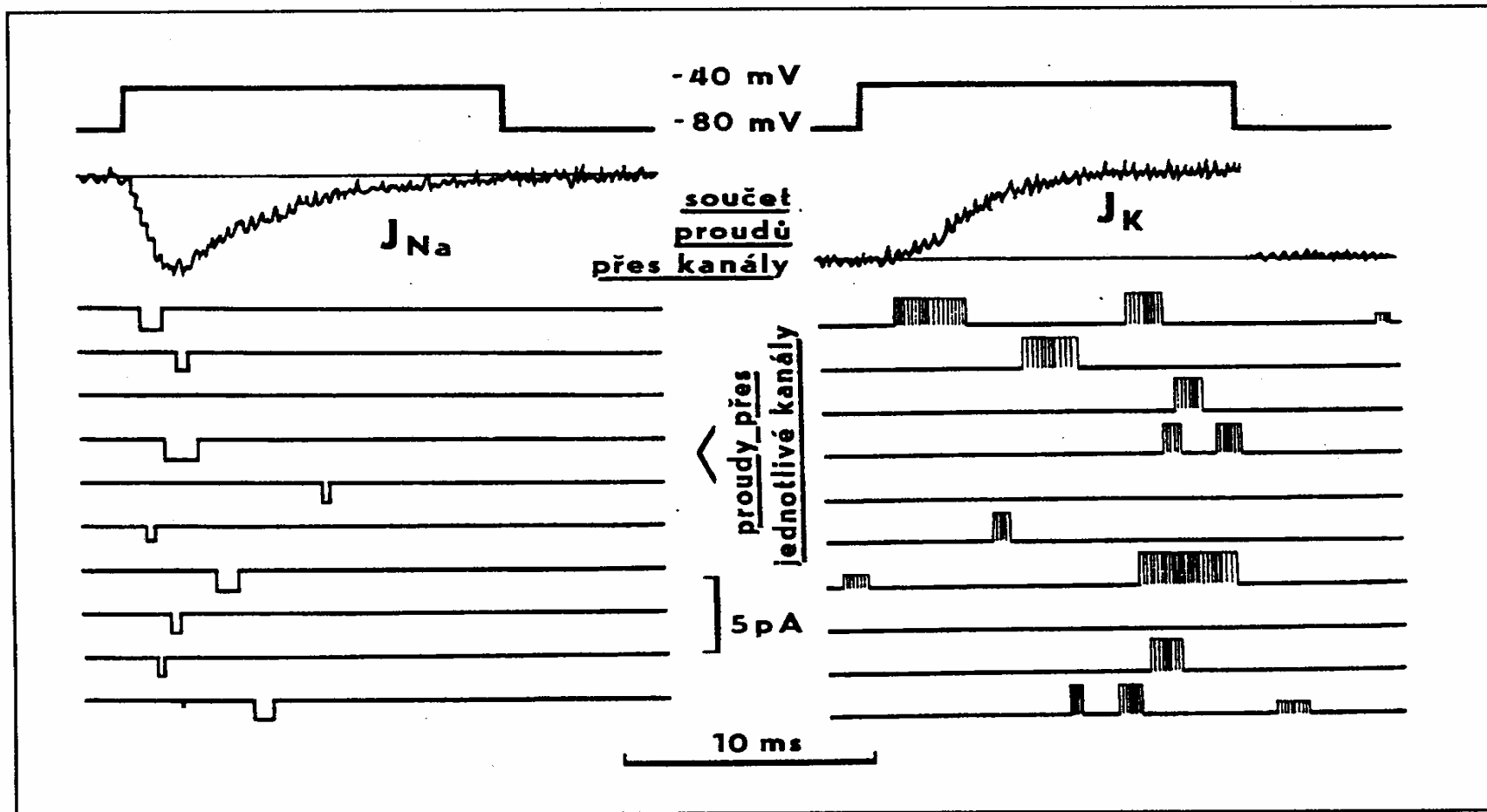


Bert Sakmann

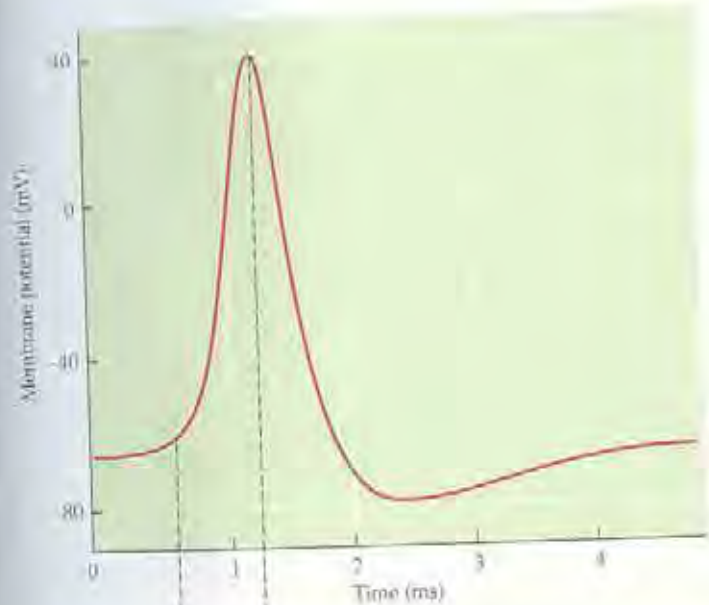
1/2 of the prize
Federal Republic of
Germany
Max-Planck-Institut für
medizinische Forschung
Heidelberg, Federal
Republic of Germany

b. 1942





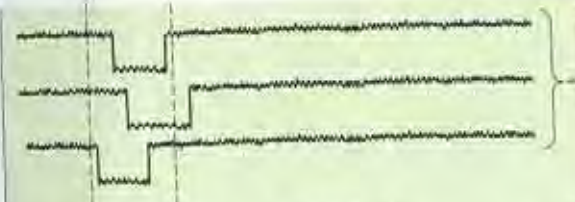
Obr. 14.18 Proudý tekoucí Na^+ -kanály (vlevo) a K^+ -kanály (vpravo). Membránové napětí bylo po dobu 14 ms experimentálně skokem přestaveno z -80 mV na -40 mV (horní křivka), a to bylo desetkrát opakováno. Přitom byly měřeny membránové proudy (10 křivek v dolejší části obr.). Proudý proteklé jednotlivými kanály se objevují porůznu během depolarisace a trvají různě dlouho. Sumací takovýchto záznamů vzniká záznam sumačního proudů, J_{Na} popř. J_K (zubatá křivka). Je vidět, že u Na^+ -kanálů je otevření nejpravděpodobněji krátce po změně napětí na membráně a že pak dochází k pozvolné inaktivaci. K^+ -kanály se naproti tomu otvírají v průměru s jistým zpožděním, pak se však ustavuje určitá střední častota otevření, která zůstává konstantní po celou dobu depolarisace. (Z DUDELA 1990b)



ing current, the time course of the site to each other: the Hodgkin cycle resulting from pe membrane pot

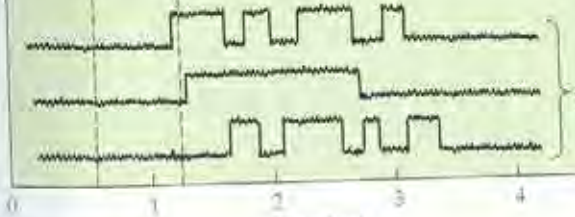
In 1952, Al landmark pap demonstrate an underlying the mental result o potential is cla current-measu required to se charge stored l not ionic curie a shift in accur

(a) Inward currents through Na⁺ channels



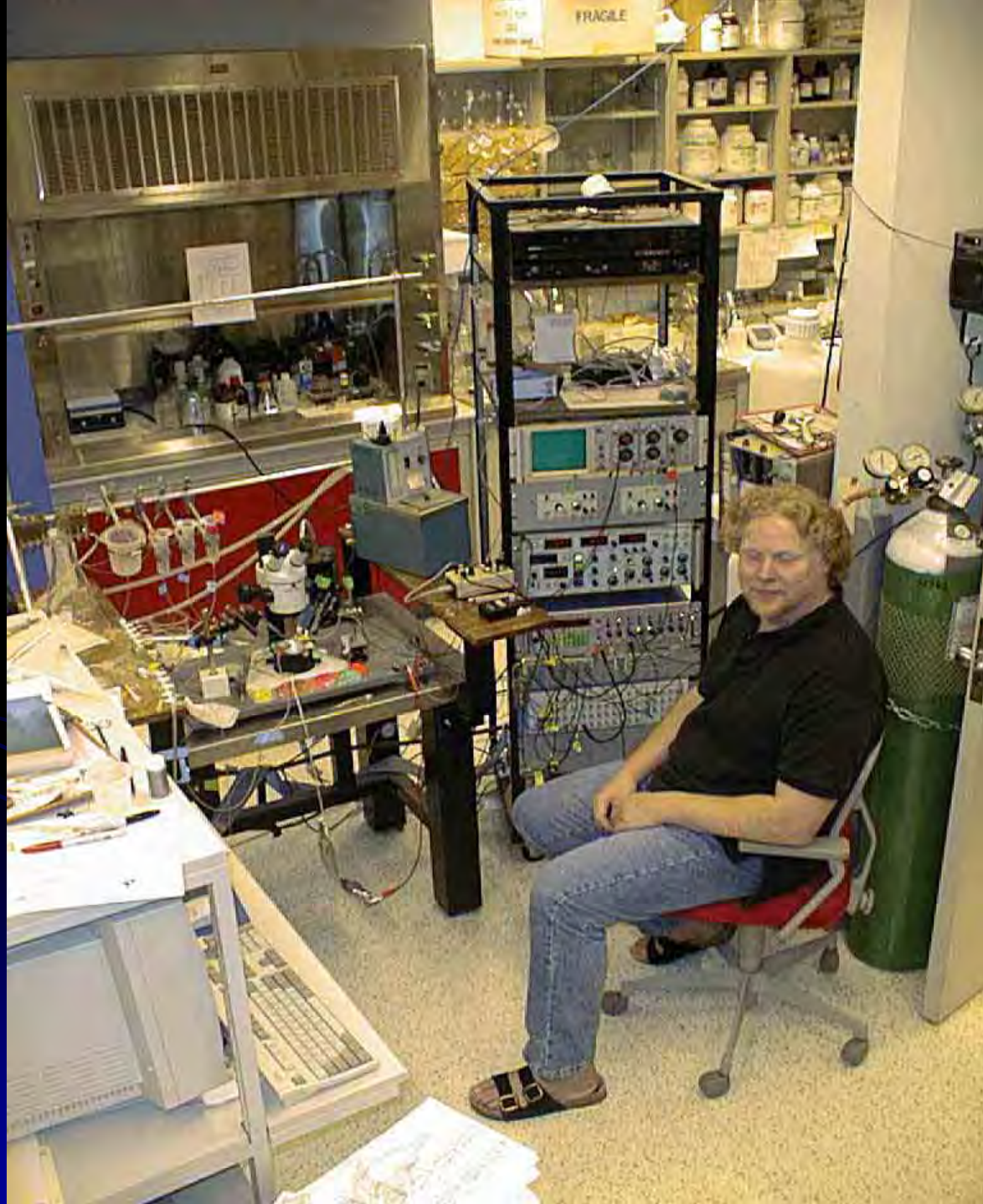
Each Na⁺ channel opens with little delay following initial depolarization, and stays open for less than a millisecond before becoming inactivated.

(b) Outward currents through K⁺ channels

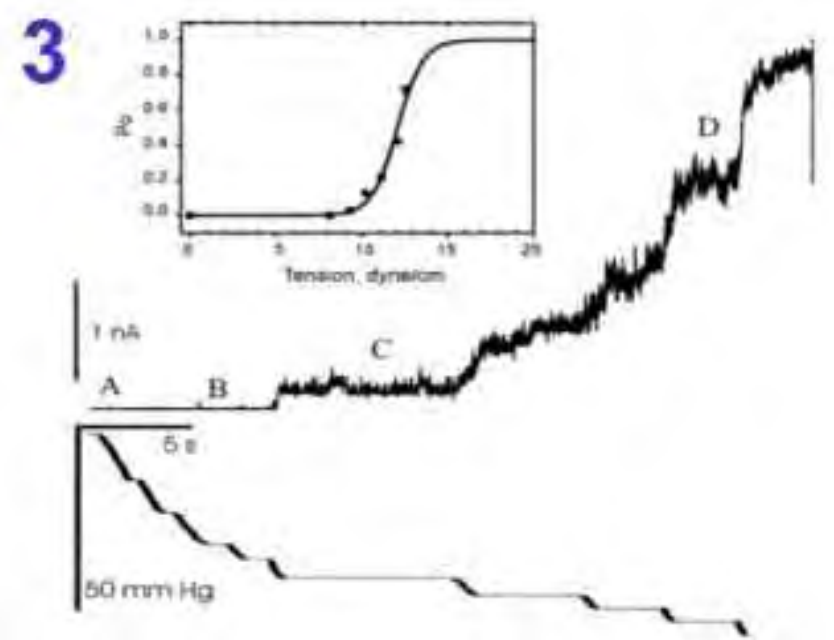
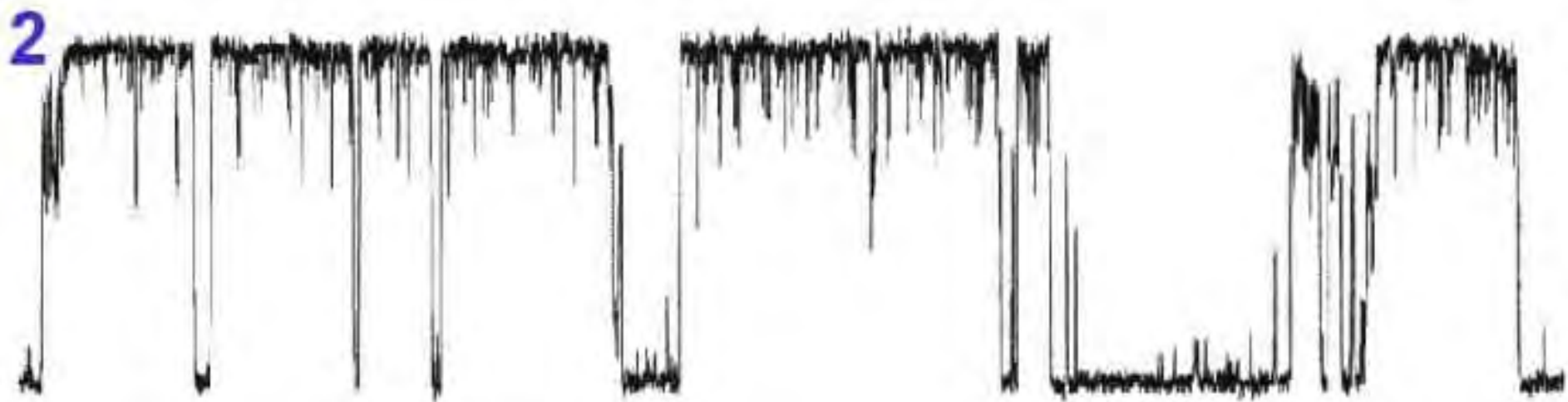


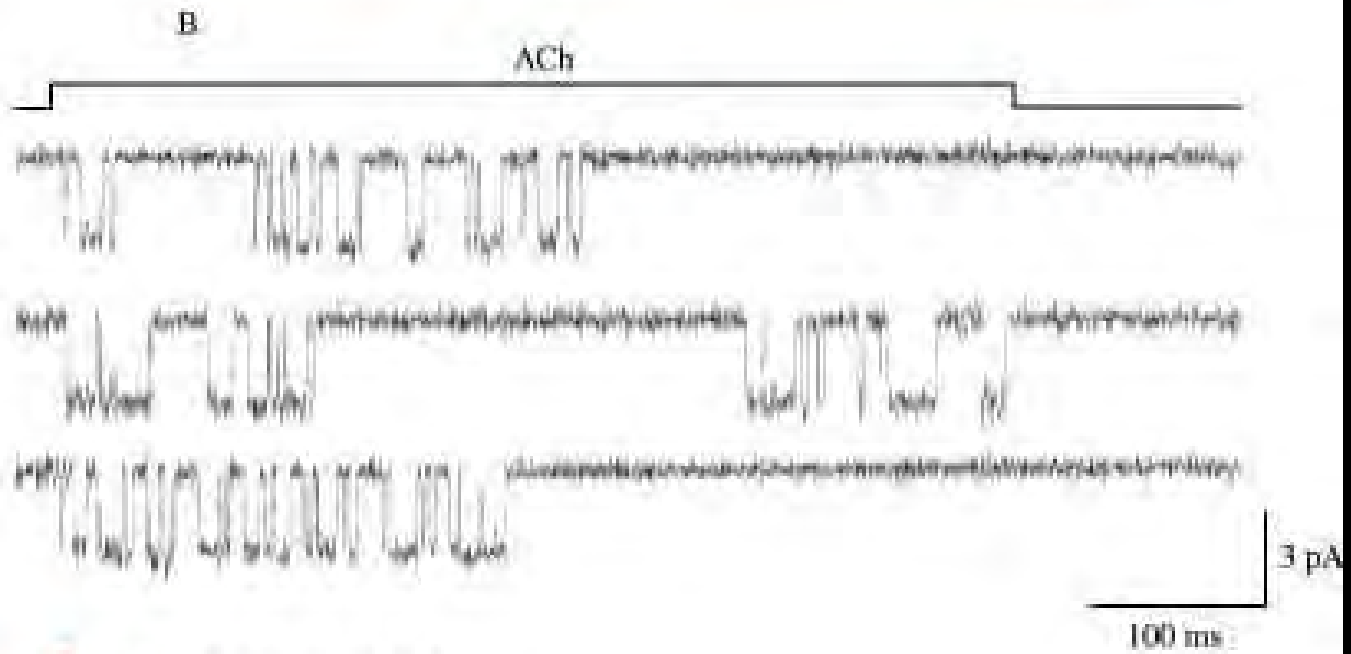
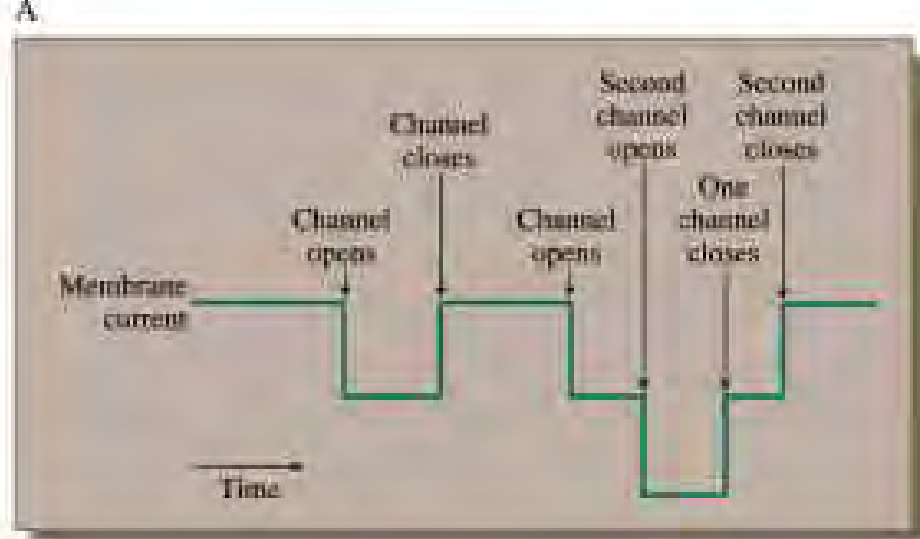
The voltage-gated K⁺ channels open slightly later and can stay open until shortly after membrane repolarization.





Animace patch clamp





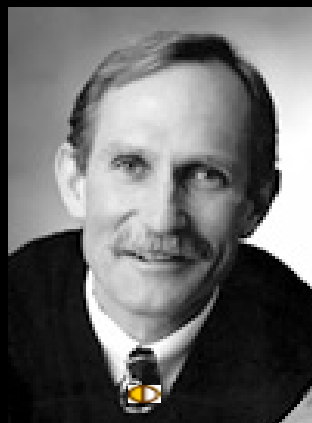
The Nobel Prize in Chemistry 2003



"for discoveries concerning channels in cell membranes"

"for the discovery of water channels"

"for structural and mechanistic studies of ion channels"



Peter Agre

1/2 of the prize

USA

Johns Hopkins University
School of Medicine
Baltimore, MD, USA

b. 1949



Roderick MacKinnon

1/2 of the prize

USA

Rockefeller University
New York, NY, USA; Howard
Hughes Medical Institute

b. 1956

Roderick MacKinnon and Ion Channels

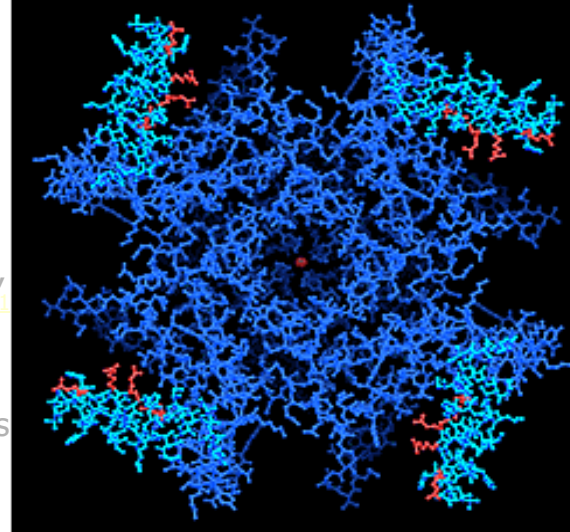


Roderick MacKinnon, M.D., a visiting researcher at the U.S. Department of Energy's Brookhaven National Laboratory, is a recipient of the 2003 Nobel Prize in Chemistry 'for structural and mechanistic studies of ion channels.,

His research explains "how a class of proteins helps to generate nerve impulses – the electrical activity that underlies all movement, sensation, and perhaps even thought. The work leading to the prize was done primarily at the Cornell High Energy Synchrotron Source [CHESS] and the National Synchrotron Light Source [NSLS] at Brookhaven.

The proteins, called ion channels, are tiny pores that stud the surface of all of our cells. These channels allow the passage of potassium, calcium, sodium, and chloride molecules called ions. Rapid-fire opening and closing of these channels releases ions, moving electrical impulses from the brain in a wave to their destination in the body."

"Potassium channels act as both gateways and gatekeepers on cell membranes, controlling the flow of ions and enabling brains to think, muscles to move, and hearts to beat. Malfunctioning ion channels contribute to epilepsy, arrhythmia, and other diseases."²



An overhead view of a voltage-dependent potassium ion channel shows four red-tipped "paddles" that open and close in response to positive and negative charges. This structure, discovered by Rockefeller scientists, shows for the first time the molecular mechanism by which potassium ions are allowed in and out of living cells during a nerve or muscle impulse.

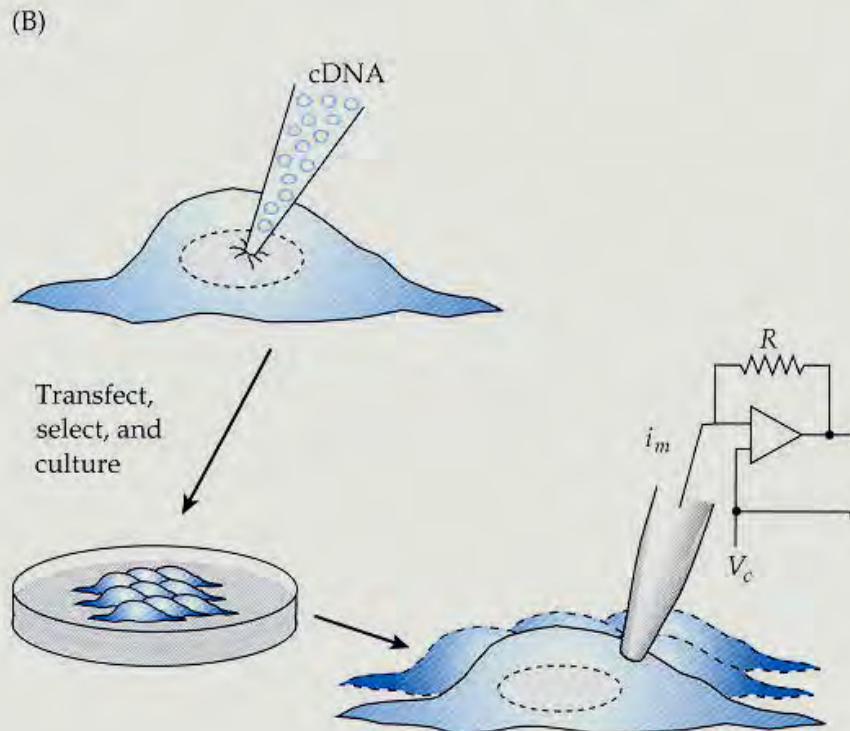
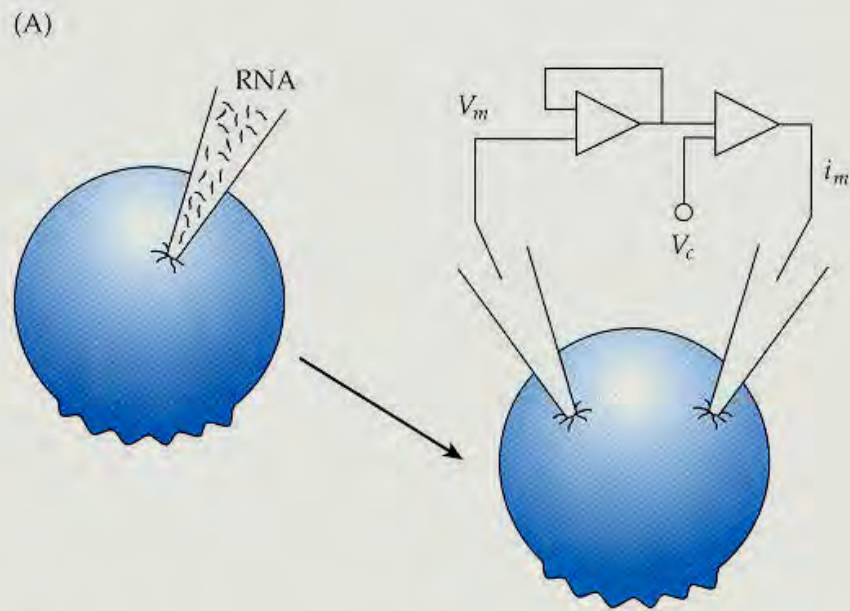
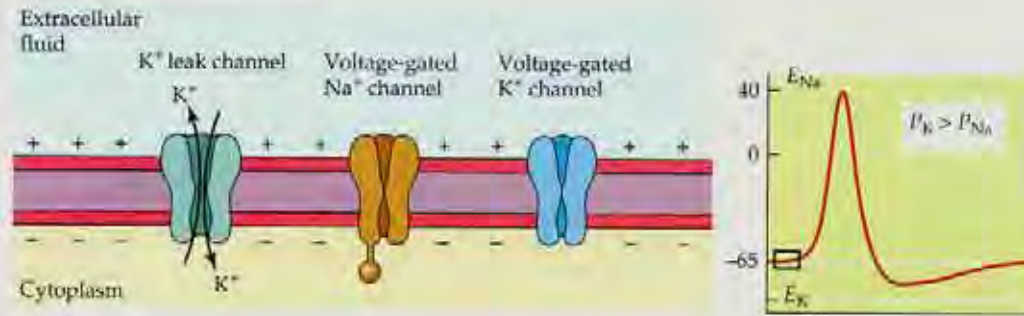
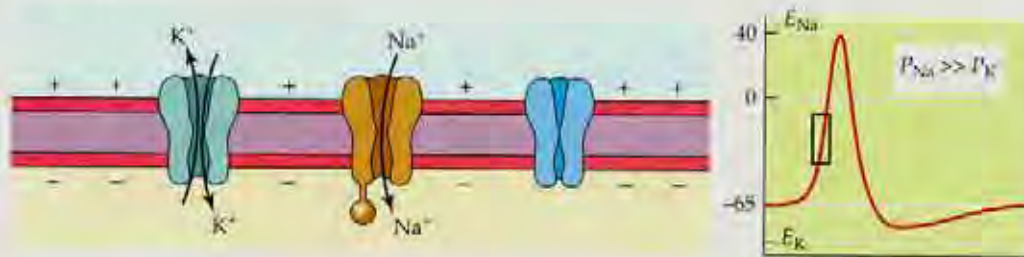


Figure 1.9
Common methods of gene expression for recording the electrical activity of ion channels and other membrane proteins (A) Injection into a *Xenopus* oocyte, which can then be studied by voltage clamping. (B) Transfection. DNA incorporated into plasmid or viral vector is introduced into the cell by electroporation, Ca^{2+} shock, or direct injection into the nucleus (as shown). Cell line may then be used for patch-clamp recording. V_m , membrane potential; V_c , command potential; R , feedback resistance of patch amplifier; i_m , membrane current. After Fain (1999).

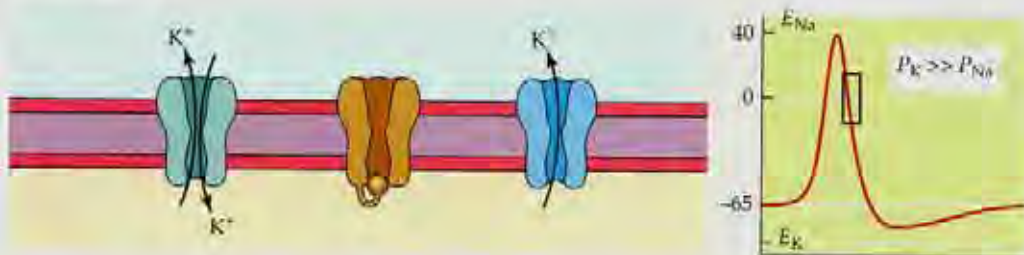
(a) Resting membrane potential



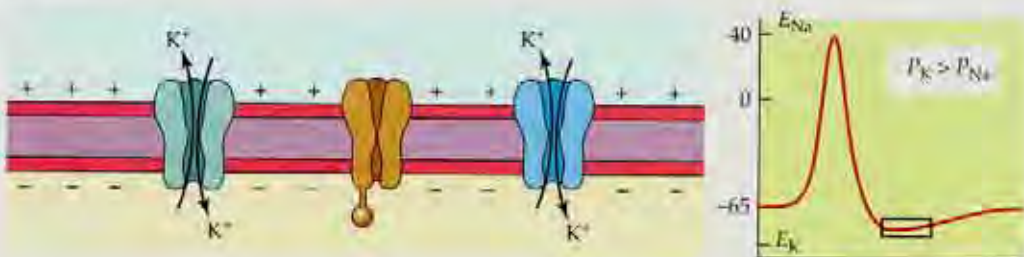
(b) Rising phase

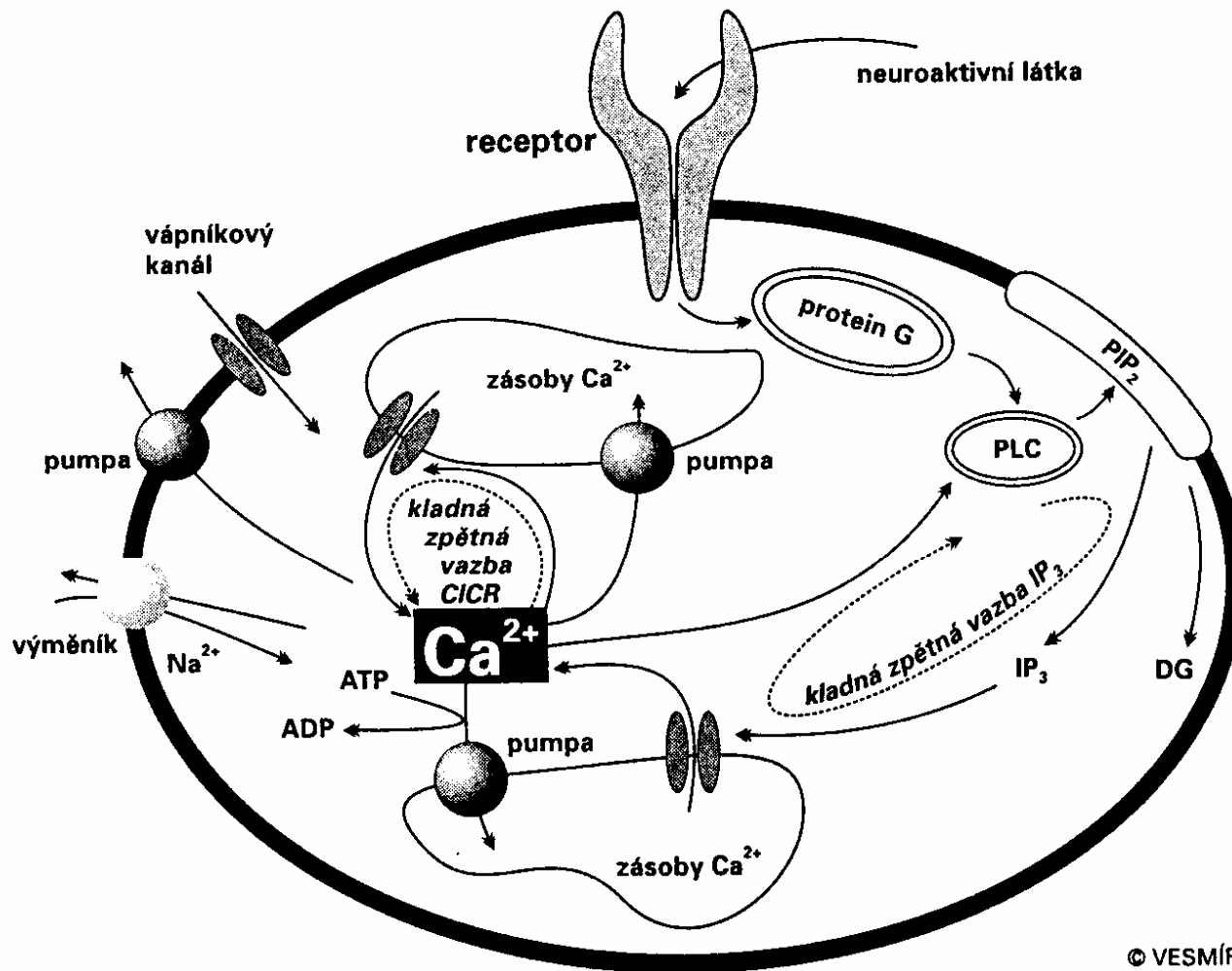


(c) Falling phase



(d) Recovery





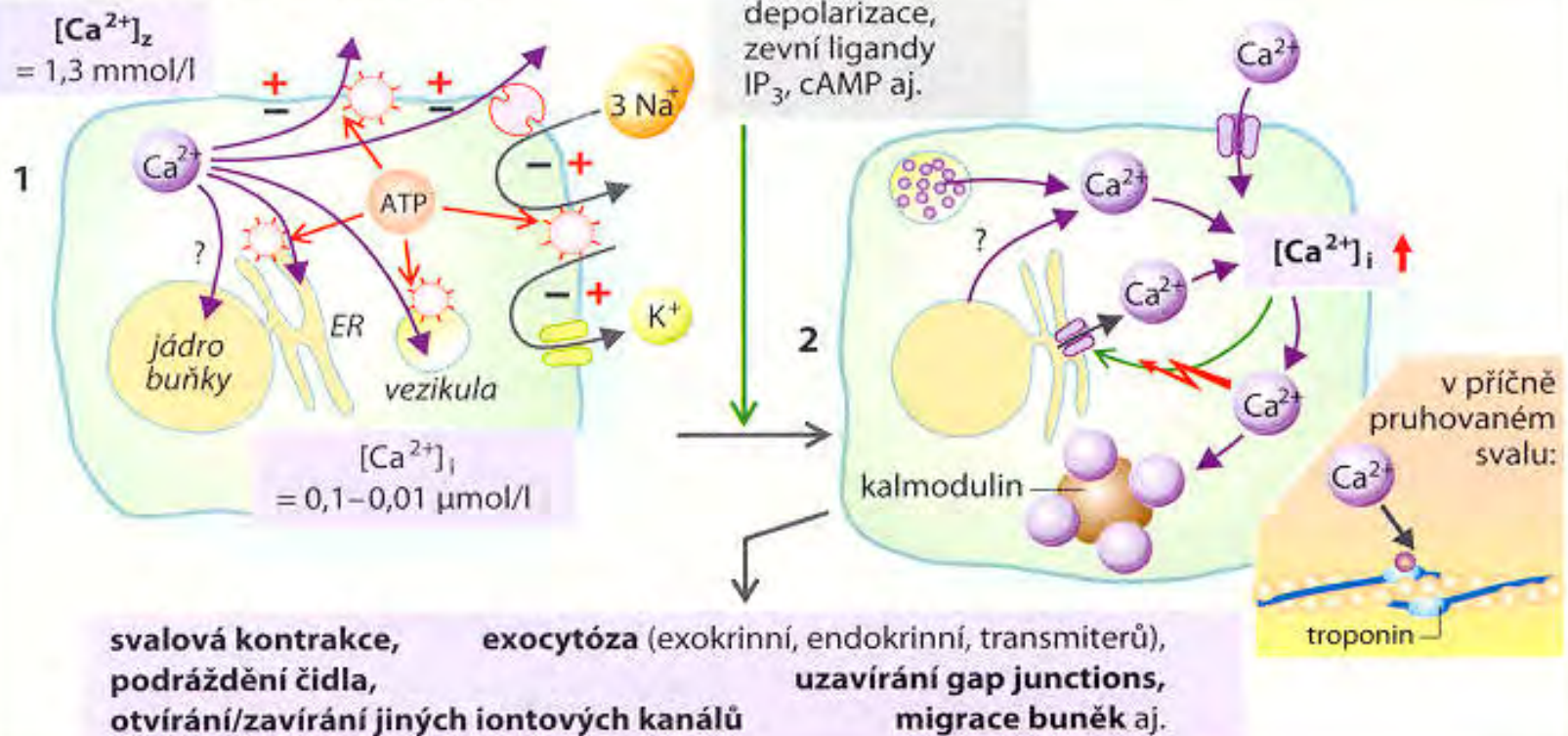
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Mechanismy regulující v buňce koncentraci vápníku: PLC – fosfolipáza C, DG – diacylglycerol, CICR – indukované uvolňování vápníku

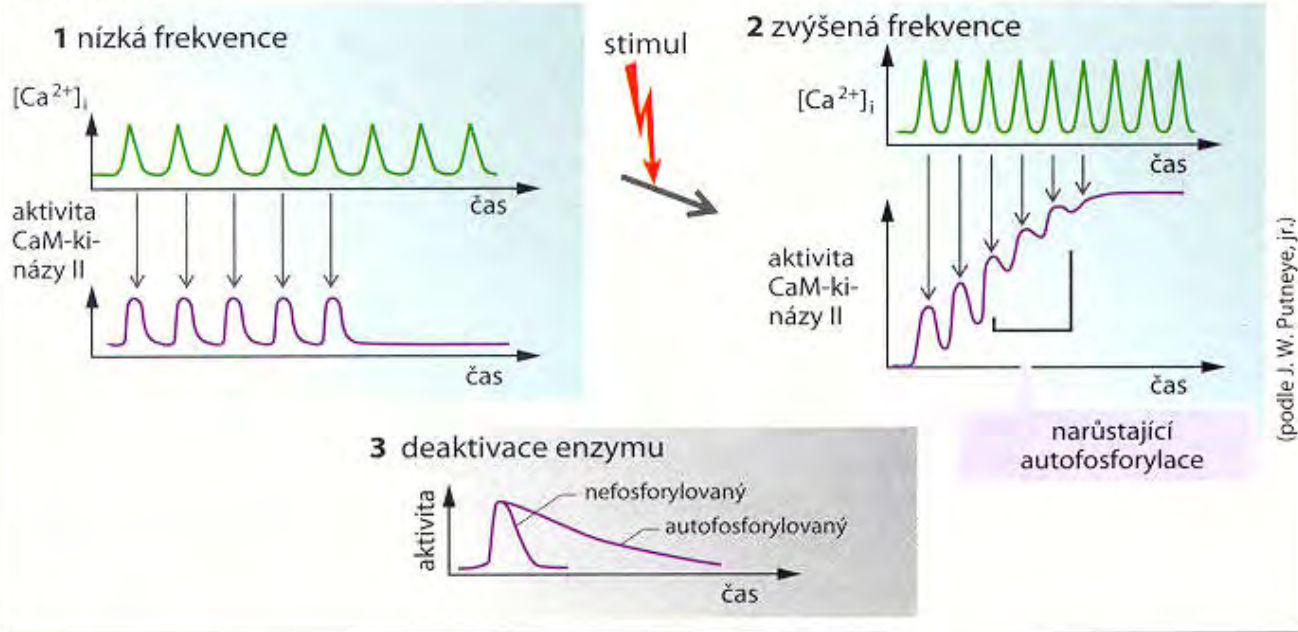
prokázat, kem. (viz Mnoho

Vápníková komunikace a Ca kanály

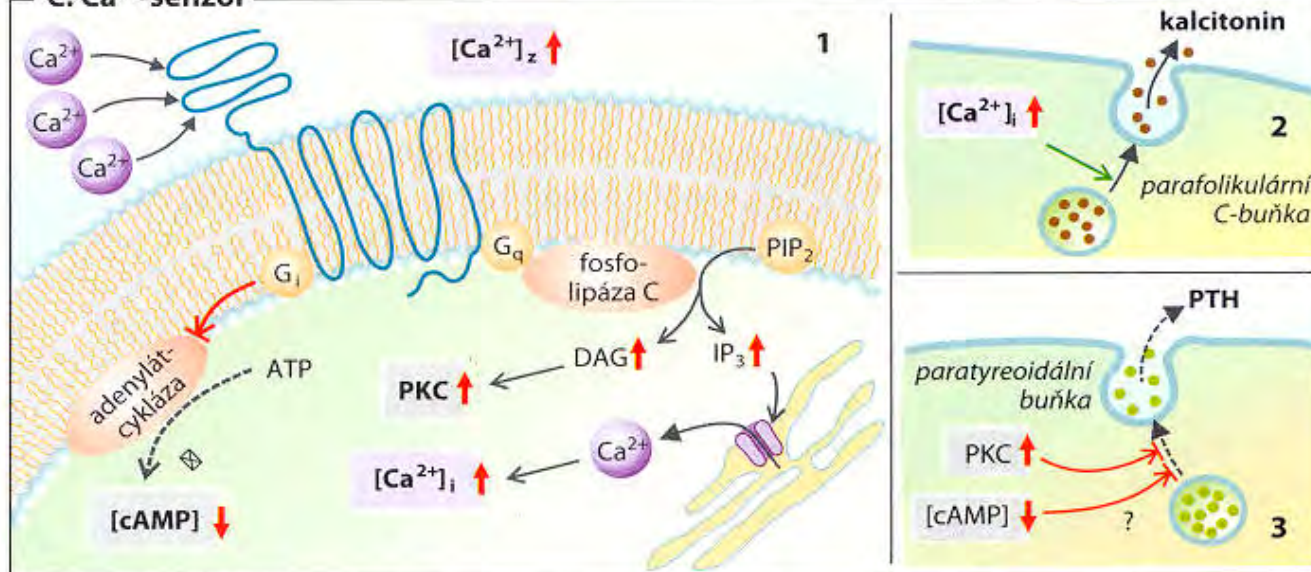
A. Regulace buňky ionty Ca^{2+}



B. Oscilace Ca^{2+}

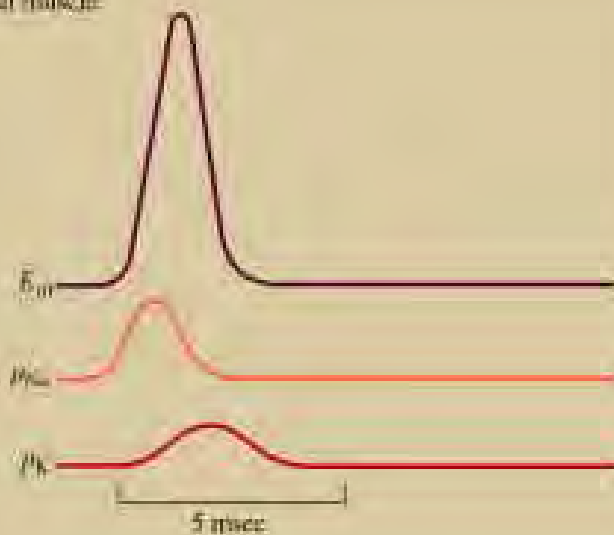


C. Ca^{2+} -senzor

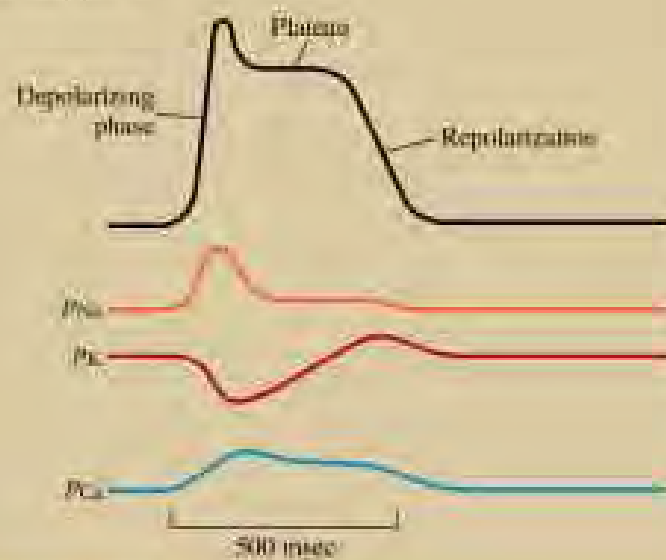


Ca v myokardu

A Skeletal muscle

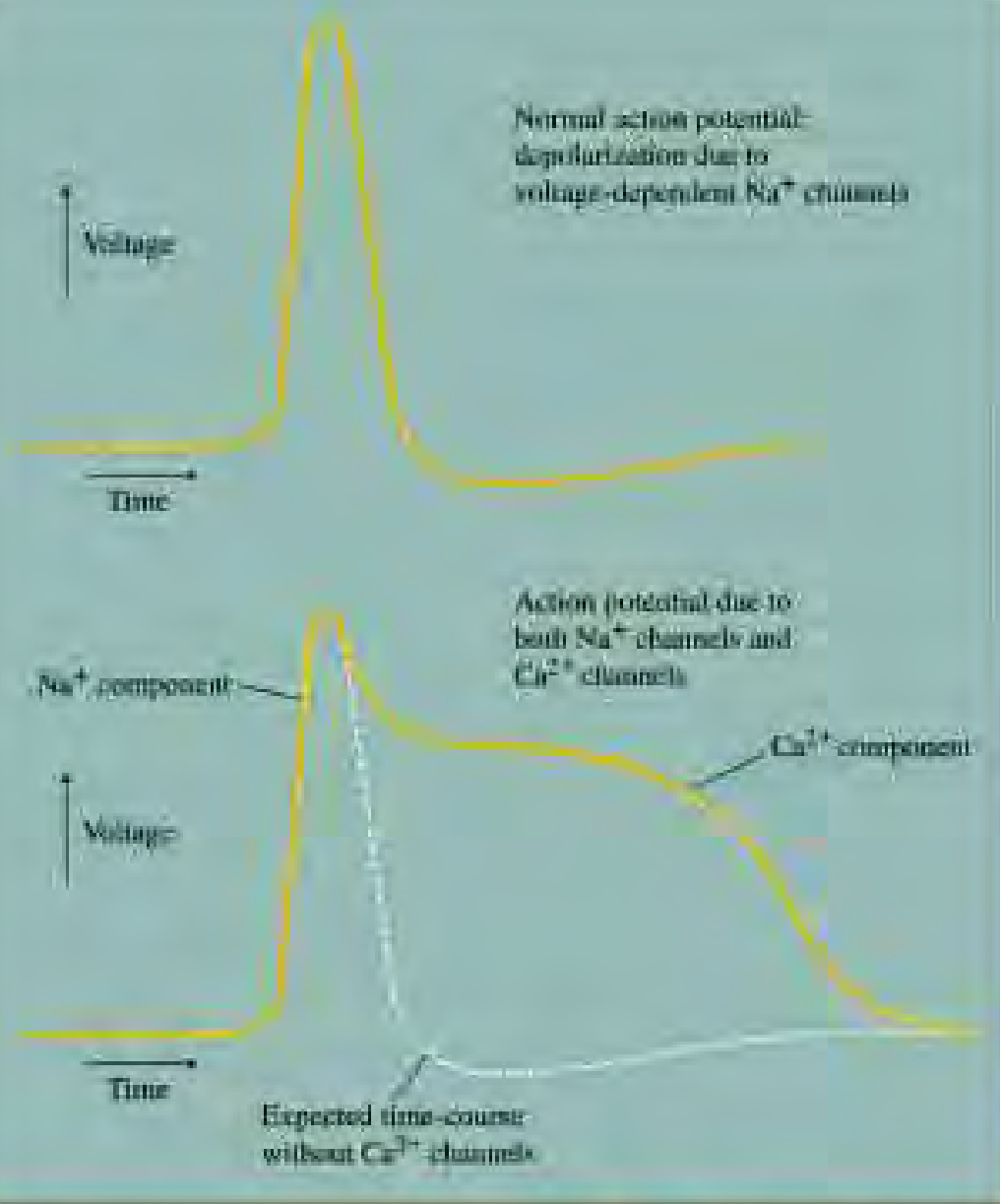


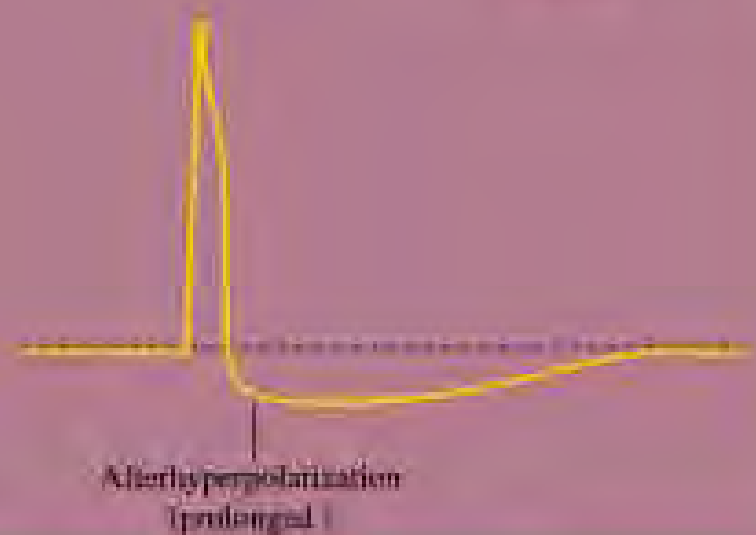
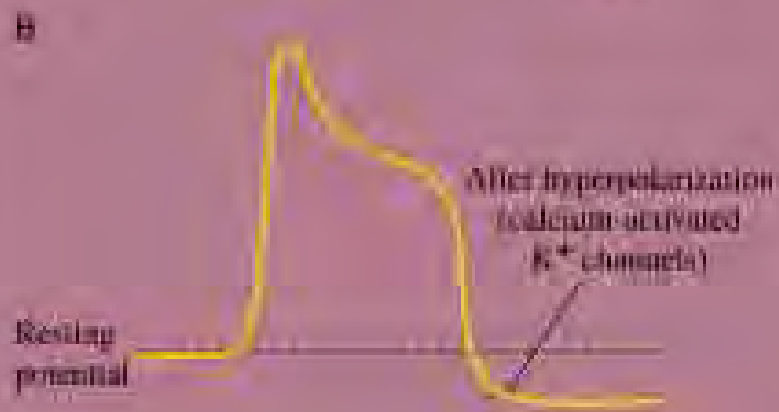
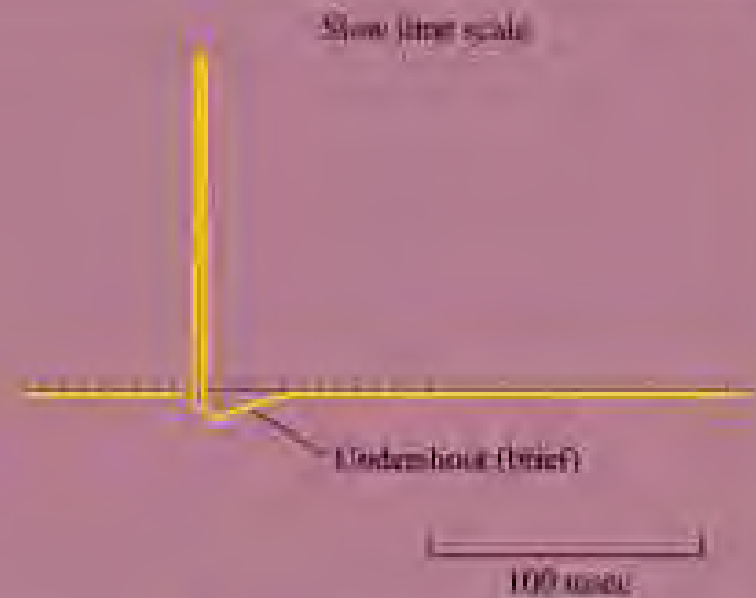
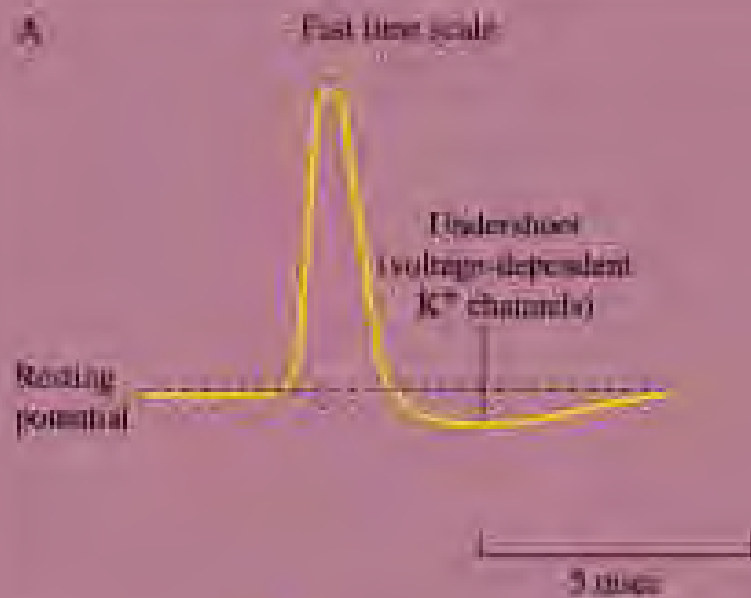
B Cardiac muscle

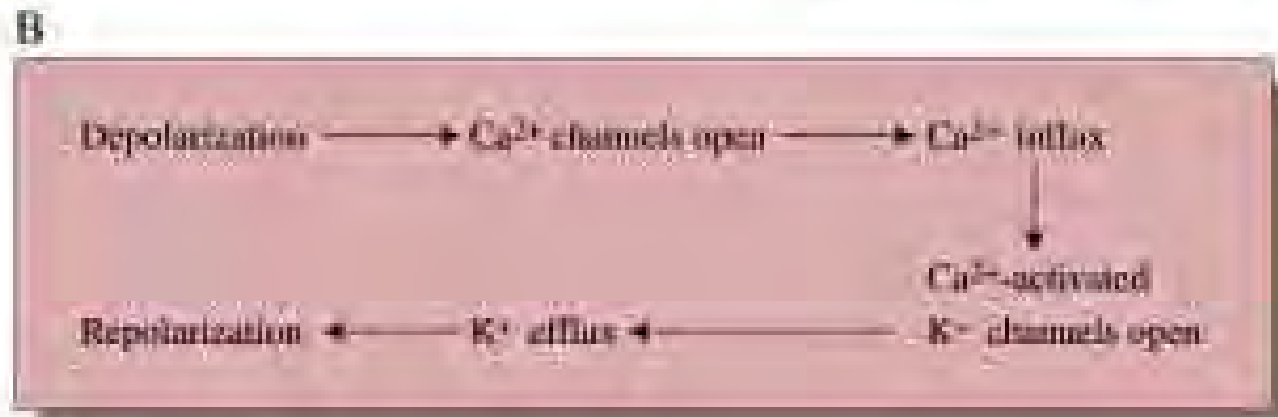
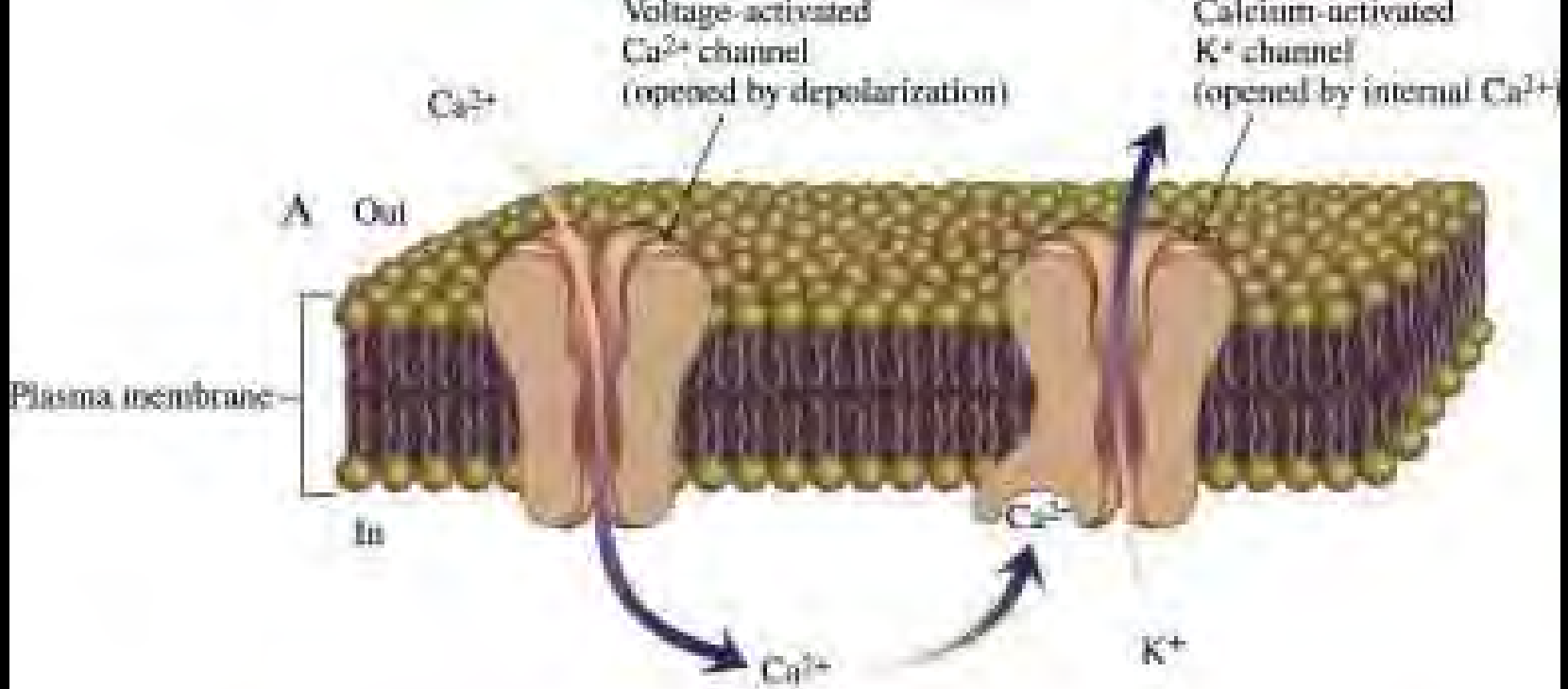


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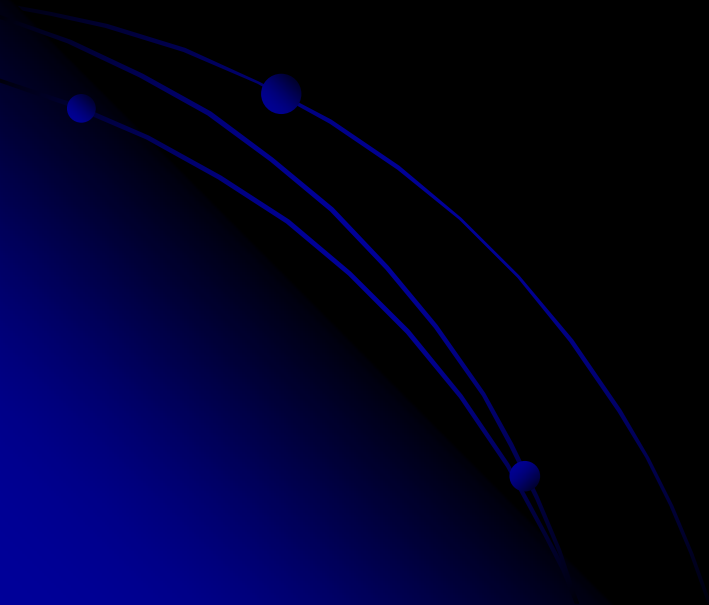




Akční potenciál kanály

Akční potenciál cartoon

Propagace, Voltage clamp



- Leukocyty, stejně jako rakovinové buňky mají napětově vrátkované kanály

