ION CHANNELS

*

ION CHANNEL DISEASES [CHANNELOPATHIES]

MOTIVATION

MEETING OF NOBEL LAUREATES AND TALENTED STUDENTS IN SZEGED

REVIEWS [1 basic + 2 ped]

Neurotherapeutics. 2007 Apr; 4(2): 184 - 98.
Ion channel pharmacology
Camerino DC, Tricario D, Desaphy JF

Curr Opin Pediatr. 2001 Apr; 13(2): 142 - 9.
Ion channels in disease
Bockenhauer D

Korean J Pediatr. 2014 Jan; 57(1): 1 - 18.
Channelopathies
Kim JB

4th MEETING OF NOBEL LAUREATES AND TALENTED STUDENTS IN SZEGED

+

30 hours continuous laboratory practice for secondary school students

Friday and Saturday, 12–13 June, 2015

FINAL PROGRAMME

Organized by the:

Foundation for the Future of Biomedical Science in Szeged

Biological Research Centre of the Hungarian Academy of Sciences the University of Szeged

Venue:

HOTEL NOVOTEL SZEGED****

1 Maros utca, H6721 Szeged, Hungary

KEYNOTE LECTURES BY:

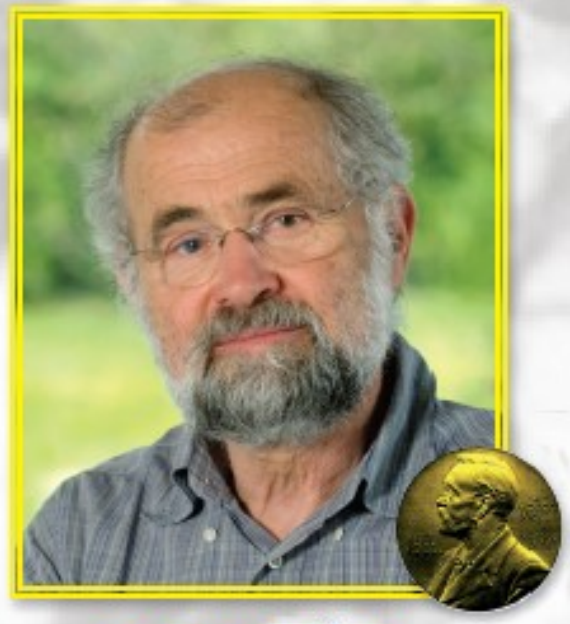
the Nobel Prize-winning biochemist

ERWIN NEHER

The Nobel Prize in Physiology or Medicine 1991

and the X-LAB founder and director

EVA-MARIA NEHER



Erwin Neher

Eva-Maria Neher

Neurotherapeutics. 2007 Apr;4(2):184-98.

Ion channel pharmacology.

Camerino DC, Tricarico D, Desaphy JF.

Because ion channels are involved in many cellular processes, drugs acting on ion channels have long been used for the treatment of many diseases, especially those affecting electrically excitable tissues. The present review discusses the pharmacology of voltage-gated and neurotransmitter-gated ion channels involved in neurologic diseases, with emphasis on neurologic channelopathies. With the discovery of ion channelopathies, the therapeutic value of many basic drugs targeting ion channels has been confirmed. The understanding of the genotype-phenotype relationship has highlighted possible action mechanisms of other empirically used drugs. Moreover, other ion channels have been pinpointed as potential new drug targets. With regards to therapy of channelopathies, experimental investigations of the intimate drug-channel interactions have demonstrated that channel mutations can either increase or decrease affinity for the drug, modifying its potential therapeutic effect. Together with the discovery of channel gene polymorphisms that may affect drug pharmacodynamics, these findings highlight the need for pharmacogenetic research to allow identification of drugs with more specific effects on channel isoforms or mutants, to increase efficacy and reduce side effects. With a greater understanding of channel genetics, structure, and function, together with the identification of novel primary and secondary channelopathies, the number of ion channel drugs for neurologic channelopathies will increase substantially.

Curr Opin Pediatr. 2001 Apr;13(2):142-9.

Ion channels in disease.

Bockenhauer D.

Diseases as different as cardiac arrhythmias, epilepsy, myotonia, malignant hyperthermia, familial hyperinsulinism, and Bartter syndrome have all been linked to mutations in genes encoding ion channels. This has been made possible by an exciting and fruitful collaboration between clinicians, geneticists, and physiologists. It has led to a more detailed understanding not only of pathology but also of physiology, as the deficiency of a certain gene helps unravel its physiologic role. Some exciting and surprising findings have recently been made in the field of "channelopathies." Understanding these diseases on the molecular level will provide the basis for a rational therapeutic approach to affected patients.

Korean J Pediatr. 2014 Jan;57(1):1-18.
Channelopathies.
Kim JB.

Channelopathies are a heterogeneous group of disorders resulting from the dysfunction of ion channels located in the membranes of all cells and many cellular organelles. These include diseases of the nervous system (e.g., generalized epilepsy with febrile seizures plus, familial hemiplegic migraine, episodic ataxia, and hyperkalemic and hypokalemic periodic paralysis), the cardiovascular system (e.g., long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia), the respiratory system (e.g., cystic fibrosis), the endocrine system (e.g., neonatal diabetes mellitus, familial hyperinsulinemic hypoglycemia, thyrotoxic hypokalemic periodic paralysis, and familial hyperaldosteronism), the urinary system (e.g., Bartter syndrome, nephrogenic diabetes insipidus, autosomal-dominant polycystic kidney disease, and hypomagnesemia with secondary hypocalcemia), and the immune system (e.g., myasthenia gravis, neuromyelitis optica, Isaac syndrome, and anti-NMDA [N-methyl-D-aspartate] receptor encephalitis). The field of channelopathies is expanding rapidly, as is the utility of molecular-genetic and electrophysiological studies. This review provides a brief overview and update of channelopathies, with a focus on recent advances in the pathophysiological mechanisms that may help clinicians better understand, diagnose, and develop treatments for these diseases.

A Szent-Györgyi Albert Nobel-díjának 75. évfordulója alkalmából a Szegedi Nemzeti Színházban tartott konferencia családi fotója. Hátsó sor (balról jobbra): Hegyi Péter a konferencia főtitkára Hernádi Klára az SZTE TTIK dékánja Wittmann Tibor a gasztroenterológiai szekció elnöke Greiner István a Richter Nyrt. kutatási igazgatóhelyettese Botka László Szeged polgármestere Kemény Lajos a SZTE ÁOK dékánhelyettese Széll Márta a genetikai szekció elnöke Pálfi György a tuberkulózis szekció elnöke. Középső sor: Pál József az SZTE rektorhelyettese Bert Sakmann Nobel-díjas német fiziológus Tim Hunt Nobel-díjas angol biokémikus Robert Huber Nobel-díjas német kémikus Szabó Gábor az SZTE rektora Vécsei László az SZTE ÁOK dékánja John E. Walker Nobel-díjas angol molekuláris biológus kutató-vegyész Eric Wieschaus Nobel-díjas amerikai biológus Varró András az SZTE rektorhelyettese. Első sor: Aaron Ciechanover és Ada E. Yonath izraeli kémikusok Andrew V. Schally lengyel születésű amerikai endokrinológus és Peter C. Doherty aus

The Nobel Prize in Physiology or Medicine 1996

Peter C. Doherty
Prize share: 1/2

Rolf M. Zinkernagel
Prize share: 1/2

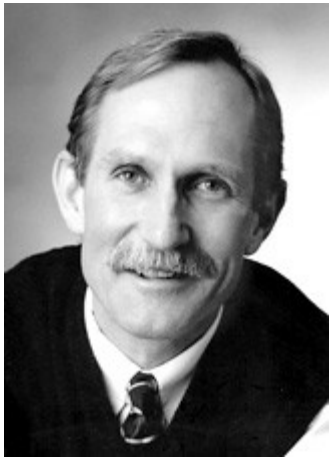
The Nobel Prize in Physiology or Medicine 1996 was awarded jointly to Peter C. Doherty and Rolf M. Zinkernagel *"for their discoveries concerning the specificity of the cell mediated immune defence"*

The Nobel Prize in Physiology or Medicine 1991

Erwin Neher
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1991 was awarded jointly to Erwin Neher and Bert Sakmann *"for their discoveries concerning the function of single ion channels in cells"*

Bert Sakmann
Prize share: 1/2



Peter Agre
Prize share: 1/2

Roderick MacKinnon
Prize share: 1/2

The Nobel Prize in Chemistry 2003

The Nobel Prize in Chemistry 2003 was awarded *"for discoveries concerning channels in cell membranes"* jointly with one half to Peter Agre *"for the discovery of water channels"* and with one half to Roderick MacKinnon *"for structural and mechanistic studies of ion channels"*.

DETAILED PROGRAMME

14:00 

PRESENTATION BY THE 2nd YEAR SZENT-GYÖRGYI STUDENTS

Chairs: **Pál Ormos, András Varró**

14:00–14:05 **László Vécsei** *(Szent-Györgyi Mentor)*
Introduction of the Neurology Research Laboratory

14:05–14:15 **Márton Szentírmai** *(2nd year Szent-Györgyi Student)*
Central nervous system-specific alterations in the tryptophan metabolism in the 3-nitropropionic acid model of Huntington's disease

14:15–14:20 **Lajos Haracska** *(Szent-Györgyi Mentor)*
Introduction of the Mutagenesis and Carcinogenesis Laboratory

14:20–14:30 **Tímea Óvári** *(2nd year Szent-Györgyi Student)*
Analysis of the regulation of DNA damage tolerance

14:30–14:35 **Imre Boros** *(Szent-Györgyi Mentor)*
Introduction of the Epigenetics and Chromatin Research Laboratory

14:35–14:45 **Petra Éva Szili** *(2nd year Szent-Györgyi Student)*
The background of collateral sensitivity in human uterine sarcoma cell lines

GALA EVENING

20:00–22:00

National Theatre Szeged

Intoduction of career perspectieves for secondary school students.
Presentation of the Szent-Györgyi Talent Award
Established by the Foundation for the Future of Biomedical Sciences in Szeged

Péter Hegyi & Zsolt Juhász: Traditional Folkdance Evening delivered by the Szeged Folkdance Ensemble and the Duna Folk Ensemble

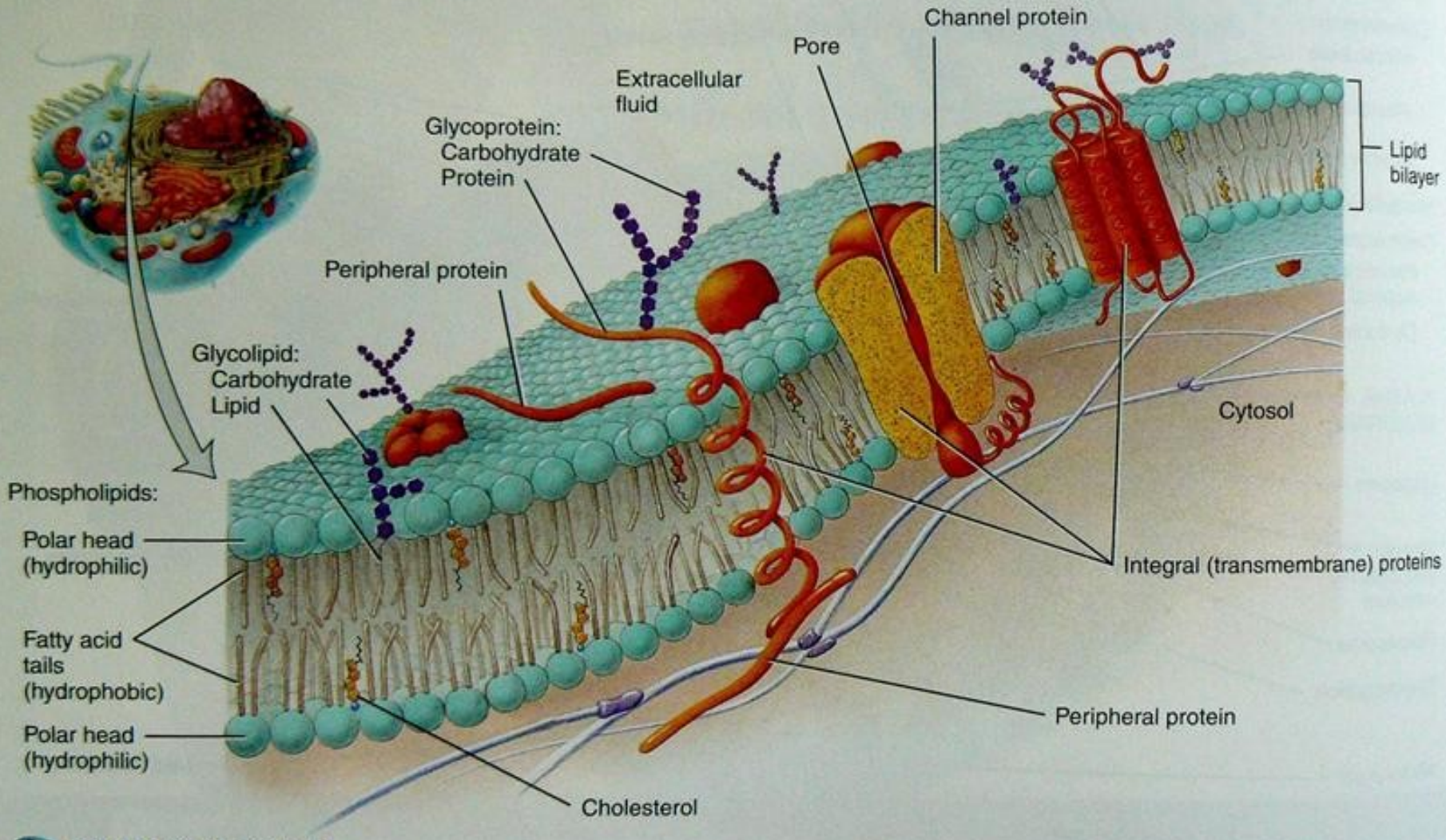
Membranes

- Provide barrier function
  - Extracellular
  - Organelles

- Barrier can be overcome by „transport proteins“
  - To mediate transmembrane movements of ions, Na^+, K^+
  - Nutrients, glucose, amino acids etc.
  - Water (aquaporins)

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?

A lipid kettősrétegbe beépülő, a membránt átívelő, integráns (transzmembrán) fehérjék funkciói:

csatornaképzők (víz és ionok számára transzportút)
szállítómolekulák (karrierek)
ligandkötő receptorok (sejtek közötti információátvitel)
perifériás fehérjékkel kapcsolódó proteinek
„struktúrfehérjék” (kapcsolat a citoszkeleton és az extracelluláris mátrix között)

A perifériás fehérjék

a sejten belüli jelátviteli mechanizmusban játszanak fontos szerepet.

MEMBRANE TRANSPORT

PASSIVE
diffusion

simple

['concentration gradient'
protein 0, ATP energy 0]

facilitated

[carrier mediated
transmembrane integral proteins,
channels]

▲

ACTIVE

primary, direct

[enzymes: transmembrane ATP-ases
e.g.
P-type ATP-ase
sodium potassium pump
calcium pump, proton pump

ATP binding casette (ABC) transporter

MDR, CFTR]

secondary, coupled

[e.g.
cotransporters
'uniporter', symporter, antiporter]

Ion channels

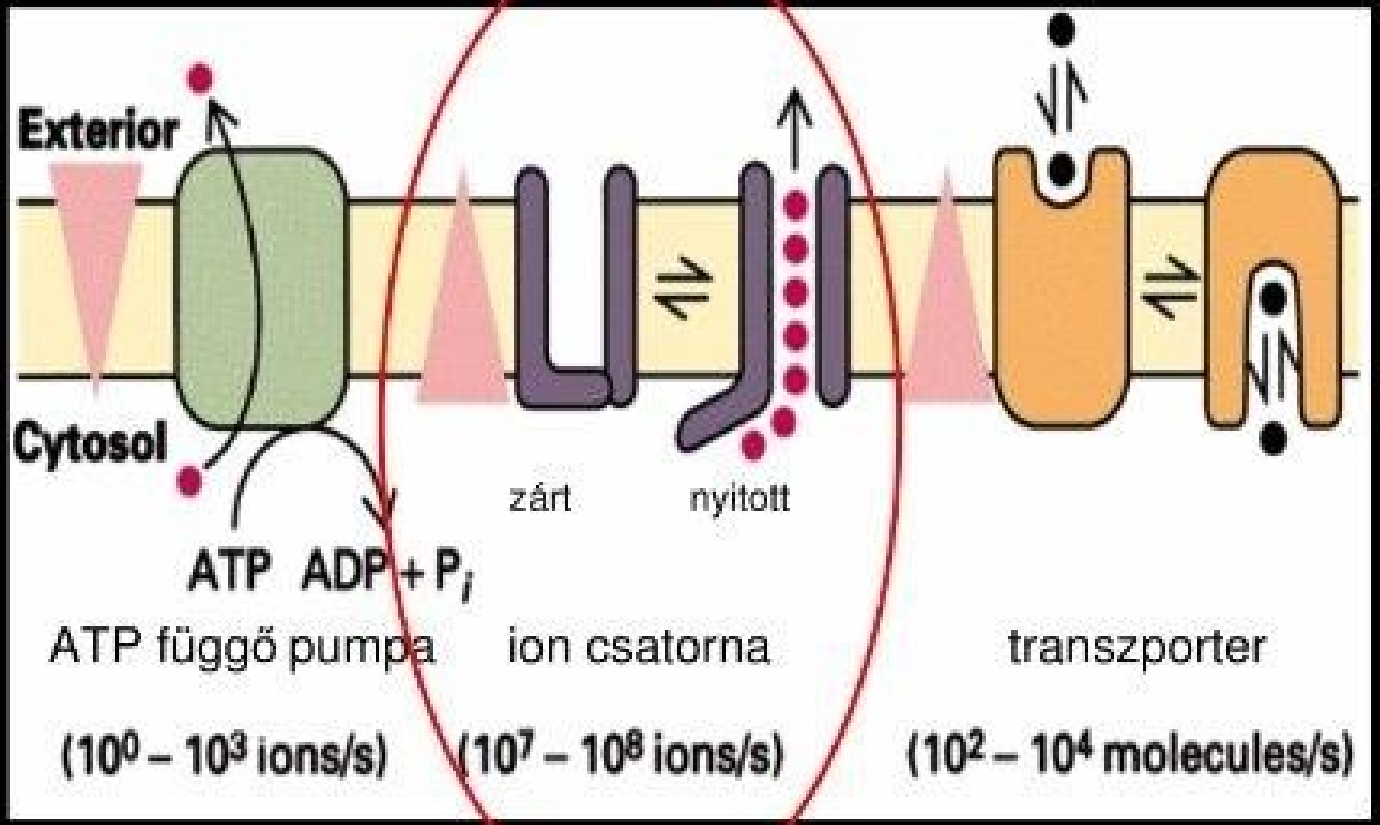
- Channel proteins form transmembrane aqueous pores which allow passive movement of small water-soluble molecules into or out of the cell or organelle
- Most channel proteins in plasma membrane form narrow pores which are only permeable to inorganic ions - ion channels
- Ion channels are highly selective for specific ions (eg Na^+, K^+, Ca^{2+}, Cl^-)
- Ion selectivity depends on:

  diameter - narrow channels can't pass large ions

  shape - only single ions of correct species can access

  charge - distribution of charged amino acids in pore
- Passage of ions through narrowest portion of channel rate limiting $\Rightarrow$ saturable transport

Az ion csatornák membránon keresztüli transzport folyamatok egyik külön csoportját képezik. Az összes transzport folyamat között ez a leggyorsabb, akár 4 nagyságrenddel nagyobb sebesség mint a transzporterek által elérhető maximum.



Az ioncsatornák hidrofil bélésű, az ionok számára kedvező fizikokémiai környezetű pórust képeznek a membránban. Két alapvető tulajdonsággal rendelkeznek e pórusok, melyek alapján a csatornák osztályozhatók.

kapuzás = megfelelő "inger" hatására bekövetkező konformáció változás a fehérjében, mely a csatornák különböző állapotaihoz vezet (pl. zárt, nyitott , inaktivált állapotok).

Szelektív permeabilitás = csak bizonyos fajta ion (vagy ionok) számára átjárható a pórus (pl. nagy szelektivitású, kis szelektivitású, és nem szelektív csatornák).

Az ioncsatornák osztályozása

- a kapuzás alapján:
  - kapuzó
  - nem-kapuzó

- a csatorna megnyílását kontrolláló hatások szerint
  - ligand-vezételt csatornák
  - feszültség-vezérelt csatornák
  - stretch aktivált csatornák

- lokalizációjuk alapján:
  - felszíni mebránban elhelyezkedő csatornák
  - intracelluláris membránban elhelyezkedő csatornák
  - intercelluláris csatornák

- ionszelektivitás alapján:
  - K^+, Na^+, Ca^{2+}, Cl^- stb.

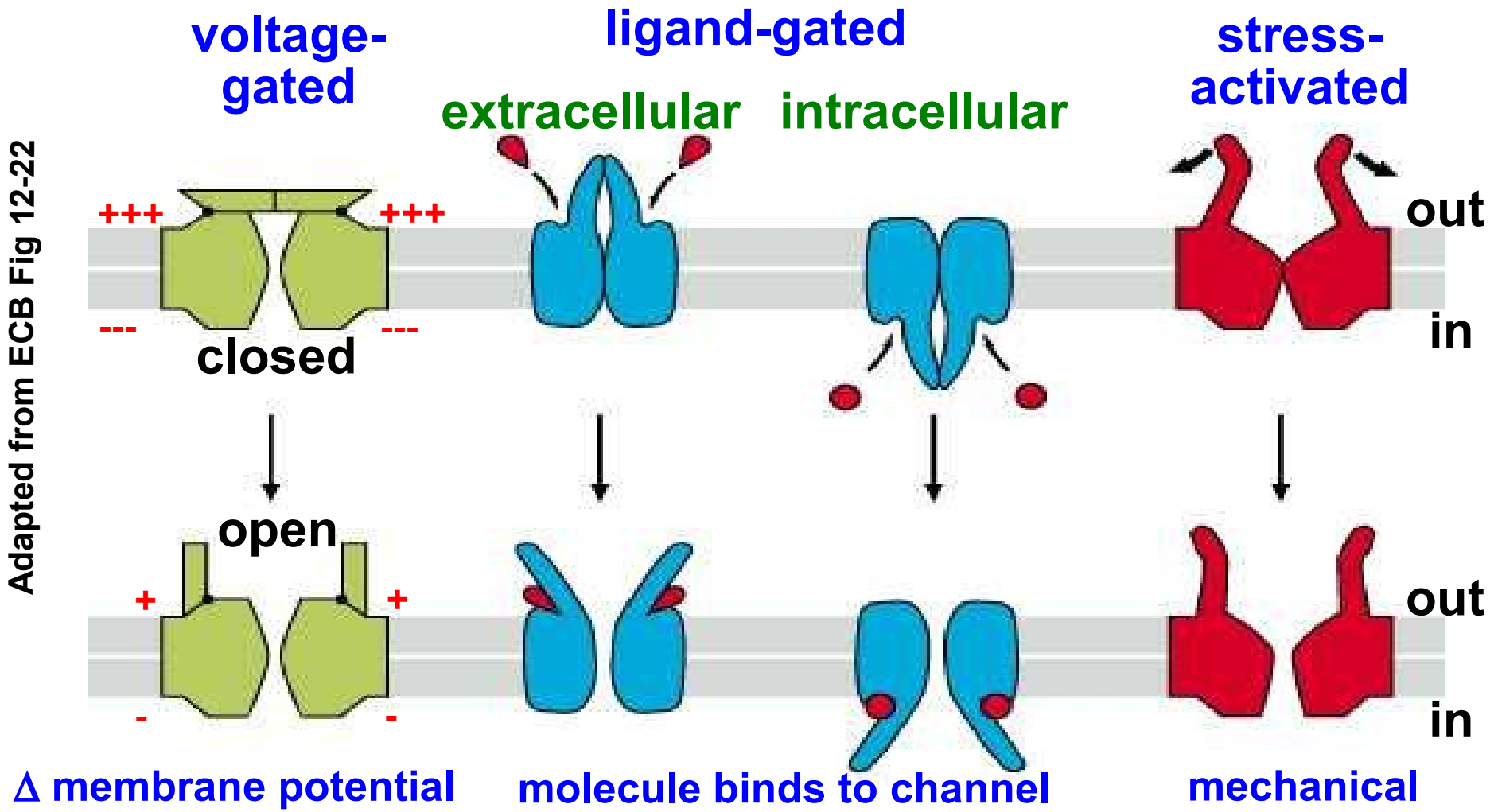
- a csatornákat kódoló gének alapján
  - Kir, K_v, $Ca_{v\ stb.}$

Classes of ion channel

Two distinct properties of ion channels:

(1) ion selectivity - type of ions which can pass

(2) gating - conditions which influence opening and closing



Adapted from ECB Fig 12-22

Specialized Functions of Ion Channels

- Mediate the generation, conduction and transmission of electrical signals in the nervous system
- Control the release of neurotransmitters and hormones
- Initiate muscle contraction
- Transfer small molecules between cells (gap junctions)
- Mediate fluid transport in secretory cells
- Control motility of growing and migrating cells
- Provide selective permeability properties important for various intracellular organelles

Outline

- Why ion channels?
- Channel structure

- Ion channels have three basic functional properties
  - Conduct
  - Select
  - Gate

- Evolutionary relationships between ion channels
- Various factors contribute to ion channel diversity

Conduction

- Ion Channels Conduct Up to 10^8 Ions/sec
- Ion Channels Act As Catalysts
  - Speed up fluxes
  - Do not impart energy
  - Driving force is provided by electrochemical potential

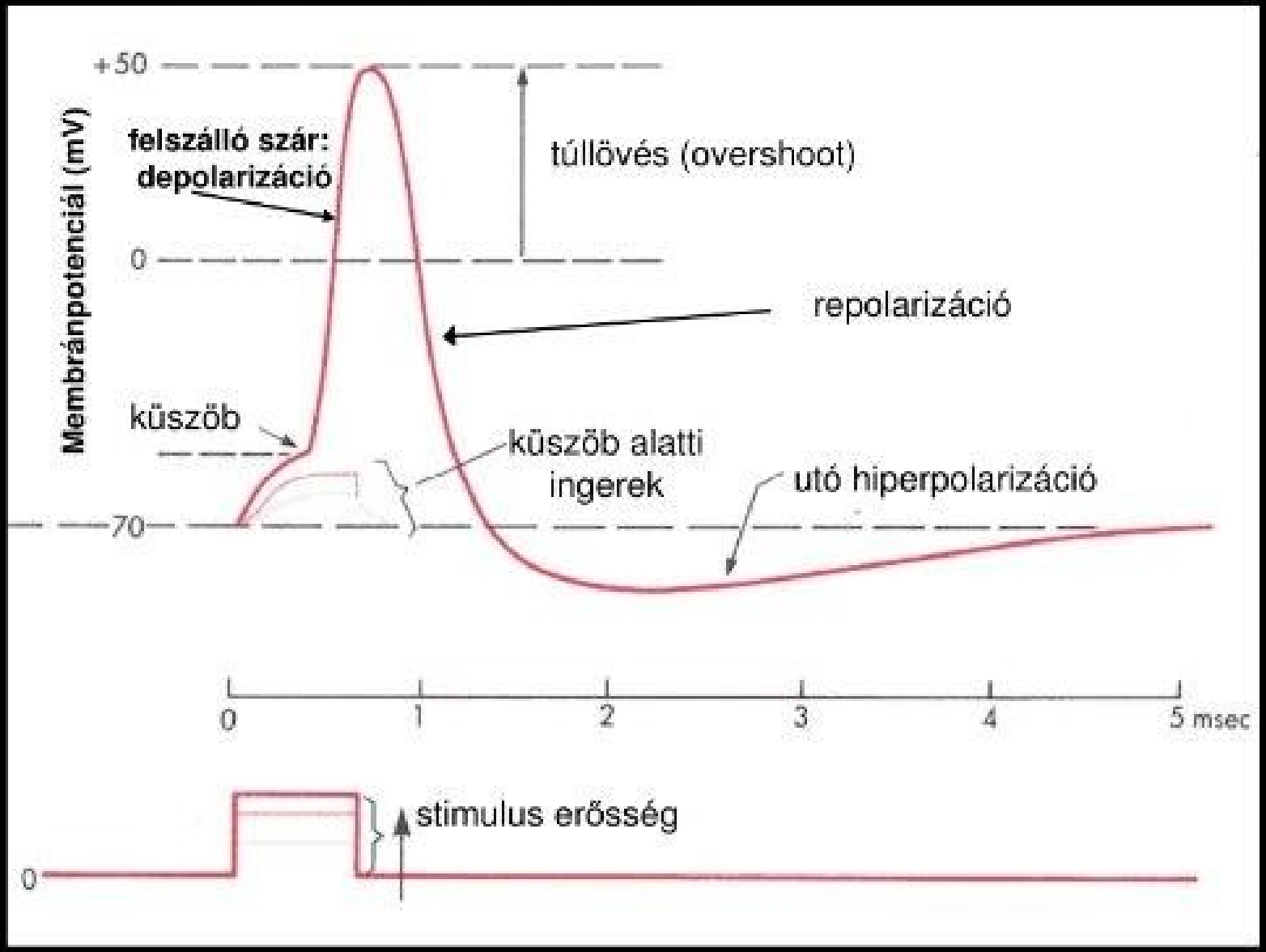
Elektrofiziológiai alapfogalmak

• **Membránpotenciál:** a membrán két oldala között mérhetı, a diffúzibilis ionok egyenlıtlen megoszlásából származó potenciálkülönbség (feszültség)

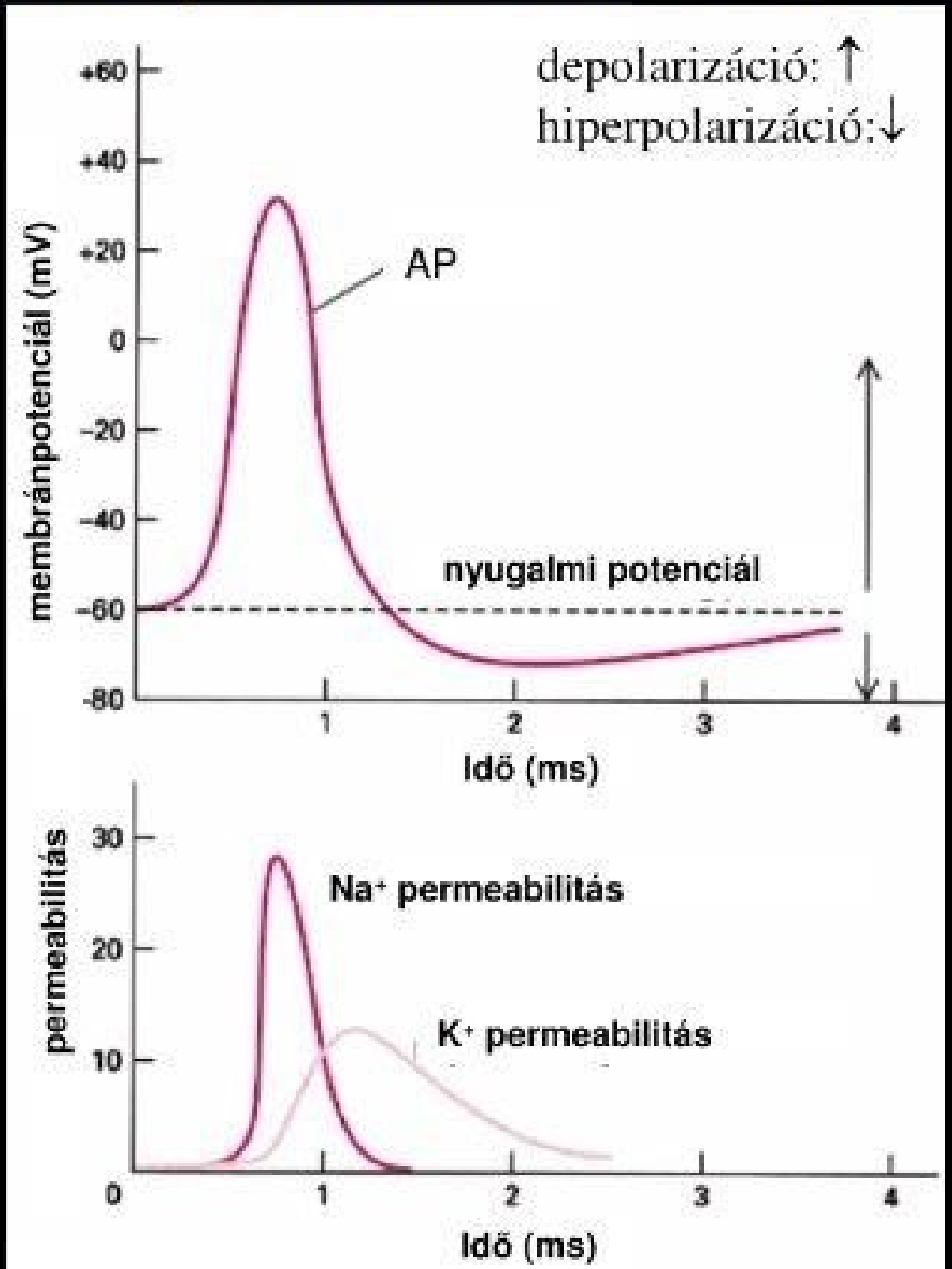
• **Nyugalmi potenciál:** a sejt nem ingerelt állapotában mérhetı membránpotenciál

• **Ingerületi folyamat**: inger hatására bekövetkezı potenciálváltozás
– Helyi (lokális, elektrotónus)
– Tovaterjedı (propagatív, akciós potenciál)

Az akciós potenciál jellemzői:



Na^+ és K^+ permeabilitás változás az AP alatt



Outline

- Why ion channels?
- Channel structure
- Ion channels have three basic functional properties
  - Conduct
  - Select
  - Gate
- Evolutionary relationships between ion channels
- Various factors contribute to ion channel diversity

Ion Channels are Selectively Permeable

Cation Permeable	Anion Permeable
Na^+	Cl^-
K^+	
Ca^{++}	
Na^+, Ca^{++}, K^+	

Szelektivitás: mi tud átjutni a csatornán?

függ a pórus méretétől
a pórust bélelő töltésektől

- nem szelektív → különböző ionok (kation, anion)
  kis szerves molekulák

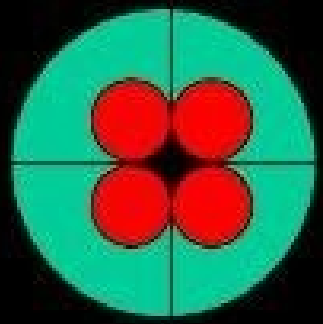
-töltés-szelektív → csak ionok számára átjárható

- ion-specifikus → specifikus egy adott ionra

Az ioncsatornák osztályozása szelektivitás alapján:

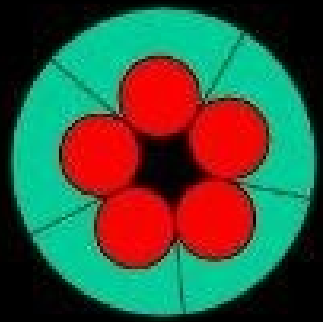
Nagy szelektivitású csatornák, négy alegység

K^+, Na^+, Ca^{2+}, Cl^-



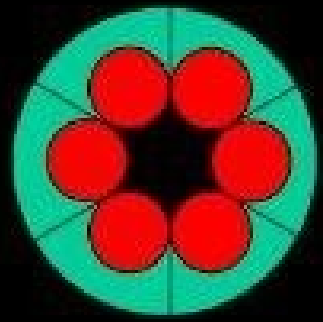
Kis szelektivitású csatornák, öt alegység:

Acetil kolin receptor, csak kationokra specifikus



Nem szelektív csatornák

Gap junction csatorna (hat alegység)

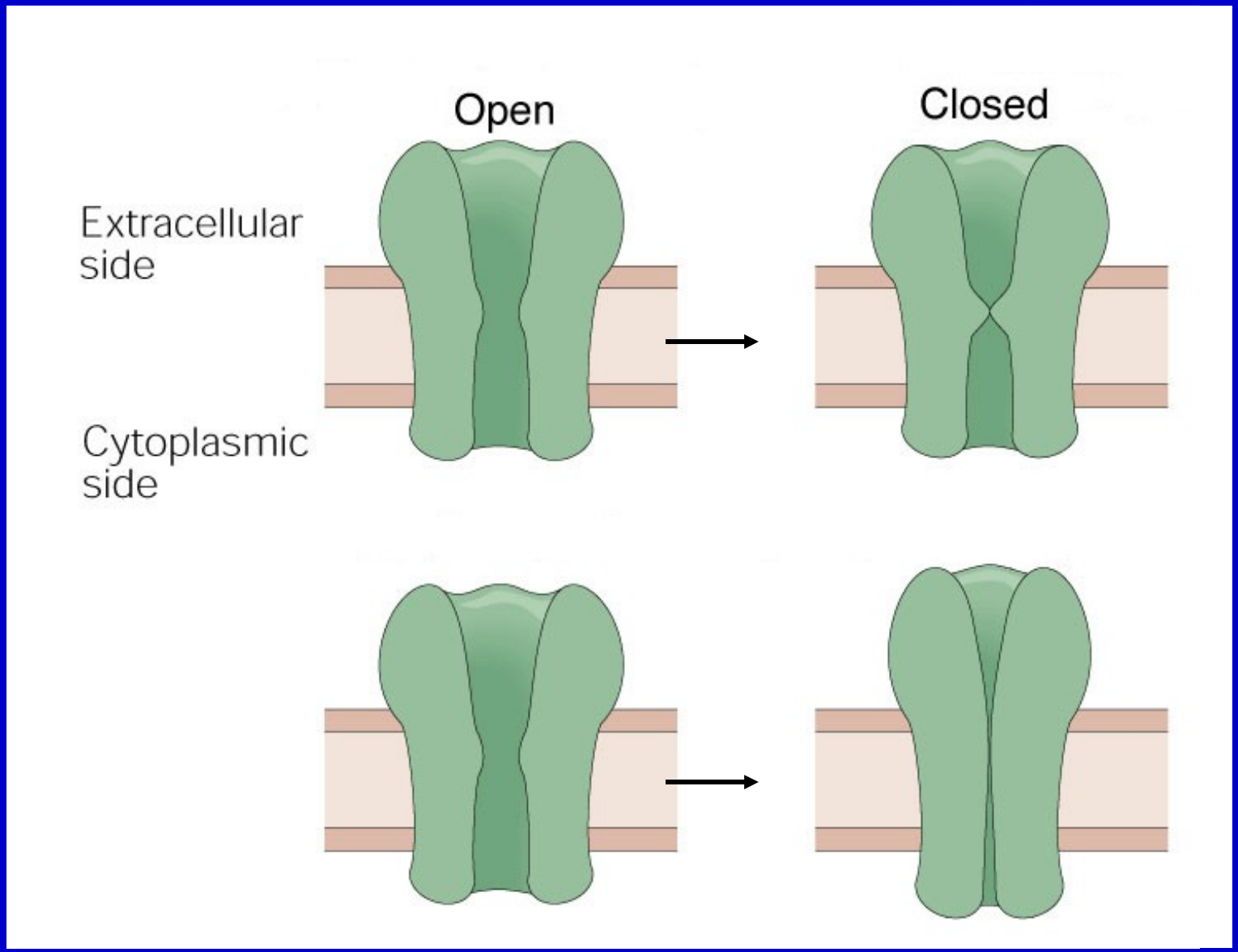


Outline

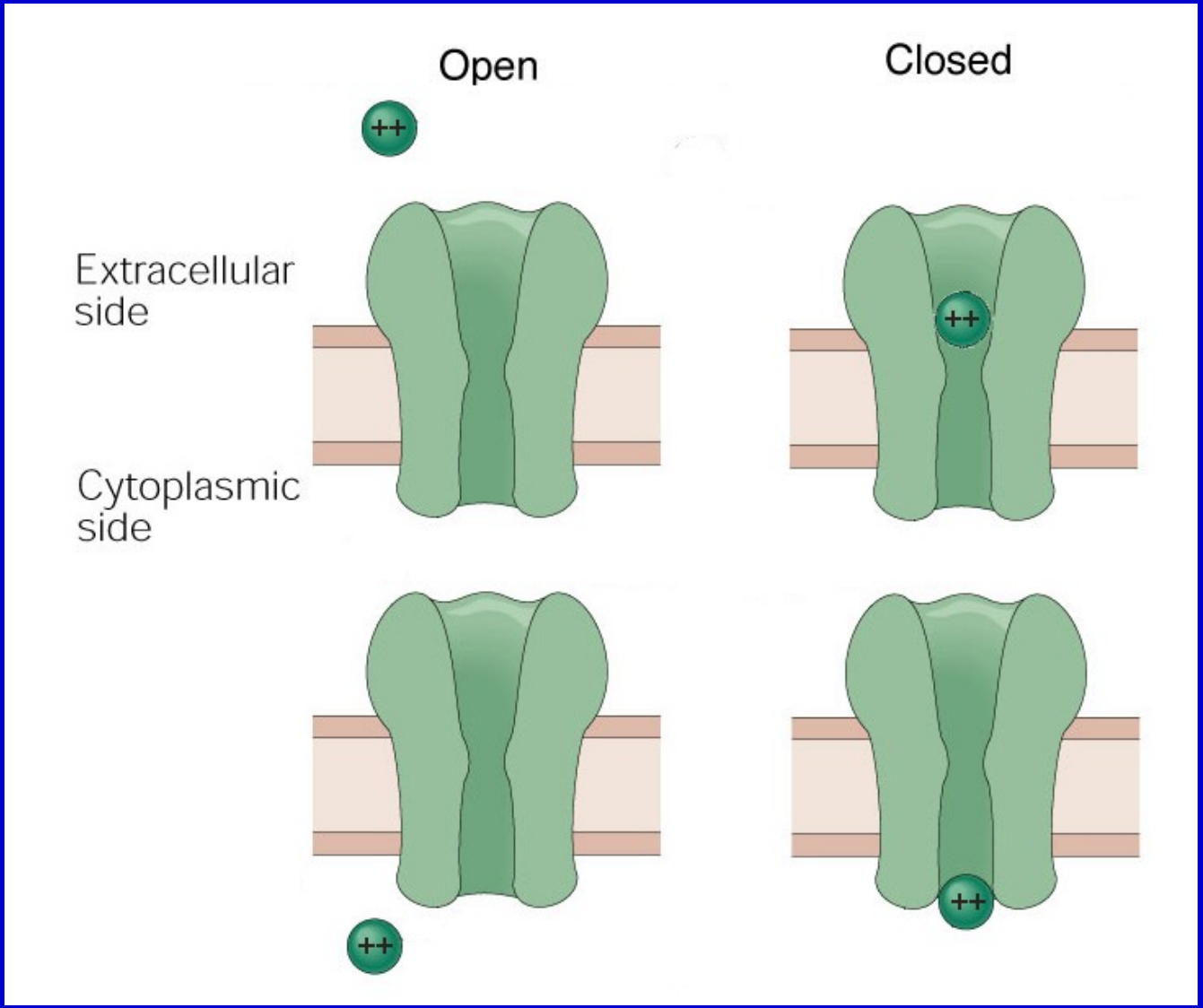
- Why ion channels?
- Channel structure
- Ion channels have three basic functional properties
  - Conduct
  - Select
  - Gate
- Evolutionary relationships between ion channels
- Various factors contribute to ion channel diversity

There are Two Major Types of Gating Actions

Gating Can Involve Conformational Changes Along the Channel Walls



Gating Can Result from Plugging by Cytoplasmic or Extracellular Gating Particles



Voltage-gated channels

- **Voltage-gated channels play major role in propagating electrical signals in nerve and muscle cells**
- **Channels have special charged protein domains - *voltage sensors* - which are extremely sensitive to changes in membrane potential**
- **When potential changes beyond threshold voltage, channel switches from closed to open configuration**
- **Open state probability increases at threshold potential**

Feszültség vezérlés (Voltage gating)

A csatorna a membránpotenciál változás hatására nyílik

- nyitott, inaktív és zárt állapotai vannak
- specifikus egy adott ionra
- hasonló domén struktúrával rendelkeznek
- pozitív töltéssel rendelkező oldalláncok (Lys, Arg)

„érzékelik” a membránpotenciál változását (voltage sensor).

depolarizált (IC pozitív): a kapu nyitva van

hiperpolarizált (IC negatív): a kapu zárva van

Feszültség vezérelt csatornák

- nátrium : I, II, III, μ1, H1, PN3
- kálium : K_A, K_v (1-5), K_v(r), K_v(s),K_{SR}, BK_{Ca}, IK_{Ca}, SK_{Ca}, K_M, $K_{ACh,}$ Kir
- kalcium: L, N, P, Q, T
- klorid: ClC-0 - ClC-8

A ligand vezérelt csatorna

- olyan ioncsatorna, amelyik neurotranszmitter kötőhellyel rendelkezik (IC vagy EC)

- nem szelektív ioncsatornák

- a ligand kötődése a receptor szerkezetének konformáció változását idézi elő, amely hatására a csatorna vezetőképessé válik.

- néhány csatorna kettős vezérléssel rendelkezik, pl. NMDA receptorok, glutamát és depolarizáció kell a megnyílásához

- az ionáram megváltoztatja a csatorna közelében a membránpotenciált, ami feszültség-függő csatornákat aktiválhat

Ligand-vezérelt ioncsatornák = ionotróp receptorok

receptor	ligand
purinerg receptorok	ATP
Cys-loop receptorok	
izom típusú nAChR	ACh
neuronális típusú nAChR	ACh
szerotonin 5-HT3R	szerotonin
$GABA_AR$	GABA
glicin R	glicin
glutamát receptorok	glutamát, glicin
kainát	
AMPA	
NMDA	

Extracelluláris ligand-vezérelt csatornák

- nicotin AChR (izmok): $\alpha_2\beta\gamma\delta$ (embryonic), $\alpha_2\beta\varepsilon\delta$ (adult)
- nicotin AChR (neuronalis): α(2-10), β(2-4)
- glutamate: NMDA, kainate, AMPA
- P2X (ATP)
- 5-HT_3
- $GABA_A$: α(1-6), β(1-4), γ (1-4), δ, ε, ρ(1-3)
- Glycine

Intracelluláris ligand-vezérelt csatornák

- leukotriene C4-gated Ca2+
- ryanodine receptor Ca2+
- IP3-gated Ca2+
- IP4-gated Ca2+
- Ca2+-gated K+
- Ca2+-gated non-selective cation

- Ca^{2+}-gated Cl^-
- cAMP cation
- cGMP cation
- cAMP chloride
- ATP Cl^-
- volume-regulated Cl^-
- arachidonic acid-activated K^+
- Na^+-gated K^+

Stretch aktivált csatornák

-kevéssé általános formája a csatorna szabályozásnak

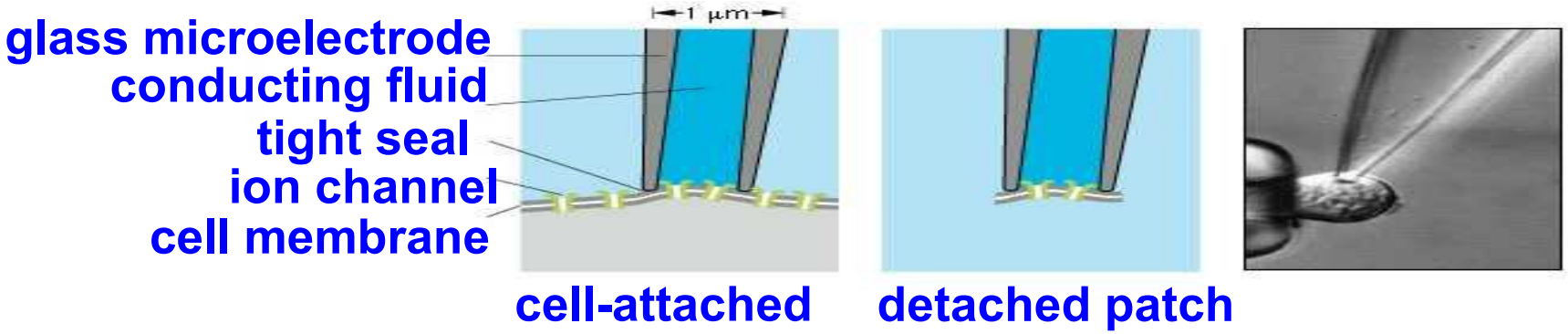
-a csatorna megnyílását a membrán disztorziója okozza
- a szenzoros idegekre jellemző, pl tapintás

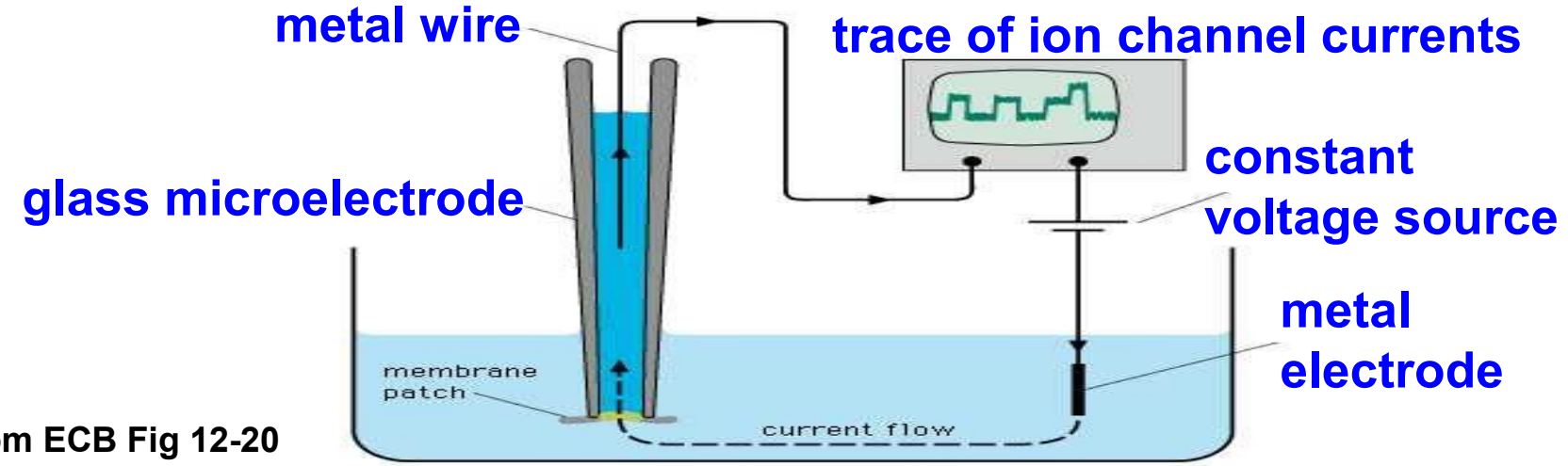
- a nyomás a bőrön az idegvégződések disztorzióját okozza, aminek hatására megnyílnak a strech-aktivált csatornák

- megváltozik a membránpotenciál, ami a Na^+ csatornák aktiválódásán keresztül akciós potenciált vált ki

Ion channel recording

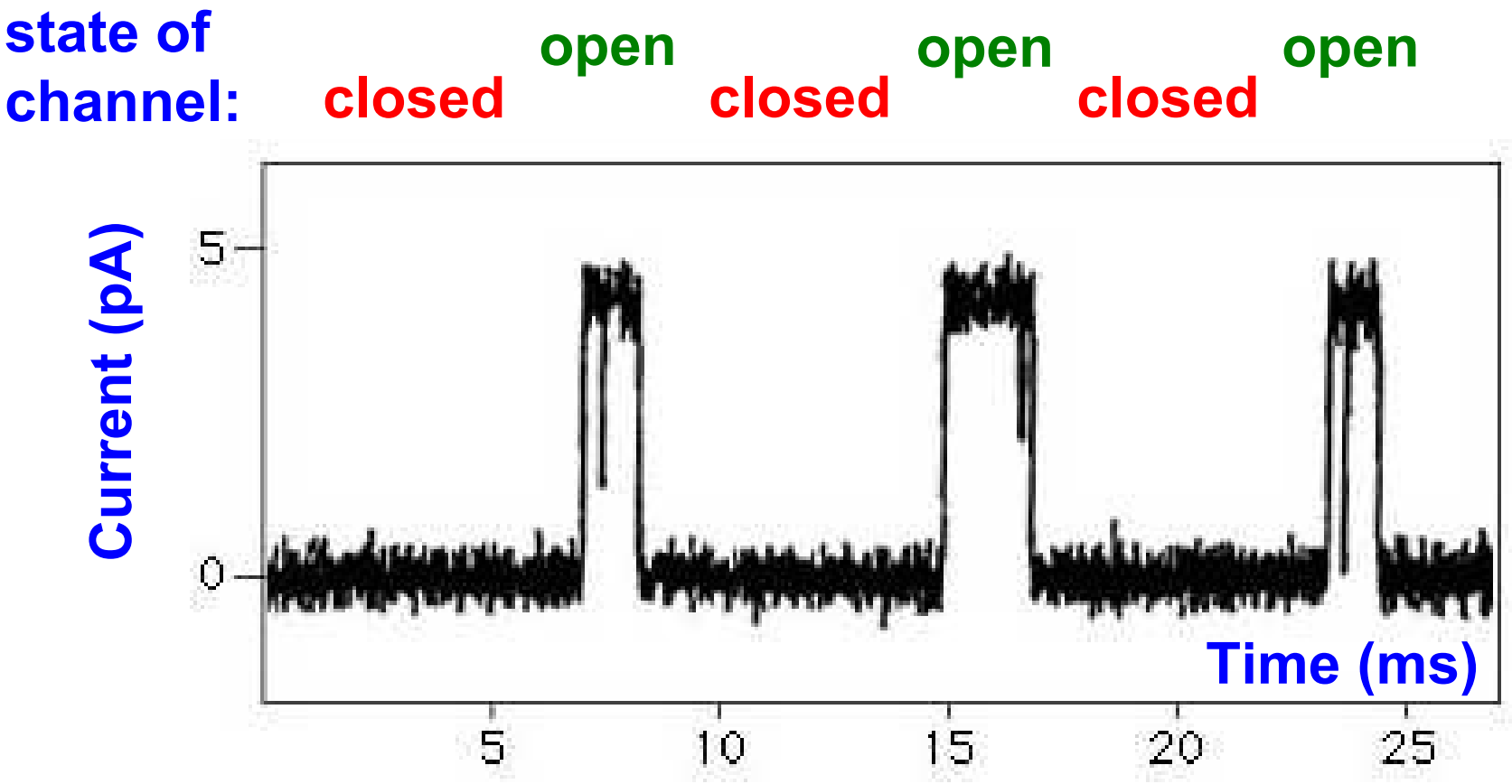
- Ion movements across membrane can be detected by electrical measurements
- Technical advances now permit measurement of electrical current through single channel molecule - patch clamp recording





Adapted from ECB Fig 12-20

Ion channel recording (cont^{d})

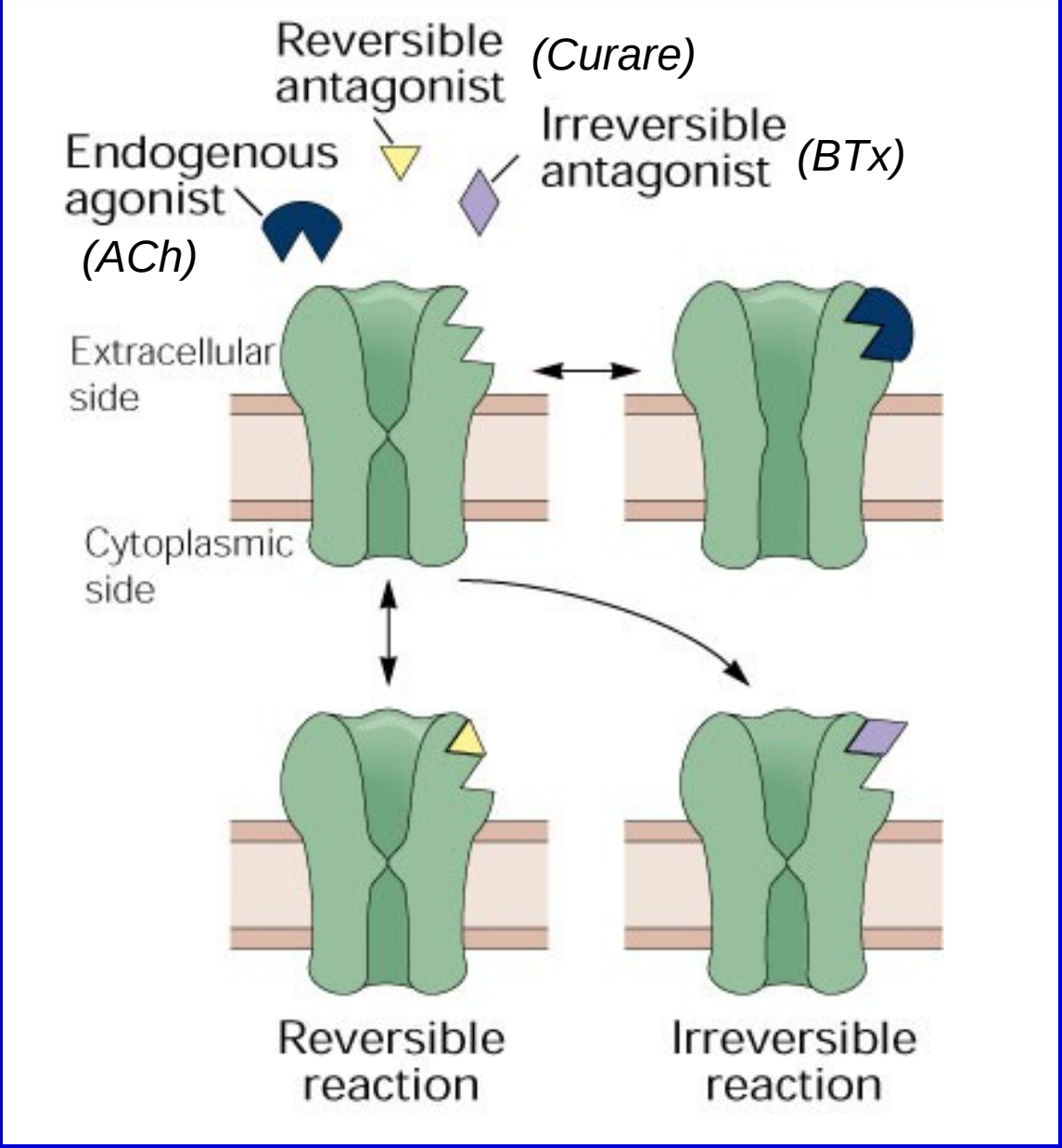


Adapted from ECB Fig 12-21

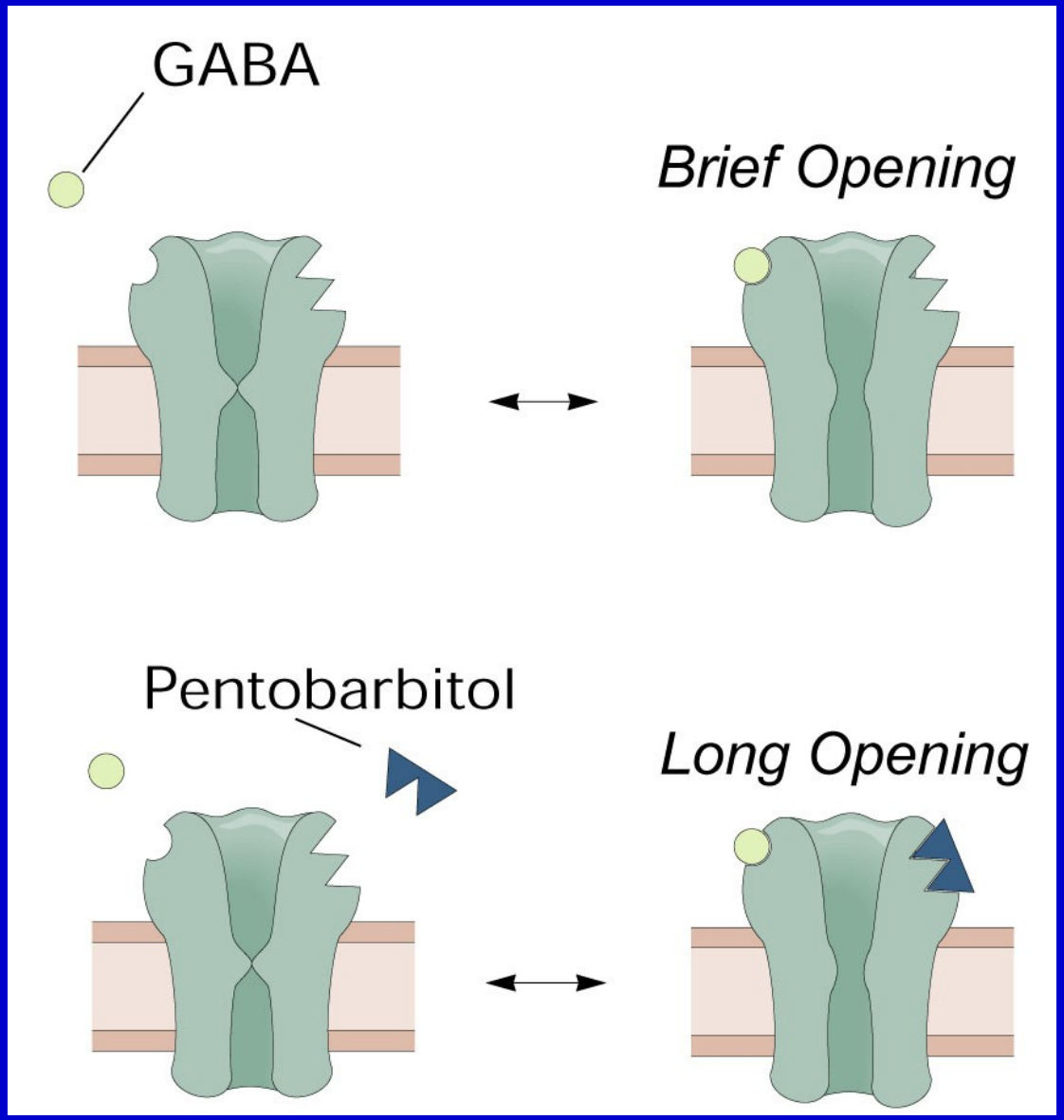
- Na^{+} channel activated by acetylcholine $\Rightarrow \uparrow$ open state probability (P_o)
- When acetylcholine absent channel spends most of time in closed state

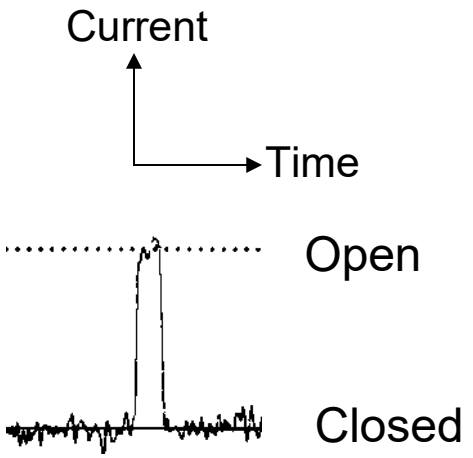
Modifiers of Channel Gating

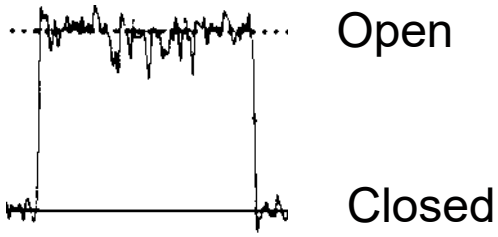
Binding of Exogenous Ligands Can Block Gating



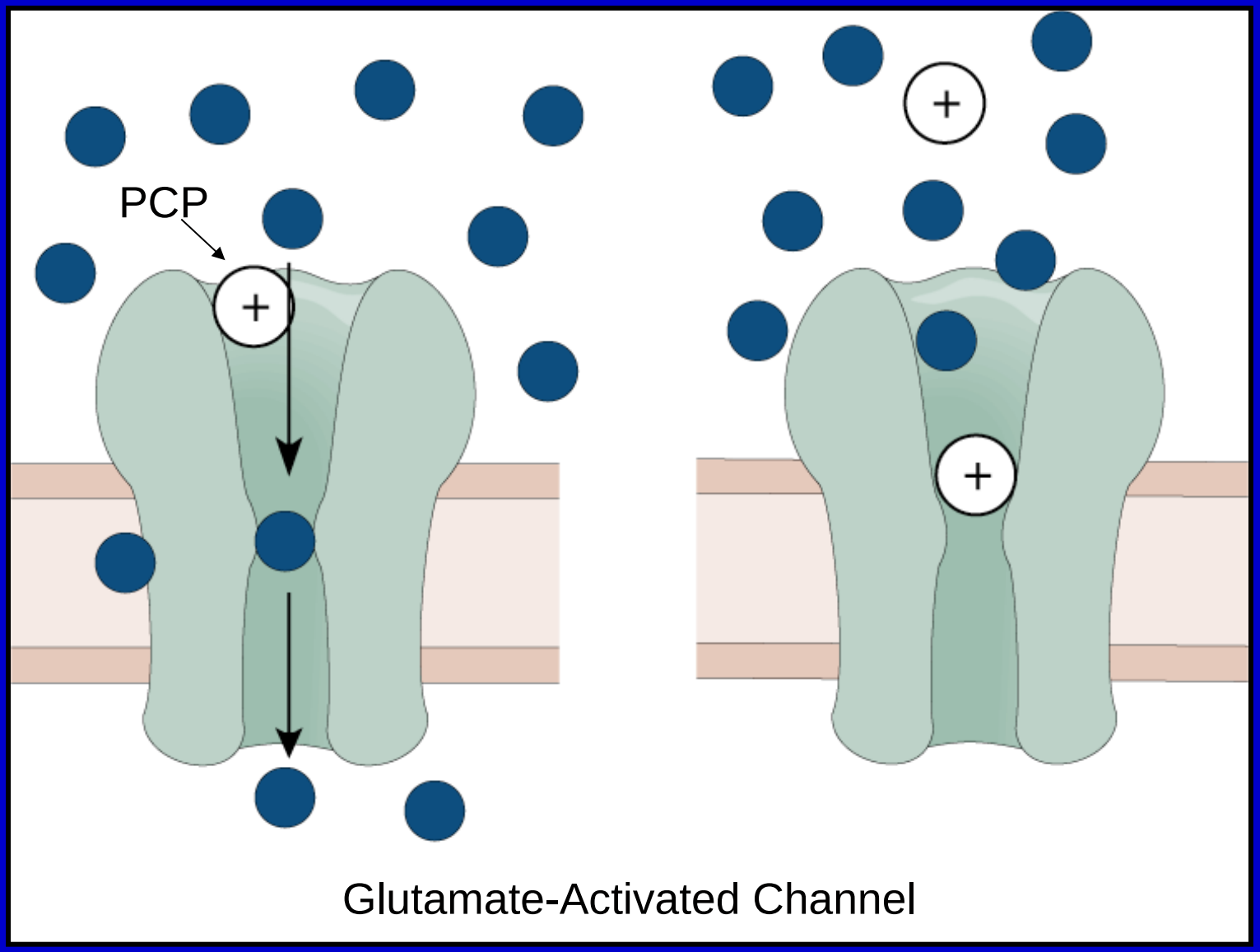
Exogenous Modulators Can Modify the Action of Endogenous Regulators







Ion Permeation Can be Prevented by Pore Blockers



Glutamate-Activated Channel

49 Human ATP-Binding Cassette Transporters

Name	ABC1	MDR	MRP	ALD	OABP	GCN20	White
Subfamily	ABCA	ABCB	ABCC	ABCD	ABCE	ABCF	ABCG
Members	12	11	13	4	1	3	5 (+ 1?)

ABC transporters are responsible for drug resistance

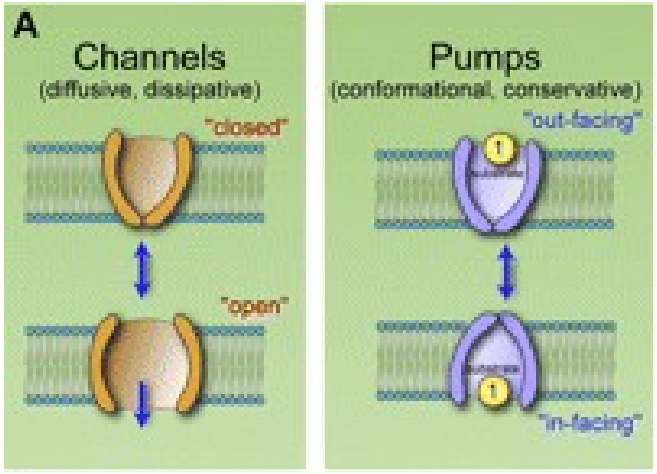
- If anti-cancer drugs do not show any positive effect, this is frequently due to overexpression of the P-glycoprotein, a member of the ABC transporter superfamily or **multidrug resistance (MDR) transporters**
- Built from 4 modules: 2x cytoplasmic nucleotide binding sites, 2x TMDs with 6 helices each,
- In bacteria these 4 domains can be coded by 2 or 4 single proteins; in eukaryotes all 4 domains on a single protein
- In bacteria, ABC transporters can act as importers or exporters, in eukaryotes only as exporters (?)

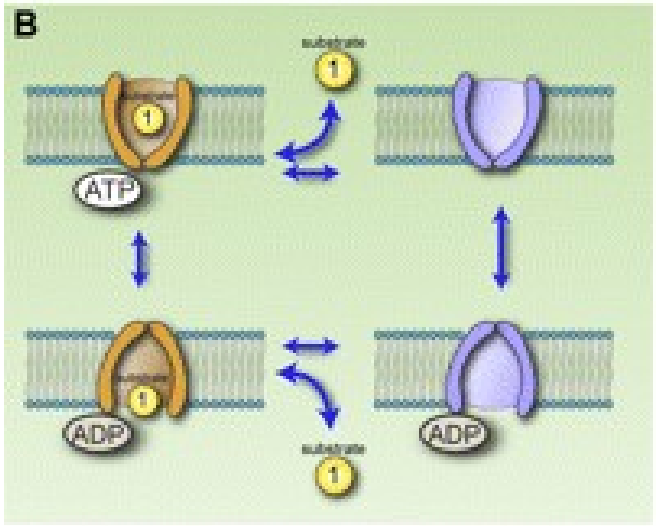
CFT is an ABC transporter

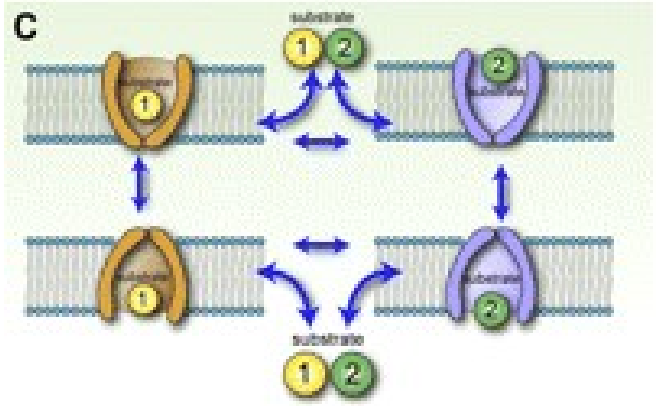
- CFTR, cystic fibrosis transmembrane conducting channel, is the only ion transporting of the ca 100 known ABC transporters (see Box 3-1)
- Allows Cl^- ions to flow out of the cell, by ATP hydrolysis
- More than 1000 mutations known, most frequent is Phe508 deletion, protein is functional, but improperly folded and degradet in the ER before transport to PM
- Homozygous have lung problems, thick mucus in the airways -> suffer from chronic lung infections, early death

Physiol Rev. 2008 Apr;88(2):351-87.
CLC-0 and CFTR: chloride channels evolved from transporters.
Chen TY, Hwang TC.

CLC-0 and cystic fibrosis transmembrane conductance regulator (CFTR) Cl(-) channels play important roles in Cl(-) transport across cell membranes. These two proteins belong to, respectively, the CLC and ABC transport protein families whose members encompass both ion channels and transporters. Defective function of members in these two protein families causes various hereditary human diseases. Ion channels and transporters were traditionally viewed as distinct entities in membrane transport physiology, but recent discoveries have blurred the line between these two classes of membrane transport proteins. CLC-0 and CFTR can be considered operationally as ligand-gated channels, though binding of the activating ligands appears to be coupled to an irreversible gating cycle driven by an input of free energy. High-resolution crystallographic structures of bacterial CLC proteins and ABC transporters have led us to a better understanding of the gating properties for CLC and CFTR Cl(-) channels. Furthermore, the joined force between structural and functional studies of these two protein families has offered a unique opportunity to peek into the evolutionary link between ion channels and transporters. A promising byproduct of this exercise is a deeper mechanistic insight into how different transport proteins work at a fundamental level.







***A*: ion channels versus transporters.**
The cartoon depicts the difference in the traditional concepts of ion channels and transporters. For ion channels (*left*), ions diffuse through the open pore, which is thought to be controlled by one gate. For transporters (*right*), because an open pore is not allowed at any time, the transport pathway must be guarded by at least two gates. The opening of the two gates is coordinated so that no open pore is allowed. The "1" represents the transported substrate that binds to the binding site in the transport pathway.

***B*: primary active transport mechanism.**
Energy directly harvested from the hydrolysis of ATP (the energy currency in cells) is used to pump the substrate across the membrane against an electrochemical gradient.

***C*: secondary active antiport mechanism.**
The two substrates, "1" and "2", are transported in opposite directions. The direction of the transport cycle ("1" out and "2" in, or "1" in and "2" out) depends on the electrochemical gradients of these two substrates.

Cystic fibrosis transmembrane conductance regulator chloride channel blockers: P harmacological, biophysical and physiological relevance.
Linsdell P.
World J Biol Chem. 2014 Feb 26;5(1):26-39. Review.

The secret life of CFTR as a calcium-activated chloride channel.
Billet A, Hanrahan JW.
J Physiol. 2013 Nov 1;591(Pt 21):5273-8. Review.

CLC-0 and CFTR: chloride channels evolved from transporters.
Chen TY, Hwang TC.
Physiol Rev. 2008 Apr;88(2):351-87. Review.

The ABC protein turned chloride channel whose failure causes cystic fibrosis.
Gadsby DC, Vergani P, Csanády L.
Nature. 2006 Mar 23;440(7083):477-83. Review.

CFTR is a conductance regulator as well as a chloride channel.
Schwiebert EM, Benos DJ, Egan ME, Stutts MJ, Guggino WB.
Physiol Rev. 1999 Jan;79(1 Suppl):S145-66. Review.

Ioncsatornák és betegség

Ioncsatornákat megtámadó autoimmun betegségek – Myasthenia gravis (AchR), Lambert–Eaton szindróma (vázizom Ca^{2+} csatorna)

Myotonia (extrém izomtenzió) – vázizom Na^{+} csatornák nem inaktiválódnak megfelelően, ami fokozza az izom ingerületi állapotát

Hosszú QT szindróma – szív Na^{+} és K^{+} csatornák

Malignus hypertermia – altatás → vázizom $[Ca^{2+}]i$ emelkedése → erős kontrakció → a testhőmérséklet potenciálisan halálos mértékű emelkedése

Cisztikus fibrózis – Cl^{-} csatorna mutációja → csökkent epiteliális Cl^{-} konduktancia
→ váladék felhalmozódás a tüdőben → krónikus fertőzés → halál

Startle disease (hyperekplexia) – glicin receptor mutációja a központi idegrendszerben; váratlan stimulusra megmerevedő testtartás, görcsbe ránduló végtagok

Channelopathies / Ion channel related diseases

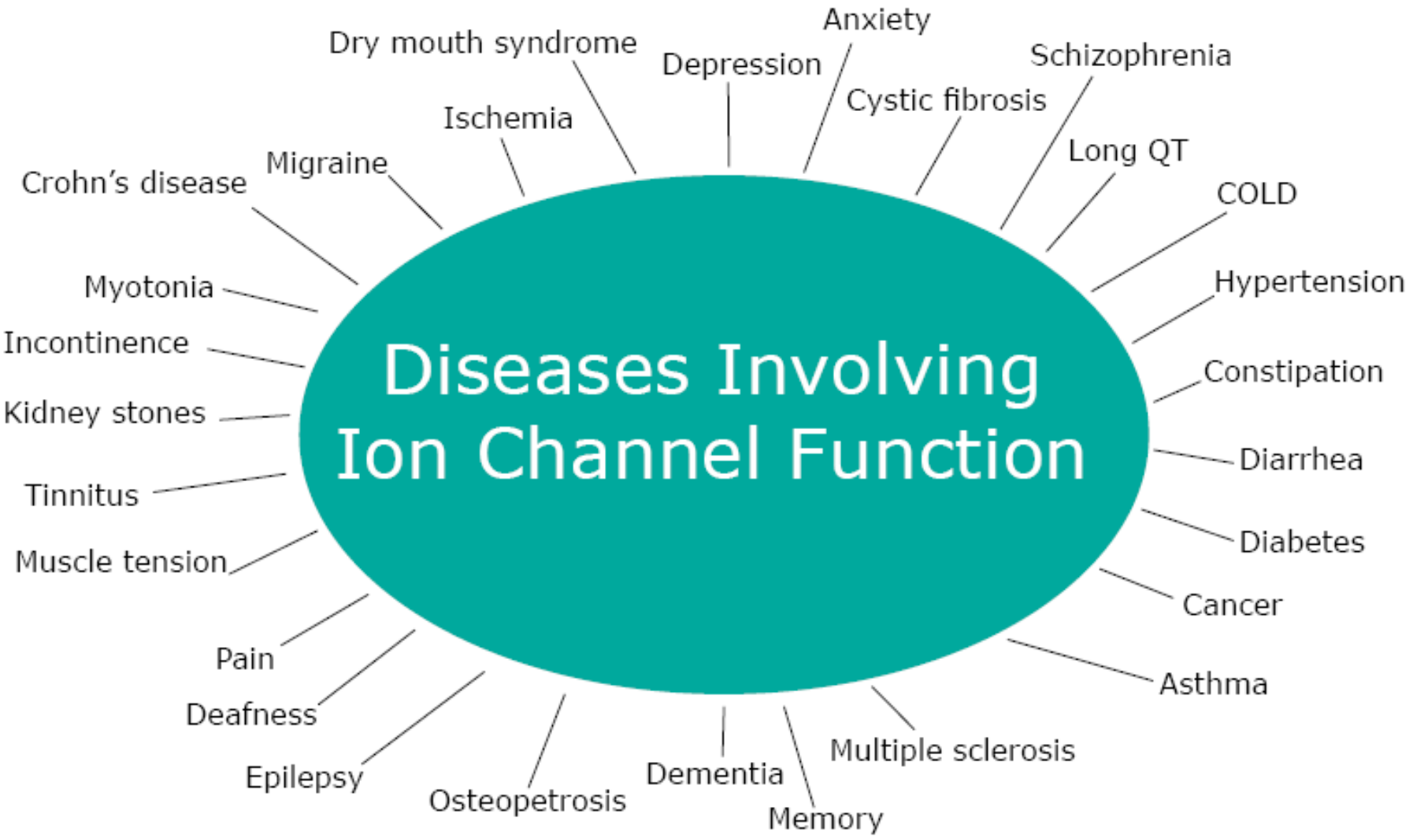
Table 1. Known ion channel diseases

Channel	Gene	Channel-forming unit/ligand	OMIM	Disease
Cation channels:				
CHRNA1/ACHRA	*CHRNA1*	α, ACh	100690	Myasthenia congenita
CHRNA4	*CHRNA4*	α, ACh	118504	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	*CHRNB2*	β, ACh	118507	Autosomal dominant nocturnal frontal lobe epilepsy
Polycystin-2	*PKD2*	α	173910	Autosomal dominant polycystic kidney disease (ADPKD)
CNGA3	*CNGA3*	α, cGMP	600053	Achromatopsia 2 (color blindness)
CNGB1	*CNGB1*	β, cGMP	600724	Autosomal recessive retinitis pigmentosa
CNGB3	*CNGB3*	β, cGMP	605080	Achromatopsia 3
Sodium channels:				
$Na_v1.1$	*SCN1A*	α	182389	Generalized epilepsy with febrile seizures (GEFS+)
$Na_v1.2$	*SCN2A*	α	182390	Generalized epilepsy with febrile and afebrile seizures
$Na_v1.4$	*SCN4A*	α	603967	Paramyotonia congenita, potassium aggressive myotonia, hyperkalemic periodic paralysis
$Na_v1.5$	*SCN5A*	α	600163	Long-QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)
SCN1B	*SCN1B*	β	600235	Generalized epilepsy with febrile seizures (GEFS+)
ENaCα	*SCNN1A*	α	600228	Pseudohypoaldosteronism type 1 (PHA1)
ENaCβ	*SCNN1B*	β	600760	PHA1, Liddle syndrome (dominant hypertension)
ENaCγ	*SCNN1G*	γ	600761	PHA1, Liddle syndrome
Potassium channels:				
$K_v1.1$	*KCNA1*	α	176260	Episodic ataxia with myokymia
KCNQ1/K_vLQT1	*KCNQ1*	α	192500	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNQ2	*KCNQ2*	α	602235	BFNC (epilepsy), also with myokymia
KCNQ3	*KCNQ3*	α	602232	BFNC (epilepsy)
KCNQ4	*KCNQ4*	α	603537	DFNA2 (dominant hearing loss)
HERG/ KCNH2	*KCNH2*	α	152427	Long-QT syndrome
Kir1.1/ROMK	*KCNJ1*	α	600359	Bartter syndrome (renal salt loss, hypokalemic alkalosis)
Kir2.1/IRK/KCNJ2	*KCNJ2*	α	600681	Long-QT syndrome with dysmorphic features (Andersen syndrome)
Kir6.2/K_{ATP}	*KCNJ11*	α	600937	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
SUR1	*SUR1*	β	600509	PHHI
KCNE1/MinK/ISK	*KCNE1*	β	176261	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNE2/MiRP1	*KCNE2*	β	603796	Long-QT syndrome
KCNE3/MiRP2	*KCNE3*	β	604433	Periodic paralysis

Calcium channels:				
$Ca_v1.1$	*CACNA1S*	α	114208	Hypokalemic periodic paralysis, malignant hyperthermia
$Ca_v1.4$	*CACNA1F*	α	300110	X-linked congenital stationary night blindness
$Ca_v2.1$	*CACNA1A*	α	601011	Familial hemiplegic migraine, episodic ataxia, spinocerebellar ataxia type 6
RyR1	*RYR1*	α	180901	Malignant hyperthermia, central core disease
RyR2	*RYR2*	α	180902	Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia type 2
Chloride channels:				
CFTR	*ABCC7*	α	602421	Cystic fibrosis, congenital bilateral aplasia of vas deferens
ClC-1	*CLCN1*	α	118425	Autosomal recessive (Becker) or dominant (Thomsen) myotonia
ClC-5	*CLCN5*	α	300008	Dent's disease (X-linked proteinuria and kidney stones)
ClC-7	*CLCN7*	α	602727	Osteopetrosis (recessive or dominant)
ClC-Kb	*CLCNKB*	α	602023	Bartter syndrome type III
Barttin	*BSND*	β	606412	Bartter syndrome type IV (associated with sensorineural deafness)
GLRA1	*GLRA1*	α, glycine	138491	Hyperekplexia (startle disease)
GABAα1	GABRA1	α, GABA	137160	Juvenile myoclonus epilepsy
GABAγ2	*GABRG2*	γ, GABA	137164	Epilepsy
Gap junction channels:				
Cx26	*GJB2*		121011	DFNA3 (autosomal dominant hearing loss) DFNB1 (autosomal recessive hearing loss)
Cx30	*GJB4*		605425	DFNA3
Cx31	*GJB3*		603324	DFNA2
Cx32	*GJB1*		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.

Examples of channelopathies

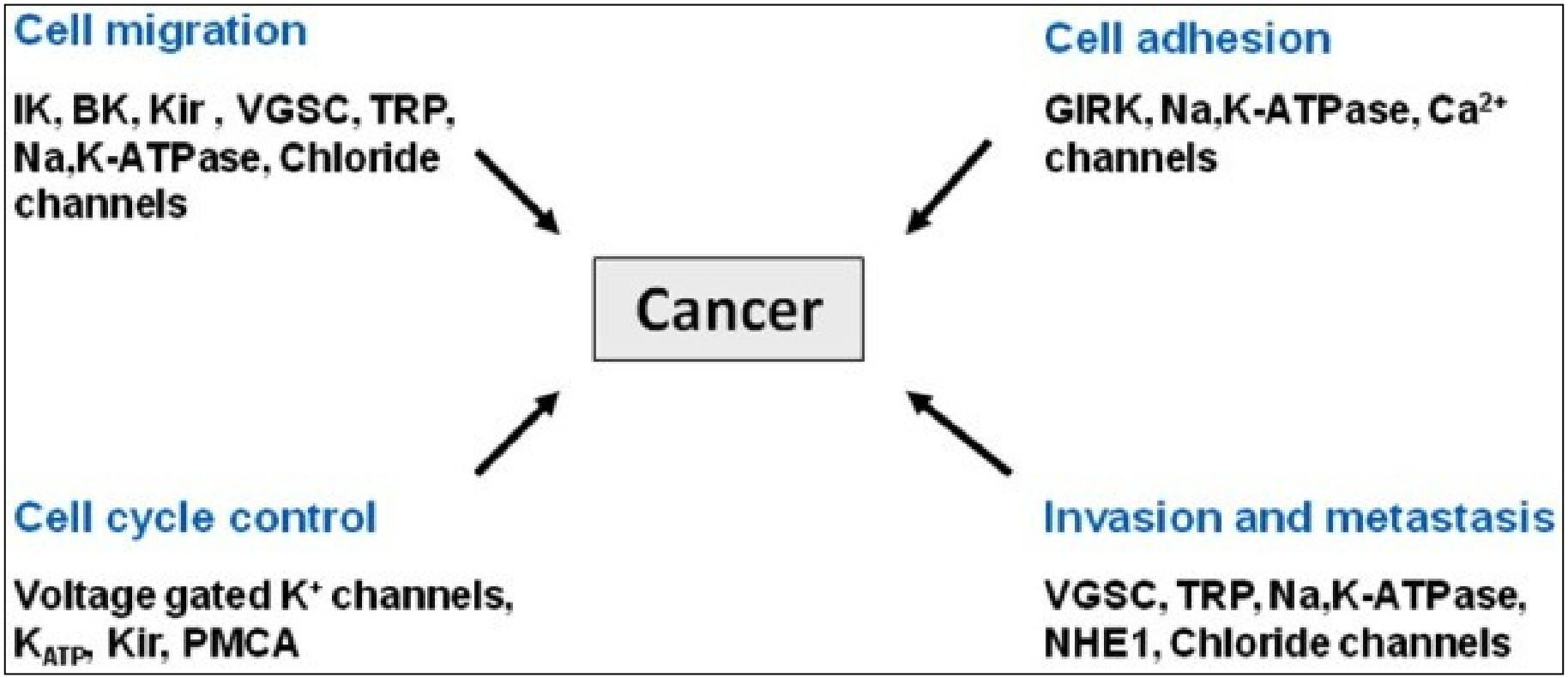


Front Cell Neurosci. 2015 Mar 17;9:86.

Cancer as a channelopathy:
ion channels and pumps in tumor development and progression.

Litan A, Langhans SA.

Increasing evidence suggests that ion channels and pumps not only regulate membrane potential, ion homeostasis, and electric signaling in excitable cells but also play important roles in cell proliferation, migration, apoptosis and differentiation. Consistent with a role in cell signaling, channel proteins and ion pumps can form macromolecular complexes with growth factors, and cell adhesion and other signaling molecules. And while cancer is still not being cataloged as a channelopathy, as the non-traditional roles of ion pumps and channels are being recognized, it is increasingly being suggested that ion channels and ion pumps contribute to cancer progression. Cancer cell migration requires the regulation of adhesion complexes between migrating cells and surrounding extracellular matrix (ECM) proteins. Cell movement along solid surfaces requires a sequence of cell protrusions and retractions that mainly depend on regulation of the actin cytoskeleton along with contribution of microtubules and molecular motor proteins such as mysoin. This process is triggered and modulated by a combination of environmental signals, which are sensed and integrated by membrane receptors, including integrins and cadherins. Membrane receptors transduce these signals into downstream signaling pathways, often involving the Rho GTPase protein family. These pathways regulate the cytoskeletal rearrangements necessary for proper timing of adhesion, contraction and detachment of cells in order to find their way through extracellular spaces. Migration and adhesion involve continuous modulation of cell motility, shape and volume, in which ion channels and pumps play major roles. Research on cancer cells suggests that certain ion channels may be involved in aberrant tumor growth and channel inhibitors often lead to growth arrest. This review will describe recent research into the role of ion pumps and ion channels in cell migration and adhesion, and how they may contribute to tumor development.

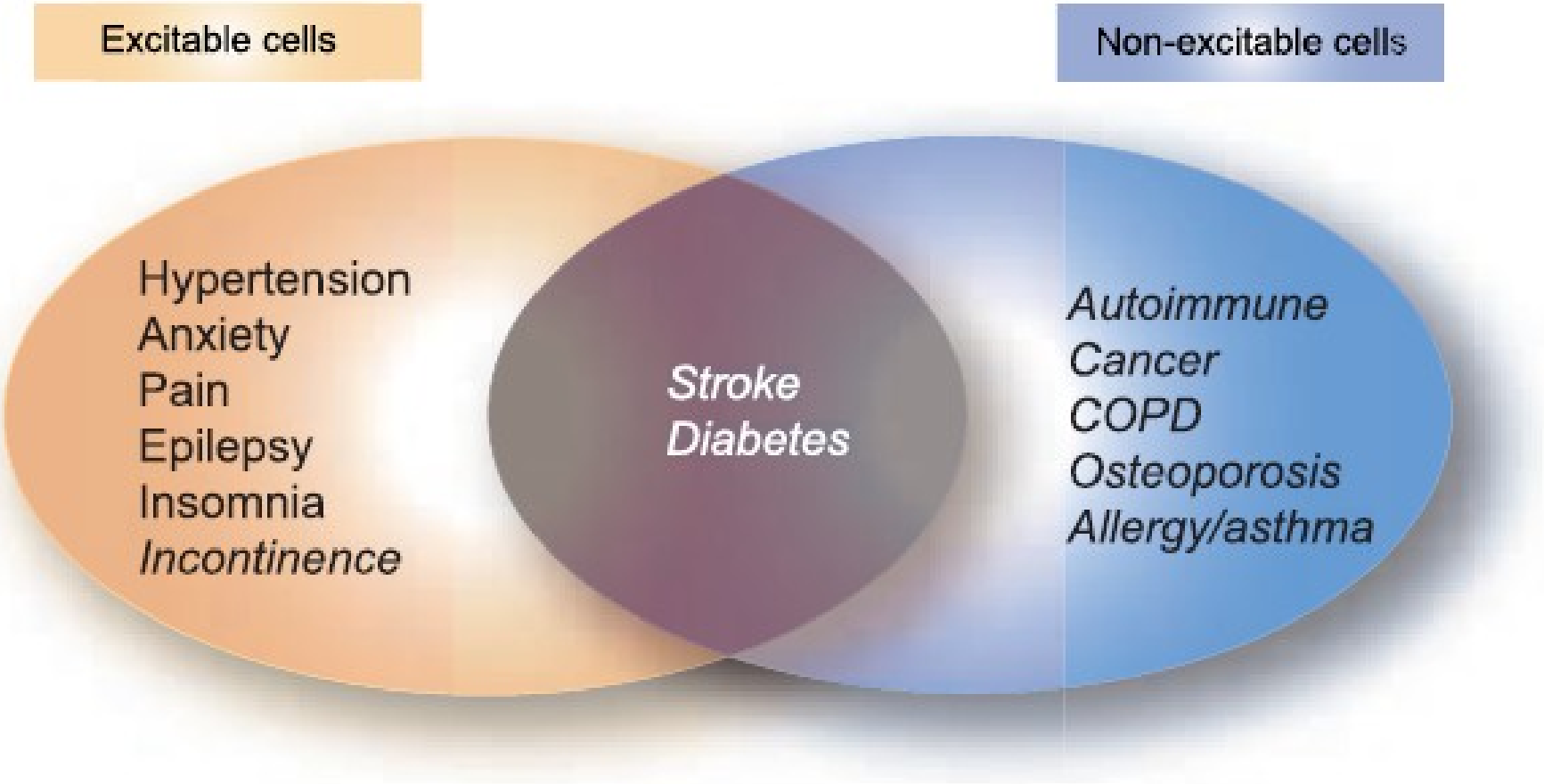

Cell migration
IK, BK, Kir , VGSC, TRP, Na,K-ATPase, Chloride channels
Cell adhesion
GIRK, Na,K-ATPase, Ca^{2+} channels
Cancer
Cell cycle control
Voltage gated K^+ channels, K_{ATP}, Kir, PMCA
Invasion and metastasis
VGSC, TRP, Na,K-ATPase, NHE1, Chloride channels

Ion channel drug discovery expands into new disease areas

Michael Xie, Mats H Holmqvist & Albert Y Hsia
Synta Pharmaceuticals, Lexington, MA, USA



Targeting recently discovered transient-receptor-potential channels and other novel ion channels allows the development of drugs for diseases such as cancer and immune disorders, expanding the traditional set of ion channel targets and enabling the discovery of first-in-class compounds.



Recent findings, primarily in non-excitable cells (immune cells, other), open new therapeutic areas (italics) for ion channel drugs.

AChR α7	Inflammation
ClC7	Osteoporosis
Ether-a-go-go	Cancer
Gardos channel	Sickle cell anemia
P2X7	Immune disorders
TRPC6	Asthma, COPD
TRPM1	Melanoma
TRPM2	Asthma
TRPM4	Immune disorders
TRPM7	Stroke
TRPM8	Prostate cancer
TRPV1	Urinary incontinence, pain

New channels, new diseases.

THE BEHAVIOR OF FOUR NEUROLOGICAL MUTANTS OF DROSOPHILA*

WILLIAM D. KAPLAN AND WILLIAM E. TROUT III

Department of Biology, City of Hope Medical Center, Duarte, California, 91010

Received August 26, 1968

SINGLE gene changes offer an efficient and attractive way to study the genetic control of behavior. Drosophila, with its numerous technical advantages, would seem to provide a fruitful approach in working out the complexities of neurological control. The four neurological mutants discovered serendipitously and described in this report present just such an opportunity.

The phenotype common to all four is a rapid shaking of the legs following etherization. Because the mutants appeared, among the progeny of four different males of the original thirty treated, they represent four independent mutational events. Subsequent study has disclosed that three separate gene loci are involved, all on the *X*-chromosome.

Genetics **61:** 399-409 February 1969.

TABLE 1

Localization of mutant genes on X-chromosome

Genotype	Number of offspring counted	Number of crossovers between:		Recombinational fraction between mutant and closer of two markers	Position on *X*-chromosome
Hyperkinetic^{1P}	2431	*ct* and *Hk*^{1P}	262	2.1	30.9 ± 0.6*
		Hk^{1P} and *v*	51		
Hyperkinetic^{2T}	2027	*cv* and *Hk*^{2T}	333	2.6	30.4 ± 0.7*
		Hk^{2T} and *v*	52		
Shaker^{5}	1770	*f* and *Sh*^{5}	24	1.4	58.2 ± 0.6*
		Sh^{5} and *car*	69		
Ether à go-go	2479	*g* and *Eag*	139	5.6	50.0 ± 1.0*
		Eag and *f*	179		

* Limits of recombinational fraction corresponding to level of significance of one in twenty. Based upon method of STEVENS (1942).


REGENCY
whiskyagogo.com
Whisky a Go Go
WED GRAVEYARD BBQ
TIME IS THE ENEMY
KAUSTIK
CHECHNYA
Clark St
NO CRUISING ZONE
DO NOT BLOCK
8901
whiskyagogo.com
BRUCE SPRINGSTEEN
THE SEEGER SESSIONS
MADONNA
DISTURBED

Mol Cancer. 2010 Jan 27;9:18.

The potassium channel Ether à go-go is a novel prognostic factor with functional relevance in acute myeloid leukemia.

Agarwal JR, Griesinger F, Stühmer W, Pardo LA.

BACKGROUND:

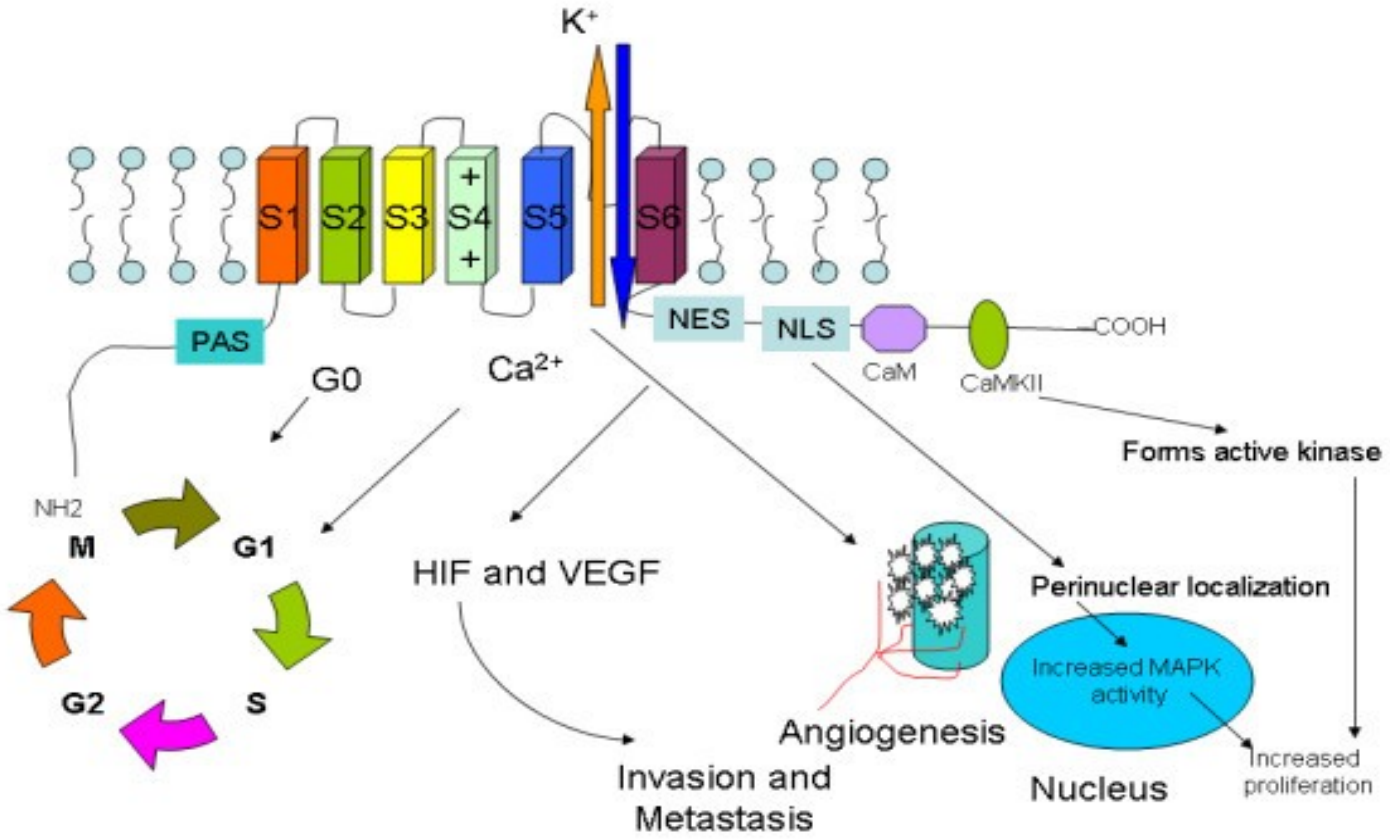
The voltage-gated potassium channel hEag1 (KV10.1) has been related to cancer biology. The physiological expression of the human channel is restricted to the brain but it is frequently and abundantly expressed in many solid tumors, thereby making it a promising target for a specific diagnosis and therapy. Because chronic lymphatic leukemia has been described not to express hEag1, it has been assumed that the channel is not expressed in hematopoietic neoplasms in general.

RESULTS:

Here we show that this assumption is not correct, because the channel is up-regulated in myelodysplastic syndromes, chronic myeloid leukemia and almost half of the tested acute myeloid leukemias in a subtype-dependent fashion. Most interestingly, channel expression strongly correlated with increasing age, higher relapse rates and a significantly shorter overall survival. Multivariate Cox regression analysis revealed hEag1 expression levels in AML as an independent predictive factor for reduced disease-free and overall survival; such an association had not been reported before. As a functional correlate, specific hEag1 blockade inhibited the proliferation and migration of several AML cell lines and primary cultured AML cells in vitro.

CONCLUSION:

Our observations implicate hEag1 as novel target for diagnostic, prognostic and/or therapeutic approaches in AML.



Potential mechanisms of malignant transformation by K^+ channels. Increased expression of K^+ channels on cell membrane results in increased influx of Ca^{2+} ions resulting in increased transition of cells through G1/S phase of cell cycle. The channels in presence of hypoxia lead to release of HIF1 and VGEF factor leading to increased angiogenesis and subsequent invasion and metastasis of tumours. The nuclear localisation sequence (NLS) in the C terminus on activation results in perinuclear localisation of the channel leading to activation of Mitogen activated protein kinase (MARP) pathway resulting in increased cell proliferation. The Eag channels also act through the Ca calmodulin pathway to activate cell proliferation.

World J Surg Oncol. 2010 Dec 29;8:113.

Eag and HERG potassium channels as novel therapeutic targets in cancer.

Asher V, Sowter H, Shaw R, Bali A, Khan R.

Voltage gated potassium channels have been extensively studied in relation to cancer. In this review, we will focus on the role of two potassium channels, Ether à-go-go (Eag), Human ether à-go-go related gene (HERG), in cancer and their potential therapeutic utility in the treatment of cancer. Eag and HERG are expressed in cancers of various organs and have been implicated in cell cycle progression and proliferation of cancer cells. Inhibition of these channels has been shown to reduce proliferation both in vitro and vivo studies identifying potassium channel modulators as putative inhibitors of tumour progression. Eag channels in view of their restricted expression in normal tissue may emerge as novel tumour biomarkers.

Pharmacol Rev. 2014 Jul;66(3):676-814.

Transient receptor potential channels as drug targets: from the science of basic research to the art of medicine.

Nilius B, Szallasi A.

KU Leuven, Department of Cellular and Molecular Medicine, Laboratory of Ion Channel Research, Campus Gasthuisberg, Leuven, Belgium (B.N.); and Department of Pathology, Monmouth Medical Center, Long Branch, New Jersey

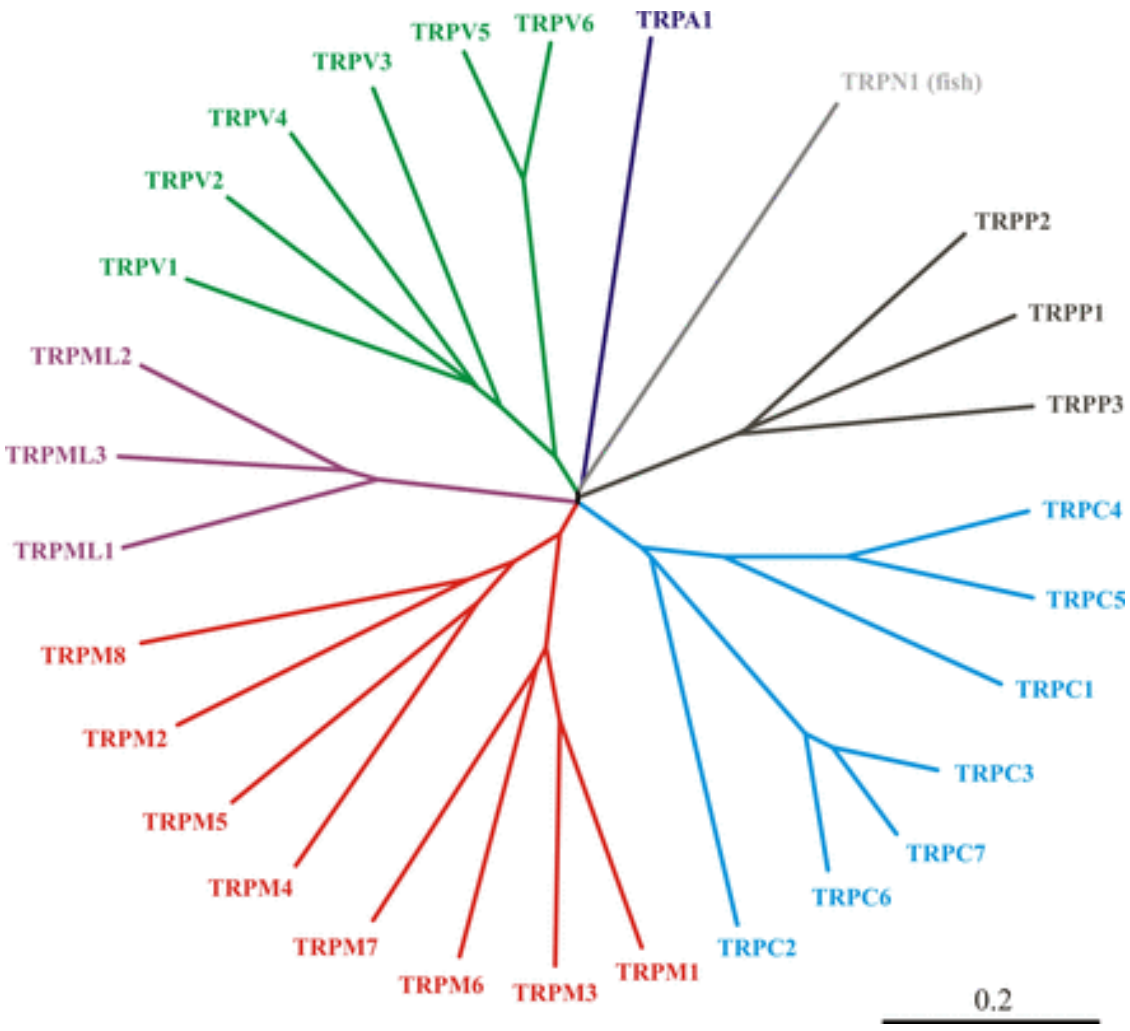
The large Trp gene family encodes transient receptor potential (TRP) proteins that form novel cation-selective ion channels. In mammals, 28 Trp channel genes have been identified. TRP proteins exhibit diverse permeation and gating properties and are involved in a plethora of physiologic functions with a strong impact on cellular sensing and signaling pathways. Indeed, mutations in human genes encoding TRP channels, the so-called „TRP channelopathies," are responsible for a number of hereditary diseases that affect the musculoskeletal, cardiovascular, genitourinary, and nervous systems. This review gives an overview of the functional properties of mammalian TRP channels, describes their roles in acquired and hereditary diseases, and discusses their potential as drug targets for therapeutic intervention.

In 1969, a Drosophila mutant was discovered that was defective in light sensing and exhibited only transient light-induced receptor potentials (TRPs) instead of the normal maintained response.

This finding was explained by a defect in an ion channel and triggered the discovery of the large gene family baptized „trp genes” that encode TRP channels.

By the latest count, the TRP channel superfamily contains 28 mammalian members (27 in humans; see Fig. for the TRP „family tree”) and is subdivided into six subfamilies, all of which permeate cations.

The phylogenic tree of human TRP channels



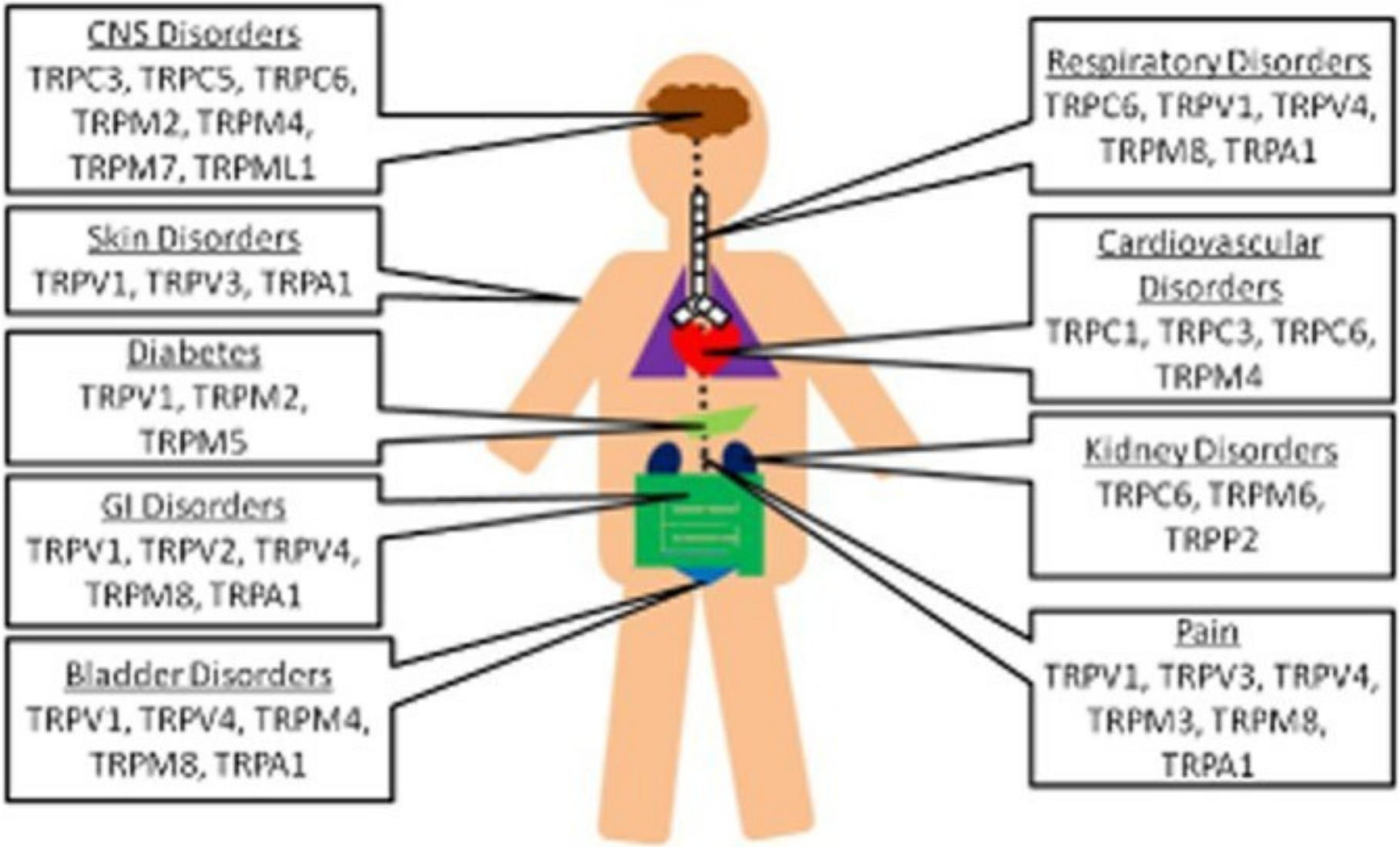
On the basis of sequence homology, all TRP channels fall into seven subfamilies that comprise proteins with distinct channel properties. Note that TRPN1 is only present in lower vertebrates (e.g., zebrafish); TRPC2 is a pseudogene in humans. The bar (0.2) indicates point accepted mutation units, which is the evolutionary distance between two amino acids (1 point accepted mutation unit = 1 point mutation event per 100 amino acids, which is accepted and is passed to progeny).

Physiol Rev. 2007 Jan;87(1):165-217.

Transient receptor potential cation channels in disease.

Nilius B, Owsianik G, Voets T, Peters JA.

The transient receptor potential (TRP) superfamily consists of a large number of cation channels that are mostly permeable to both monovalent and divalent cations. The 28 mammalian TRP channels can be subdivided into six main subfamilies: the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and the TRPA (ankyrin) groups. TRP channels are expressed in almost every tissue and cell type and play an important role in the regulation of various cell functions. Currently, significant scientific effort is being devoted to understanding the physiology of TRP channels and their relationship to human diseases. At this point, only a few channelopathies in which defects in TRP genes are the direct cause of cellular dysfunction have been identified. In addition, mapping of TRP genes to susceptible chromosome regions (e.g., translocations, breakpoint intervals, increased frequency of polymorphisms) has been considered suggestive of the involvement of these channels in hereditary diseases. Moreover, strong indications of the involvement of TRP channels in several diseases come from correlations between levels of channel expression and disease symptoms. Finally, TRP channels are involved in some systemic diseases due to their role as targets for irritants, inflammation products, and xenobiotic toxins. The analysis of transgenic models allows further extrapolations of TRP channel deficiency to human physiology and disease. In this review, we provide an overview of the impact of TRP channels on the pathogenesis of several diseases and identify several TRPs for which a causal pathogenic role might be anticipated.



Schematic illustration of the tissue-distribution of TRP channels and their putative roles in the pathogenesis of human disease.

Ioncsatornák mint gyógyszerek célpontjai

A helyi érzéstelenítők (pl. lidokain) gátolják a Na^+ csatornákat:

- nagy koncentrációjú helyi alkalmazás gátolja az idegi ingerületvezetést – érzéstelenítő hatás
- alacsony koncentrációjú szisztémás alkalmazás – antiarritmiás hatás

Ca^{2+} csatorna gátlók (verapamil, diltiazem, nifedipin):

- antiarritmiás hatás (verapamil, diltiazem)
- értágító hatás → szív munkájának csökkentése (magas vérnyomás)

Ioncsatornák mint gyógyszerek célpontjai

Nyugtatók, altatók:

- a központi idegrendszer gátló szinapszisait aktivizálják; a GABA receptorok gyakrabban nyitnak ki (benzodiazepinek) vagy tovább tartanak nyitva (barbiturátok) – repolarizáció, nyugtató hatás

Ioncsatornák mint gyógyszerek célpontjai

Limfocita K^+ csatornagátló-szerek, mint potenciális immunszuppresszorok:
(az intézet elektrofiziológiai munkacsoportjának munkája)

- bizonyos T limfociták (effektor memória sejtek), melyek részt vesznek egyes autoimmun betegségek (pl. sclerosis multiplex, I-es típusú diabetes) kialakulásában, nagy számban fejezik ki a Kv1.3 K^+ csatornát. E csatornákat gátló szereket alkalmazva az autoreaktív T sejtek aktivitása, proliferációja csökkenthető, így a betegség előrehaladása gátolható.

Br J Pharmacol. 2014 May;171(10):2474-507.
Transient receptor potential (TRP) channels: a clinical perspective.
Kaneko Y, Szallasi A.

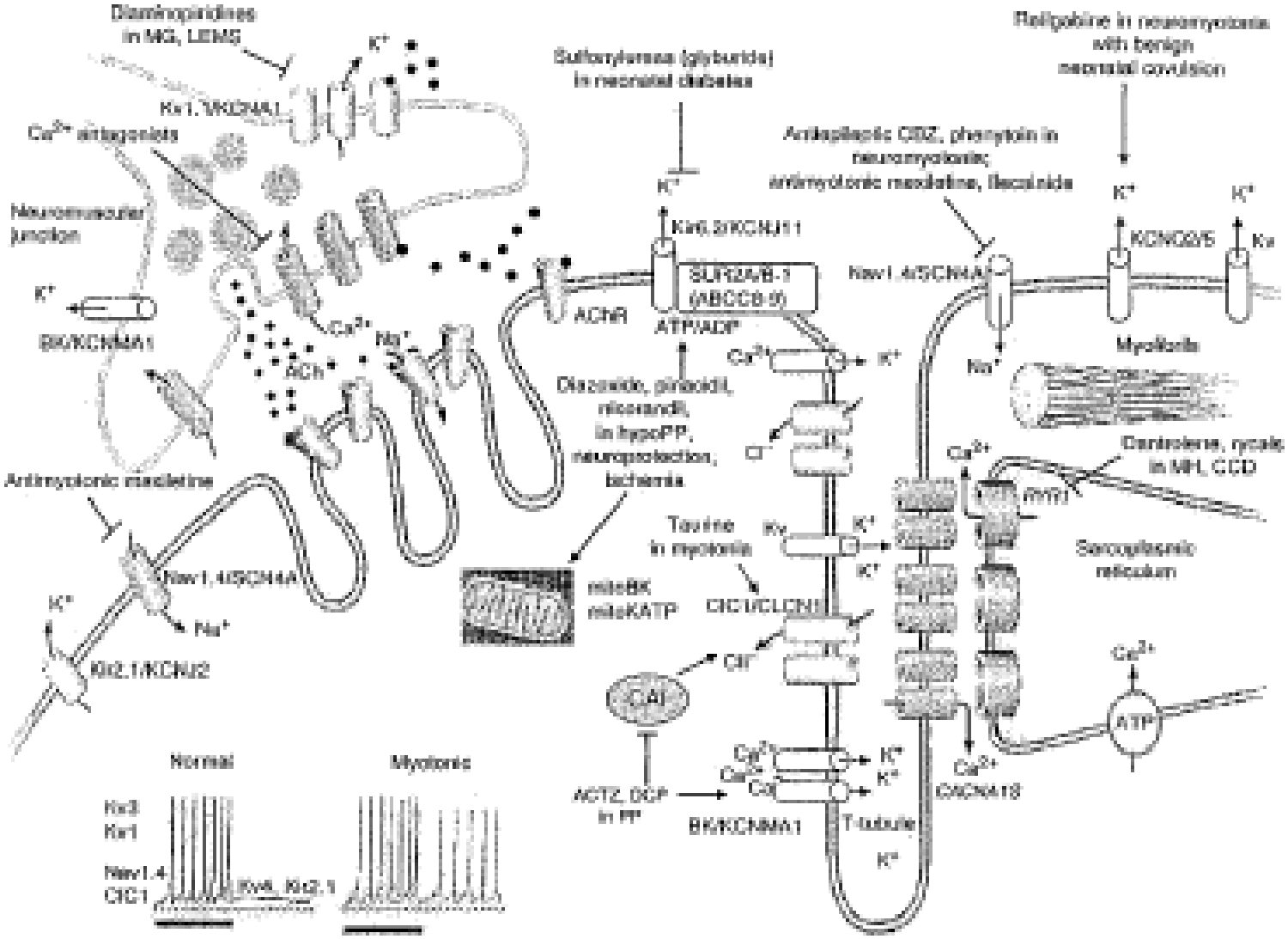
Transient receptor potential (TRP) channels are important mediators of sensory signals with marked effects on cellular functions and signalling pathways. Indeed, mutations in genes encoding TRP channels are the cause of several inherited diseases in humans (the so-called 'TRP channelopathies') that affect the cardiovascular, renal, skeletal and nervous systems. TRP channels are also promising targets for drug discovery. The initial focus of research was on TRP channels that are expressed on nociceptive neurons. Indeed, a number of potent, small-molecule TRPV1, TRPV3 and TRPA1 antagonists have already entered clinical trials as novel analgesic agents. There has been a recent upsurge in the amount of work that expands TRP channel drug discovery efforts into new disease areas such as asthma, cancer, anxiety, cardiac hypertrophy, as well as obesity and metabolic disorders. A better understanding of TRP channel functions in health and disease should lead to the discovery of first-in-class drugs for these intractable diseases. With this review, we hope to capture the current state of this rapidly expanding and changing field.

Adv Genet. 2008;64:81-145..

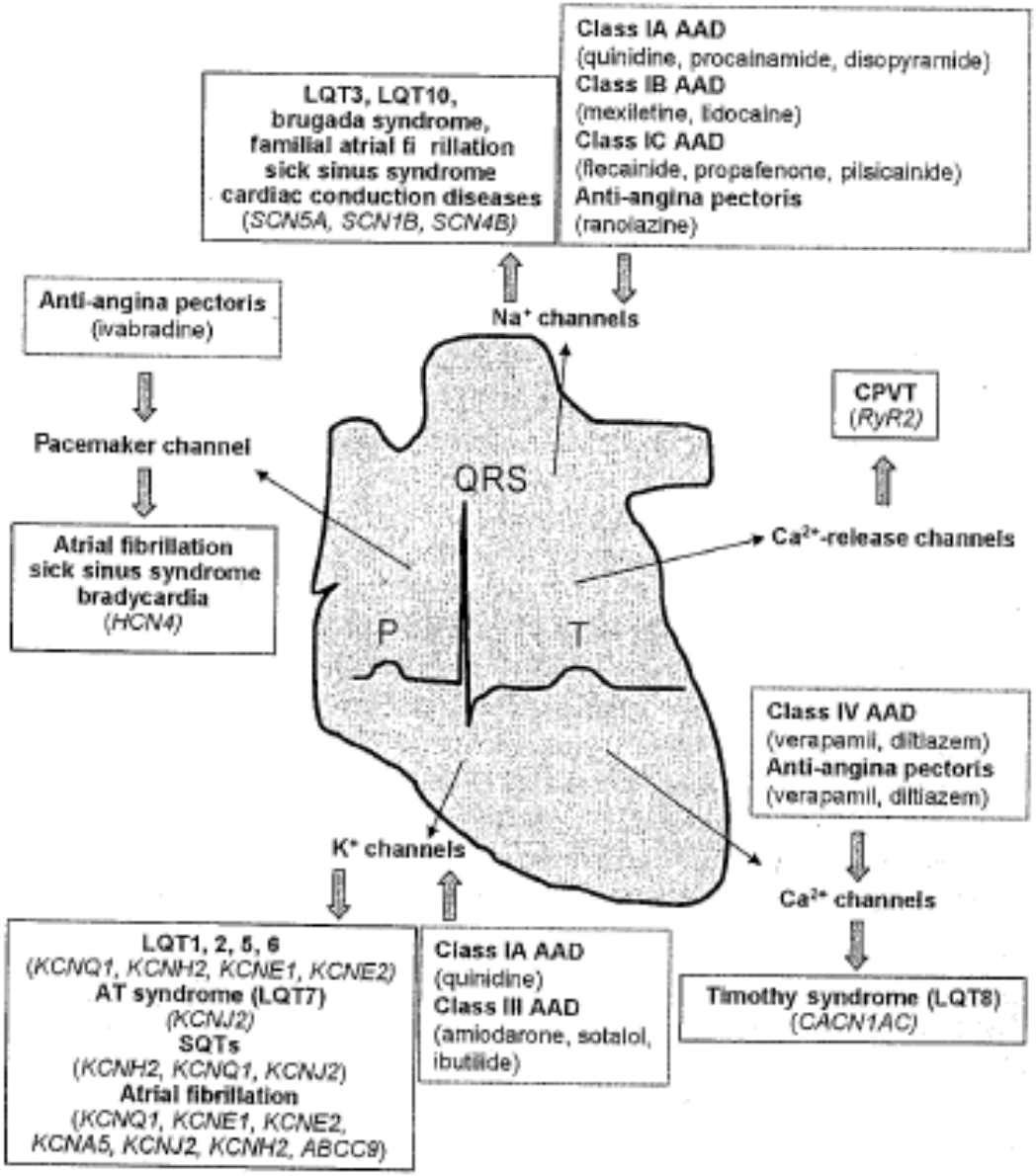
Therapeutic approaches to ion channel diseases.

Camerino DC, Desaphy JF, Tricarico D, Pierno S, Liantonio A.

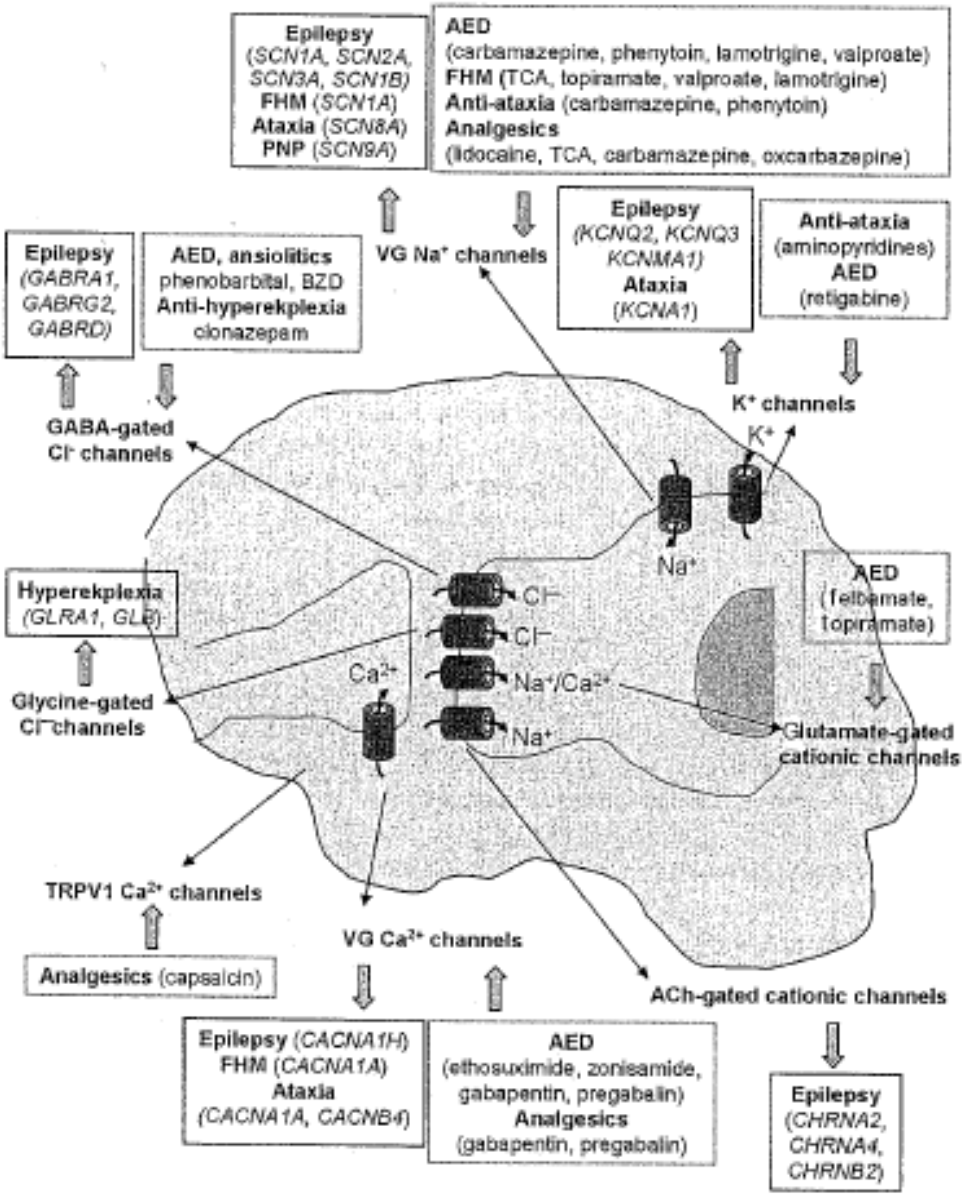
More than 400 genes are known that encode ion channel subunits. In addition, alternative splicing and heteromeric assembly of different subunits increase tremendously the variety of ion channels. Such many channels are needed to accomplish very complex cellular functions, whereas dysfunction of ion channels are key events in many pathological processes. The recent discovery of ion channelopathies, which, in its more stringent definition, encloses monogenic disorders due to mutations in ion channel genes, has largely contributed to our understanding of the function of the various channel subtypes and of the role of ion channels in multigenic or acquired diseases. Last but not least, ion channels are the main targets of many drugs already used in the clinics. Most of these drugs were introduced in therapy based on the experience acquired quite empirically, and many were discovered afterward to target ion channels. Now, intense research is being conducted to develop new drugs acting selectively on ion channel subtypes and aimed at the understanding of the intimate drug-channel interaction. In this review, we first focus on the pharmacotherapy of ion channel diseases, which includes many drugs targeting ion channels. Then, we describe the molecular pharmacology of ion channels, including the more recent advancement in drug development. Among the newest aspect of ion channel pharmacology, we draw attention to how polymorphisms or mutations in ion channel genes may modify sensitivity to drugs, opening the way toward the development of pharmacogenetics.



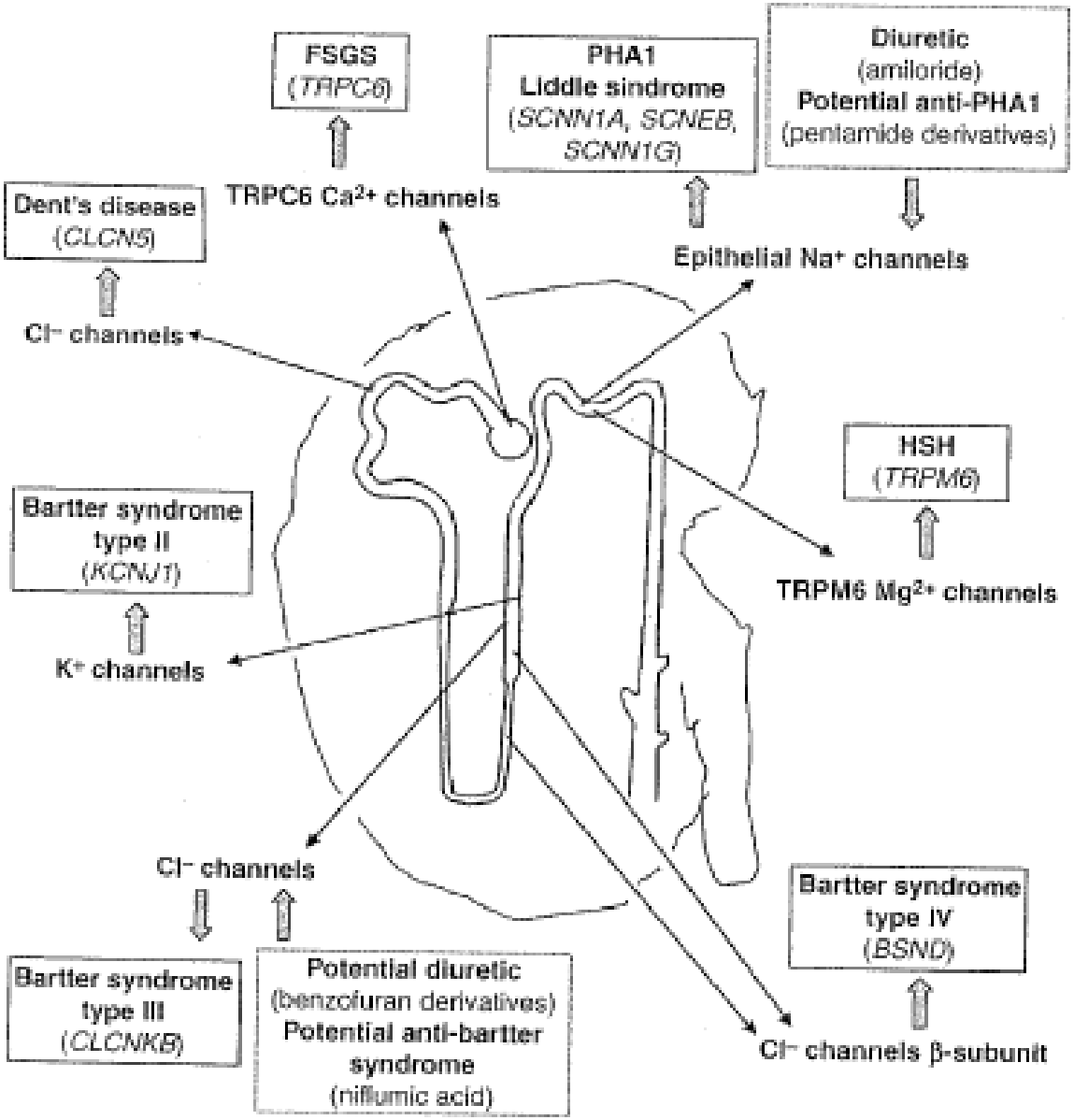
Ion channels involved in channelopathies of skeletal muscle and target of drugs. Channels and related genes, classes of drugs with examples, and therapeutic indications are reported. Modified from Ashcroft (2006).



Cardiac ion channels involved in channelopathies and targets of drugs. Channelopathies related to cardiac ion channel genes are indicated in plain boxes, while classes of drugs with examples are listed in dashed boxes. AAD, antiarrhythmic drugs. Please refer to the text for other abbreviations.



Ion channels of central and peripheral nervous system involved in channelopathies and targets of drugs. Channelopathies related to ion channel genes are indicated in plain boxes, while classes of drugs with examples are listed in dashed boxes. VG, voltage gated. Please refer to the text for other abbreviations.



Kidney ion channels involved in channelopathies and targets of drugs. Channelopathies related to ion channel genes are indicated in plain boxes, while classes of drugs with examples are listed in dashed boxes. Please refer to the text for abbreviations.