Cellular and Molecular Biophysics

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UNIVERSITÀ DI TORINO

Department of Life Sciences and Systems Biology

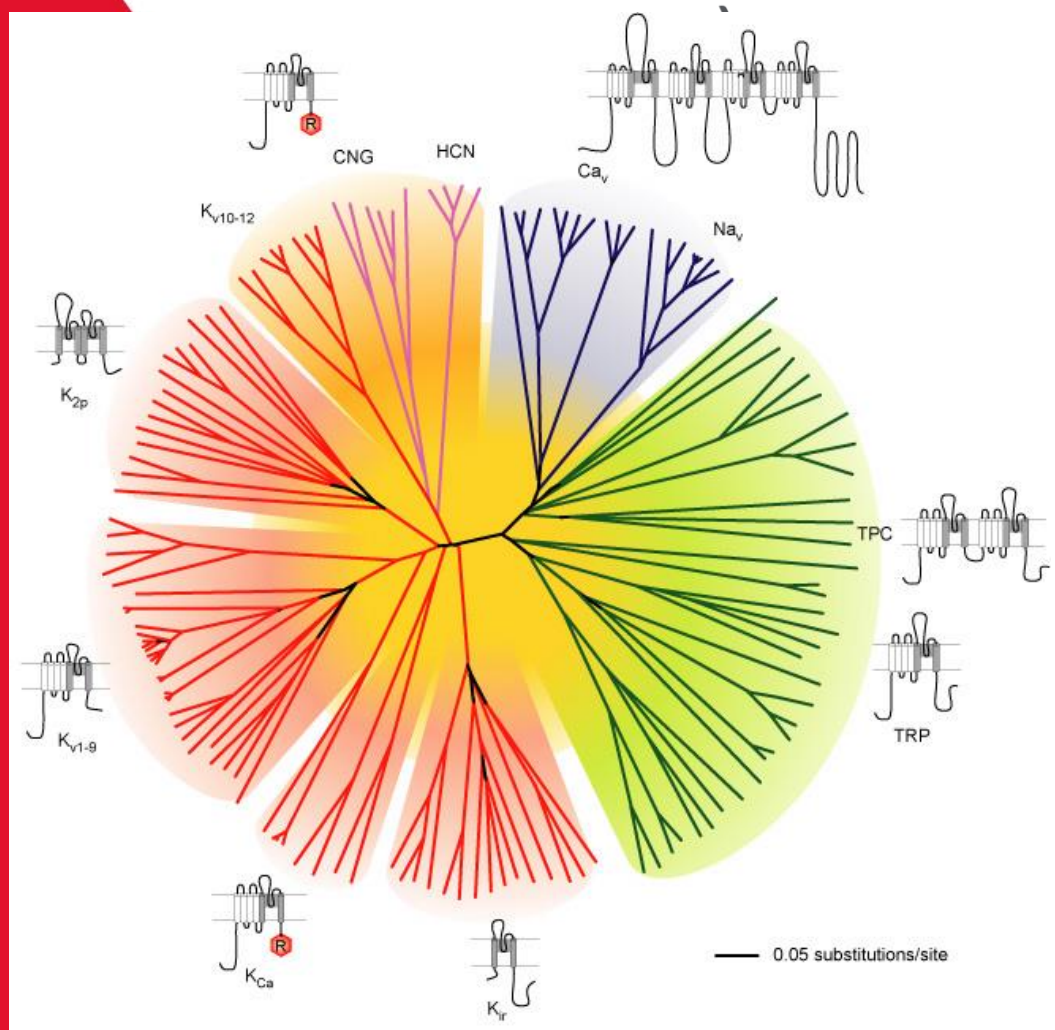
CFU 5 LM Biotecnologie Industriali- 6 LM Fisica - A.A. 2024/25

Corso di laurea in LM Biotecnologie Industriali- LM Fisica

Department of
Life Sciences
and Systems Biology

Ion Channels

STRUCTURE AND FUNCTION



Class objectives

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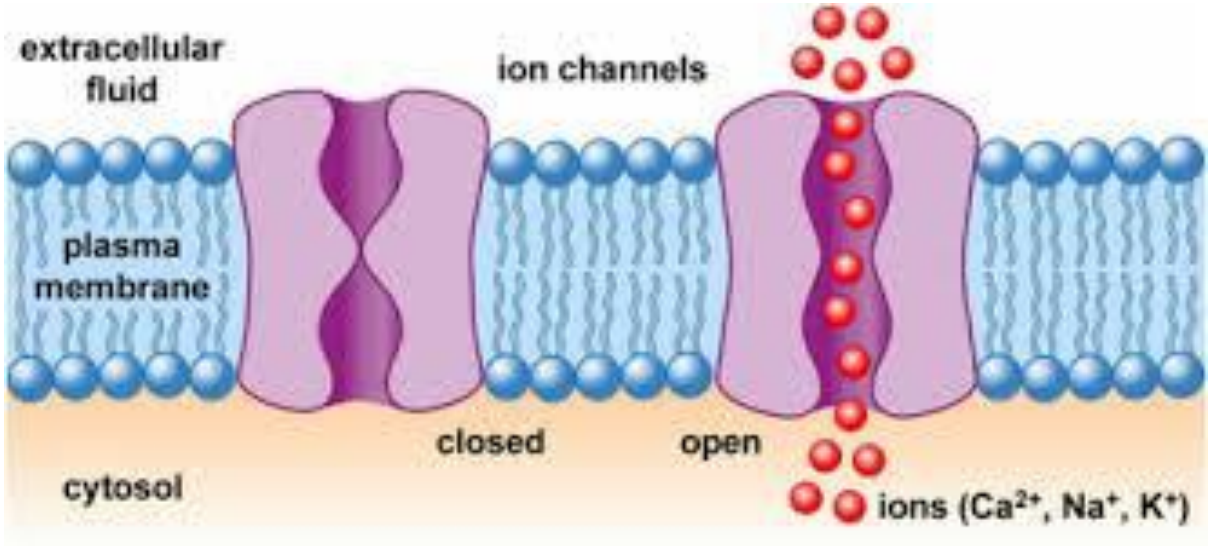
- Understand differences between
  - Leak channels
  - Gated channels
- Knowledge of principal gated channels
  - Voltage gated
  - Ligand gated
  - Mechanical-gated

- Ion channels are membrane proteins with a pore allowing the **passive fluxes of ions** along their electrochemical gradient.
- Ion channels exists in two conformational states:

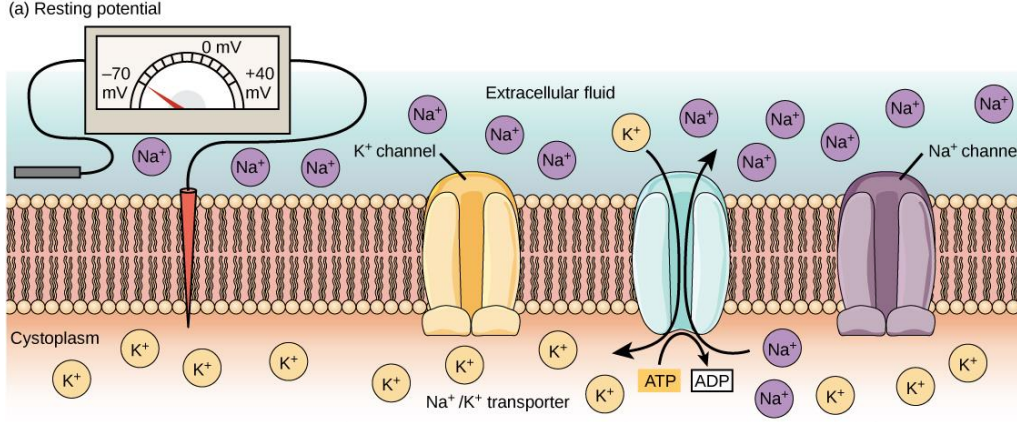
OPEN = allows ion fluxes

CLOSE = very low probability of ion permeation

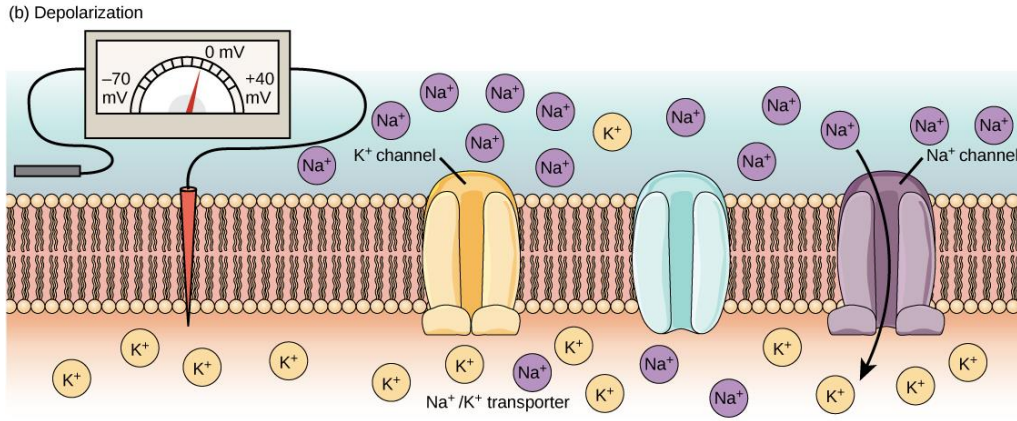


In the open state channels allows highly efficient ion fluxes allowing single channels current measurements which is very difficult for Transporters

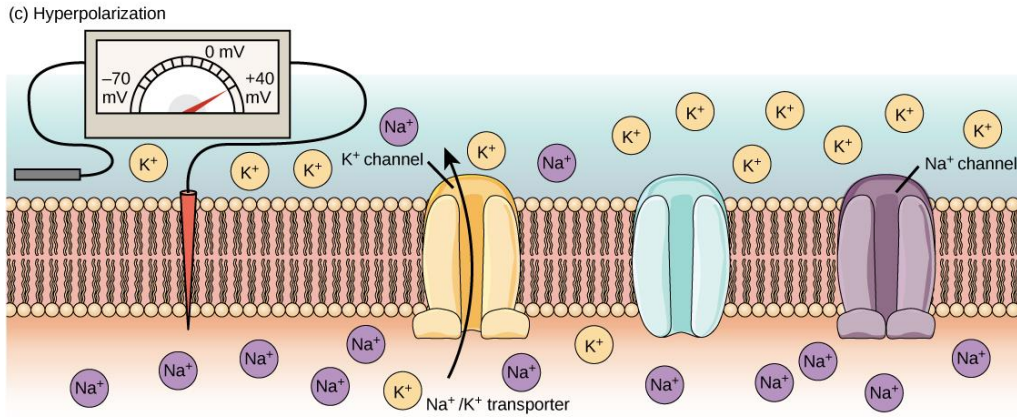
- The ion fluxes through ion channels significantly change Vm. Therefore In channels play a significant role in cell excitability



At the resting potential, all voltage-gated Na^+ channels and most voltage-gated K^+ channels are closed. The Na^+/K^+ transporter pumps K^+ ions into the cell and Na^+ ions out.



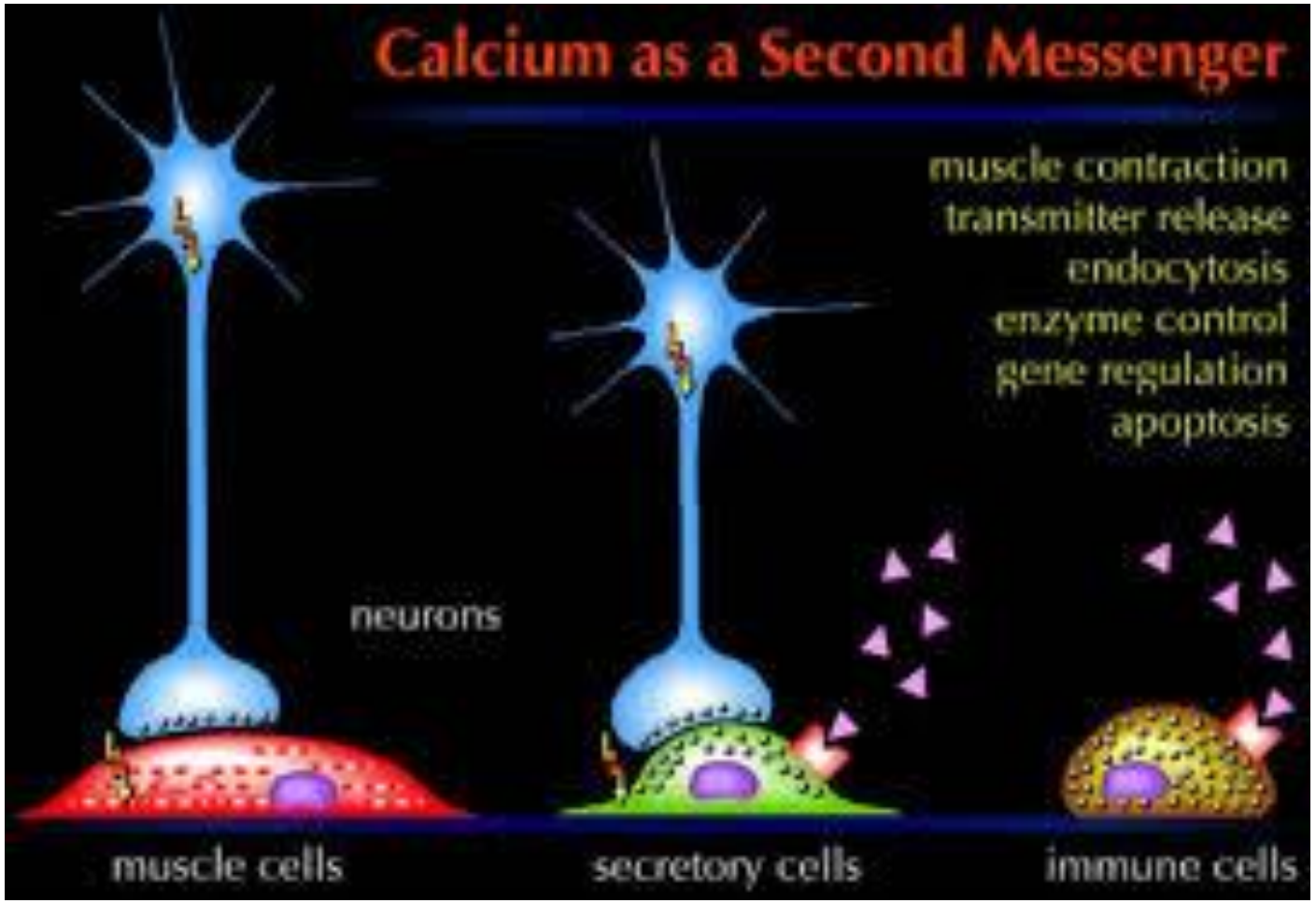
In response to a depolarization, some Na^+ channels open, allowing Na^+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na^+ channels open.

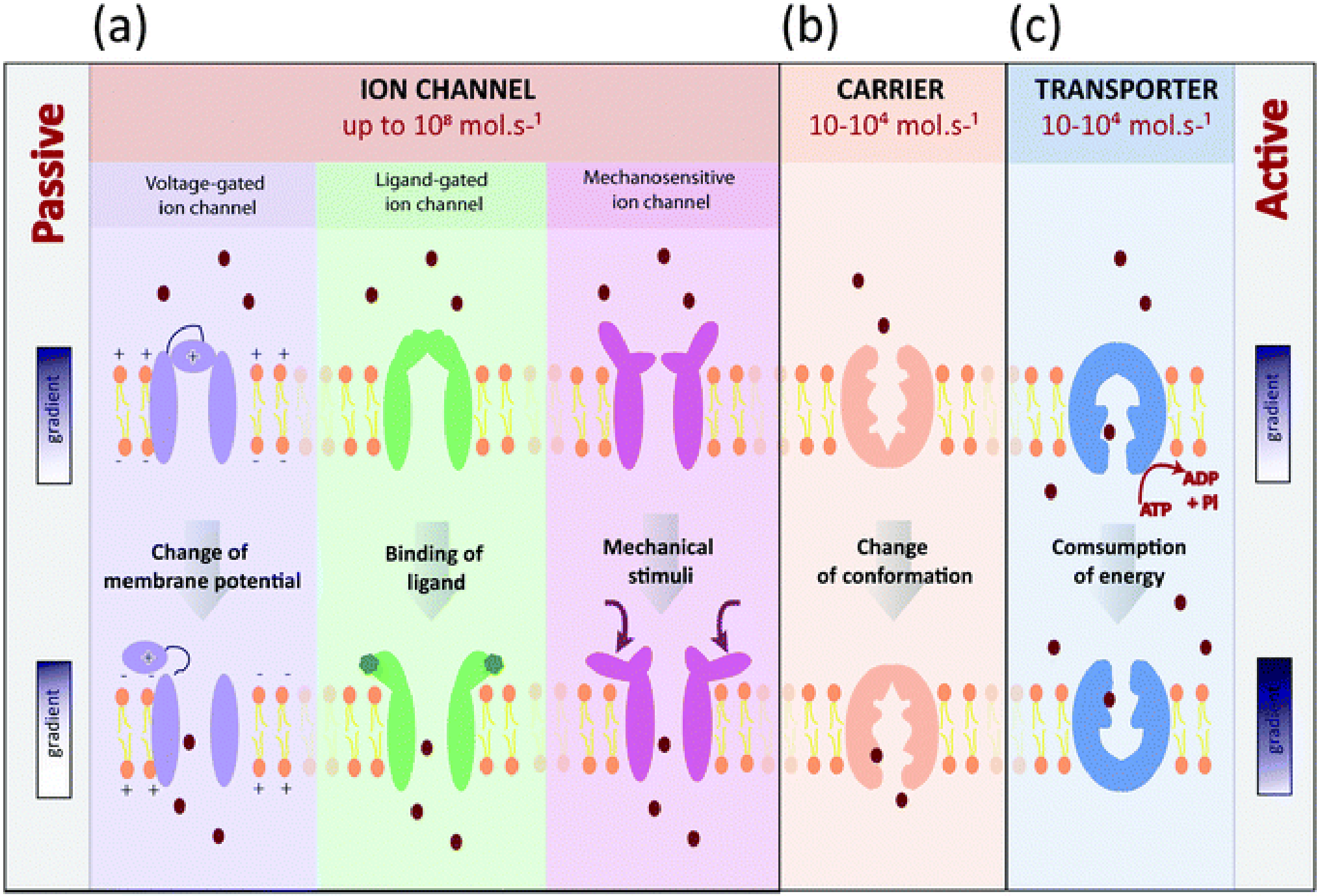


At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

Beside the passage of charges, ION CHANNELS allows also the passage of ions which play roles as SECOND MESSENGER

Ca2+




(a)
(b)
(c)
Passive
Active
ION CHANNEL
up to 10⁸ mol.s-1
CARRIER
10-10⁴ mol.s-1
TRANSPORTER
10-10⁴ mol.s-1
Voltage-gated ion channel
Ligand-gated ion channel
Mechanosensitive ion channel
gradient
gradient
gradient
gradient
ADP + PI
ATP
Change of membrane potential
Binding of ligand
Mechanical stimuli
Change of conformation
Comsumption of energy

ION CHANNELS classification: basic types of ion channels

- **Leakage channels**: constitutively open channels.
- **Gated channels**: open/close in response to a stimulus

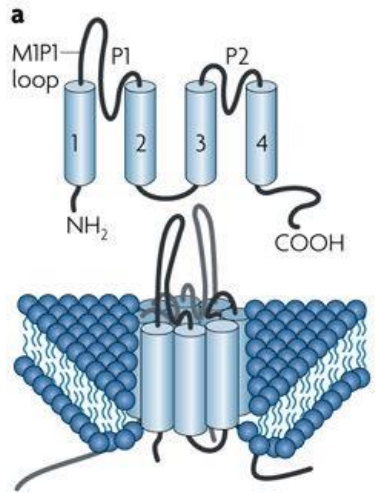
ION CHANNELS classification: basic types of ion channels

- **Leakage channels**: constitutively open channels.
  - **Leak K+ currents**: constitutively open they contribute to the neurons resting membrane potential (RMP, normally between -50 and -70 mV).

ION CHANNELS classification: basic types of ion channels

Two pore family of K+ leak channels (K2P).

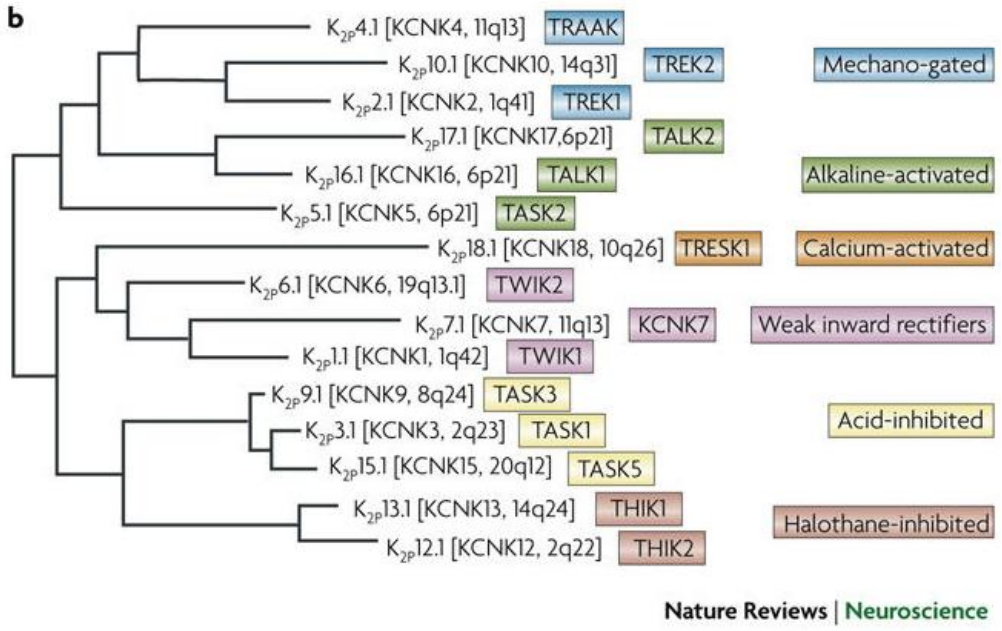
The resting activity of these K+ channels drives the membrane potential (through hyperpolarization) closer to the K+ equilibrium potential of about –90 mV, and therefore tends to reduce excitability.



ION CHANNELS classification: basic types of ion channels

Two pore family of K+ leak channels (K2P).

This family has 15 members that are subdivided in six distinct subfamilies, TWIK, TRAAK (TWIK Related Arachidonic acid Activated K+ channel), TREK (TWIK RElated K+channels), TASK (TWIK related Acid-Sensitive K+ channels), TALK (TWIK related ALkaline pH-activated K+ channels), THIK (Tandem pore domain Halothane Inhibited K+ channels)and TRESK (TWIK RElated Spinal cord K+ channel).

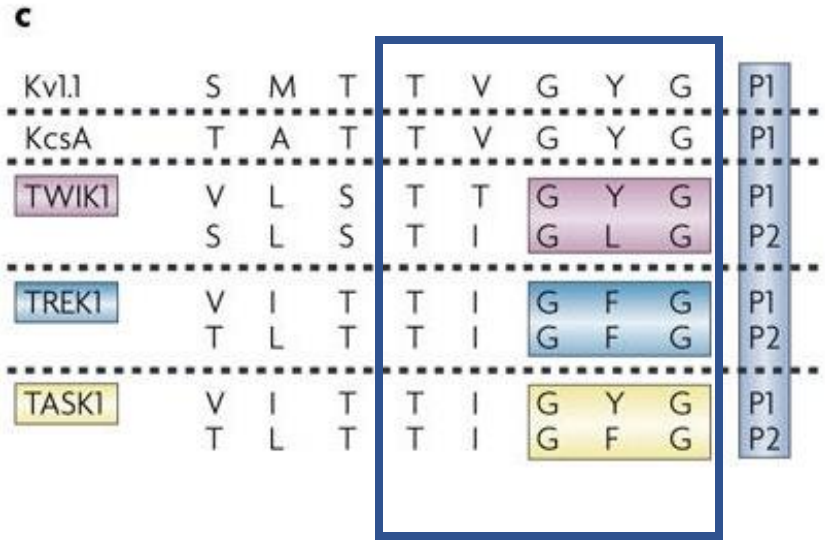


ION CHANNELS classification: basic types of ion channels

Two pore family of K+ leak channels (K2P).

Besides conserved K+ channel signature sequence T-X-G-X-G in the pore loop, the sequence homology between K2P channels is moderate,

usually as low as about 20%



ION CHANNELS classification: basic types of ion channels

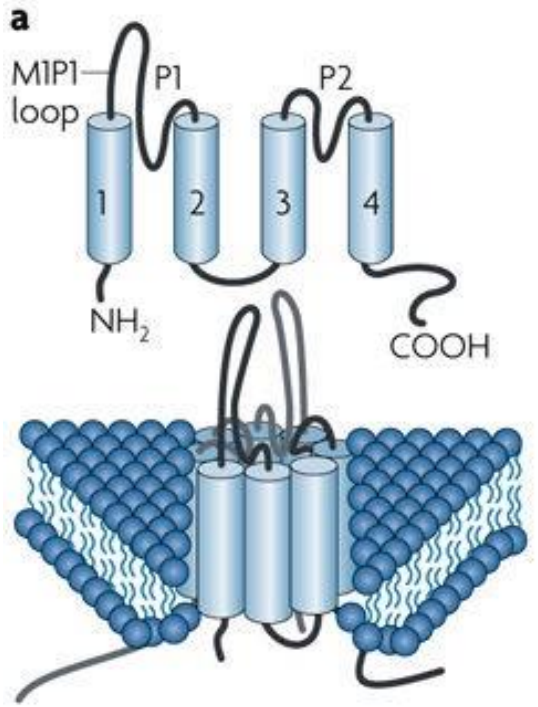
Two pore family of K+ leak channels (K2P).

All K2P channels have identical topology. Each subunit has two pore-forming loops, P1 and P2, arranged in tandem with four TMDs.

A characteristic extracellular loop with a short α-helix extend between TMD1 and P1. This TMD1-P1 loop is a coiled-coiled domain promoting dimerization.

This unique topology with **two-P loops has given its family name to K2P channels.**

Subunits arrange as dimers with additional bilateral symmetry such that two P1 and two P2 loops form the K+ selective pore with identical P loops probably facing each other diagonally across the central pore.



ION CHANNELS classification: basic types of ion channels

- **Leakage channels**: constitutively open channels.
  - **Leak Na+ currents**:

many neurons exhibit a TTX-resistant, voltage independent, “true” background Na+ conductance (Na+ leak current, IL-Na). The most obvious function of the tonically active background Na+ conductance is perhaps to balance the K+ leak to set the RMP, which would be at ~ −90 mV (EK) in all the neurons if there were only basal K+ conductance.

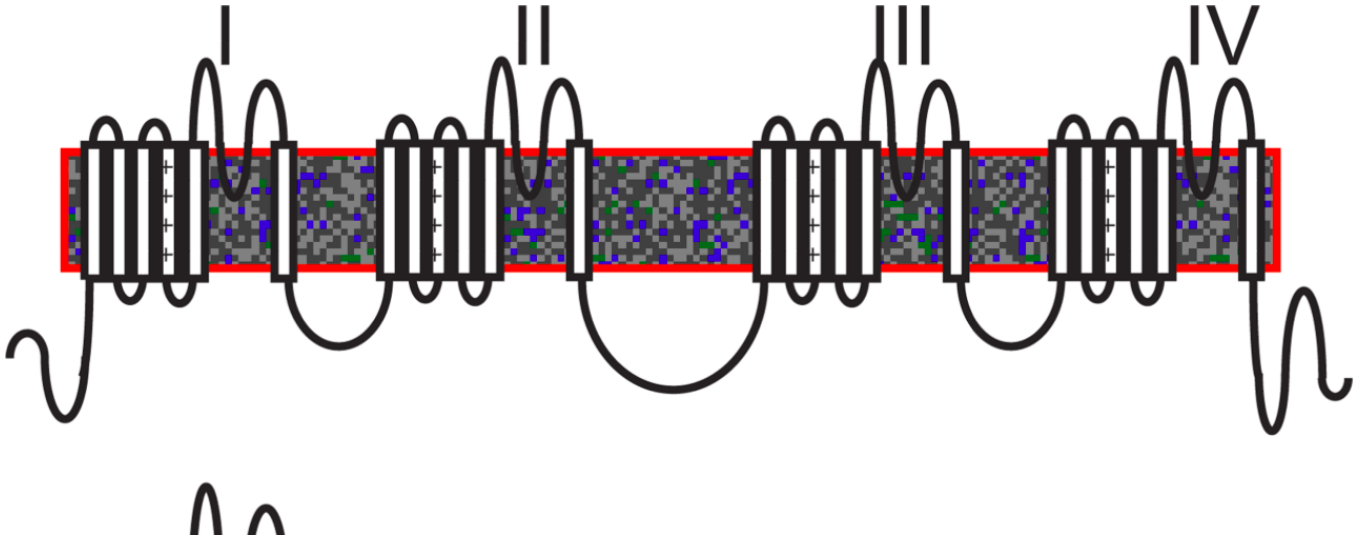
A tonic leak of other ions such as Ca2+, Mg2+ and H+ can hypothetically achieve the same goal, but excessive leak of these ions into neurons can be damaging to the cells because of the cellular metabolism’s high sensitivity to the intracellular concentrations of the ions.

By varying the basal PNa/PK, the nervous system can have a wide range of RMPs among different neurons, a heterogeneity in neuronal intrinsic properties known to exist in the brain.

• Leak Na+ currents: NALCN

Data accumulated in the past several years suggest that NALCN, a Na+ -permeable, non-selective cation channel widely expressed in the nervous system, contributes a TTX-resistant Na+ leak conductance.

NALCN is a member of the 24-transmembrane domain (24-TM) ion channel super-family, which also includes the ten voltage-gated Ca2+ channels (the L-type CaV1.1–1.4, P/Q type CaV2.1, N-type CaV2.2, R-type CaV2.3, and T-type CaV3.1–3.3 channels) and ten Na+ channels (NaV1.1–1.9 voltage-gated channels and the non-voltage gated NaX). The pore-forming α subunits of these channels have four homologous domains (I–IV), each of which has six transmembrane segments (S1–S6).



- **NALCN**
- **Na^+ channels** ($Na_V1.1$-1.9, Na_x)
- **Ca^{2+} channels**
  - $Ca_V1.1$-1.4 (L-type)
  - $Ca_V2.1$-2.3 (P/Q, N, R type)
  - $Ca_V3.1$-3.3 (T-type)

Cell permeability to any ion changes with opening/closing of ion channels

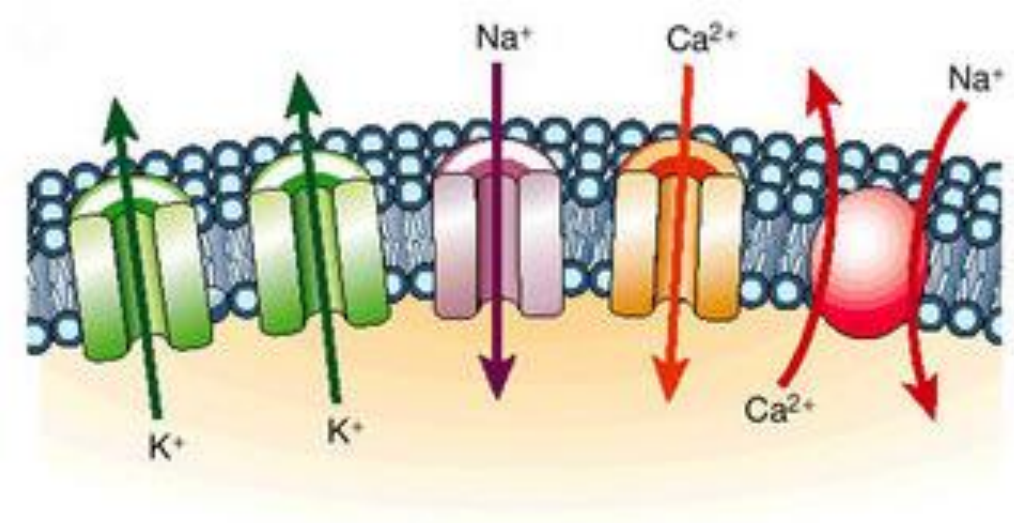
Direction of movement of one ion is dictated by the electrochemical driving force:

(V_m - V_{ion})

Resting Membrane potential

Nernst potential

Driving force



GHK equation

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

NERNST equation

$$V_{eq} = \frac{RT}{zF} \log \frac{C_{out}}{C_{in}}$$

$$V_{eq} = \frac{RT}{zF} \log \frac{C_{out}}{C_{in}}$$

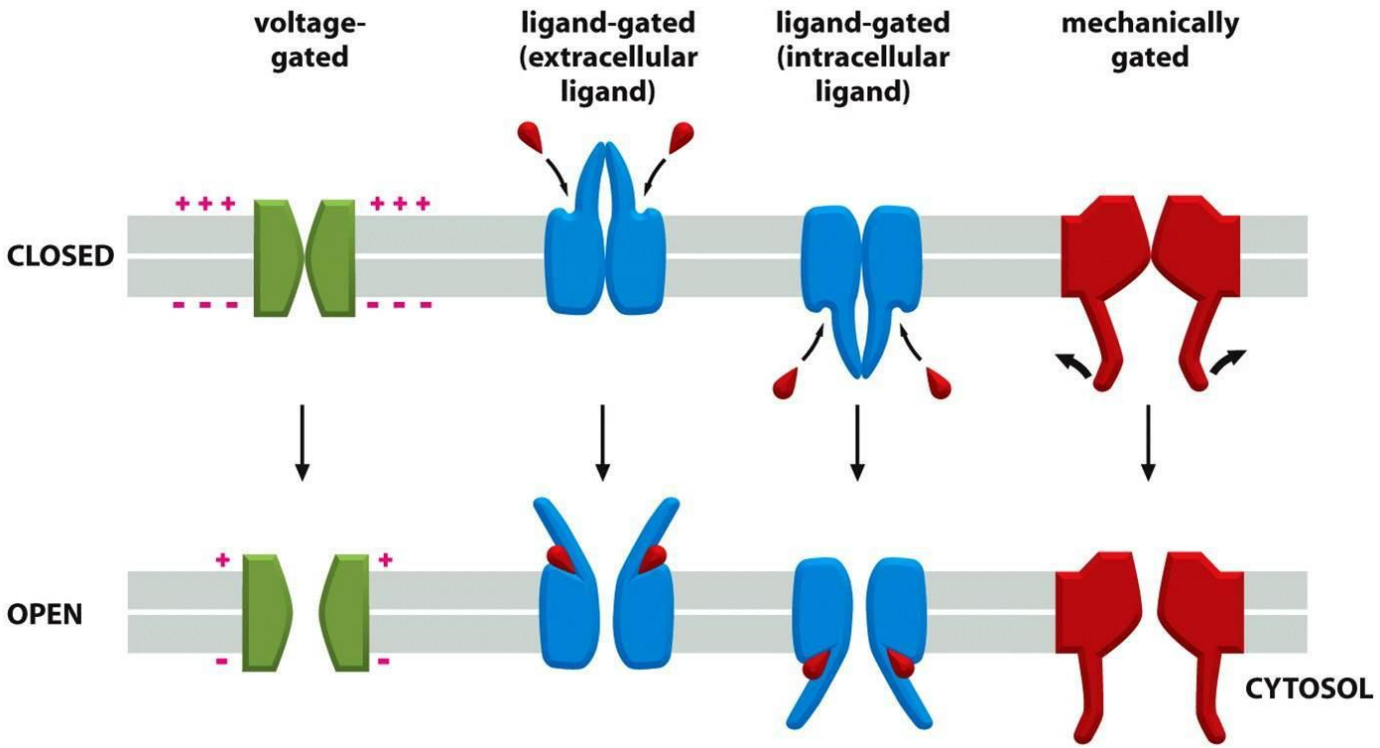
Equilibrium potential (E) for important ions in a neuron.

E_{Cl^-}	-70mV
E_{K^+}	-90mV
E_{Na^+}	+60mV
$E_{Ca^{2+}}$	+130mV

ION CHANNELS classification: basic types of ion channels

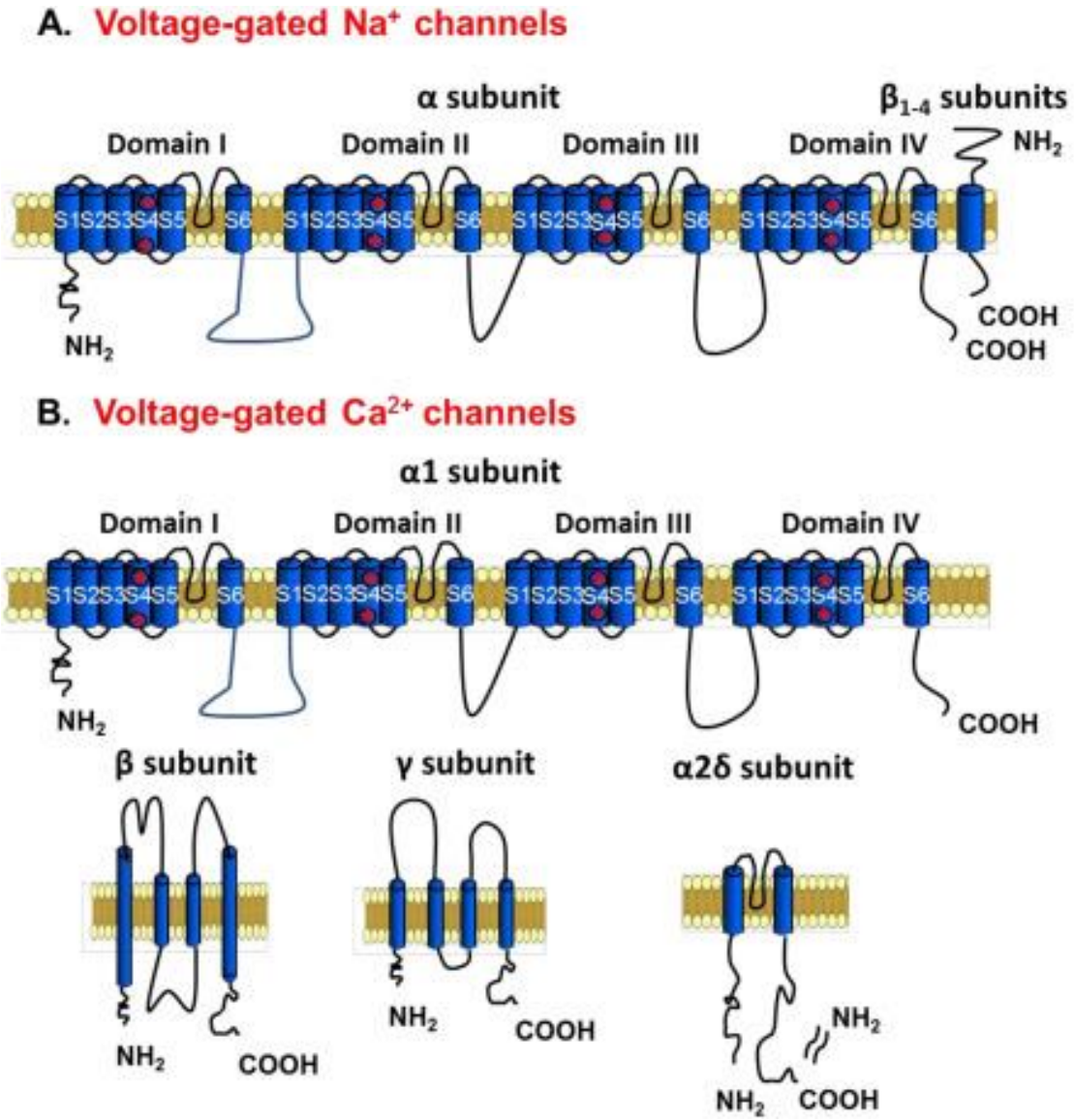
- **Leakage channels**: constitutively open channels.
- **Gated channels**: open/close in response to a stimulus

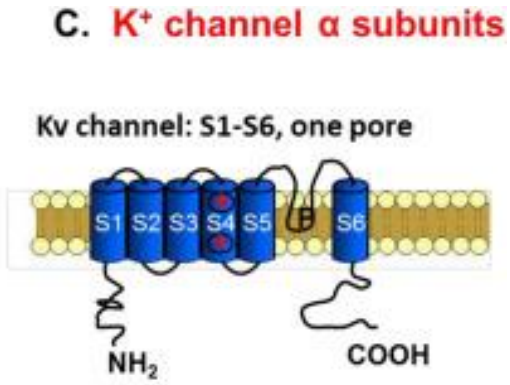
- **GATING**: mechanism that controls conformational transitions between open and closed state and therefore control OPENING and CLOSING of the channel

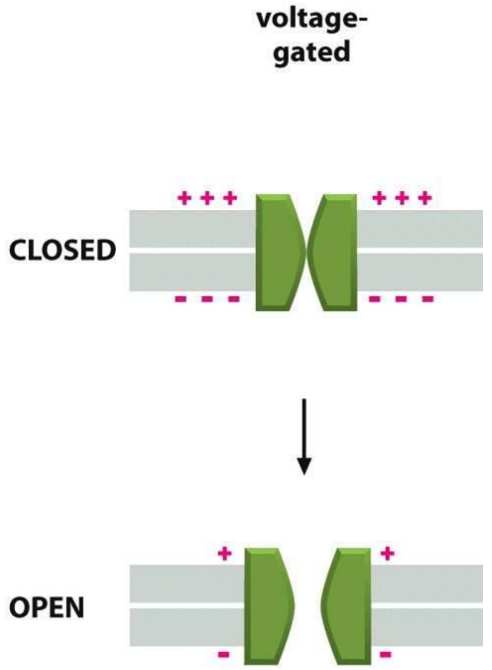


3 main mechanisms of gating

Voltage gated ion channels

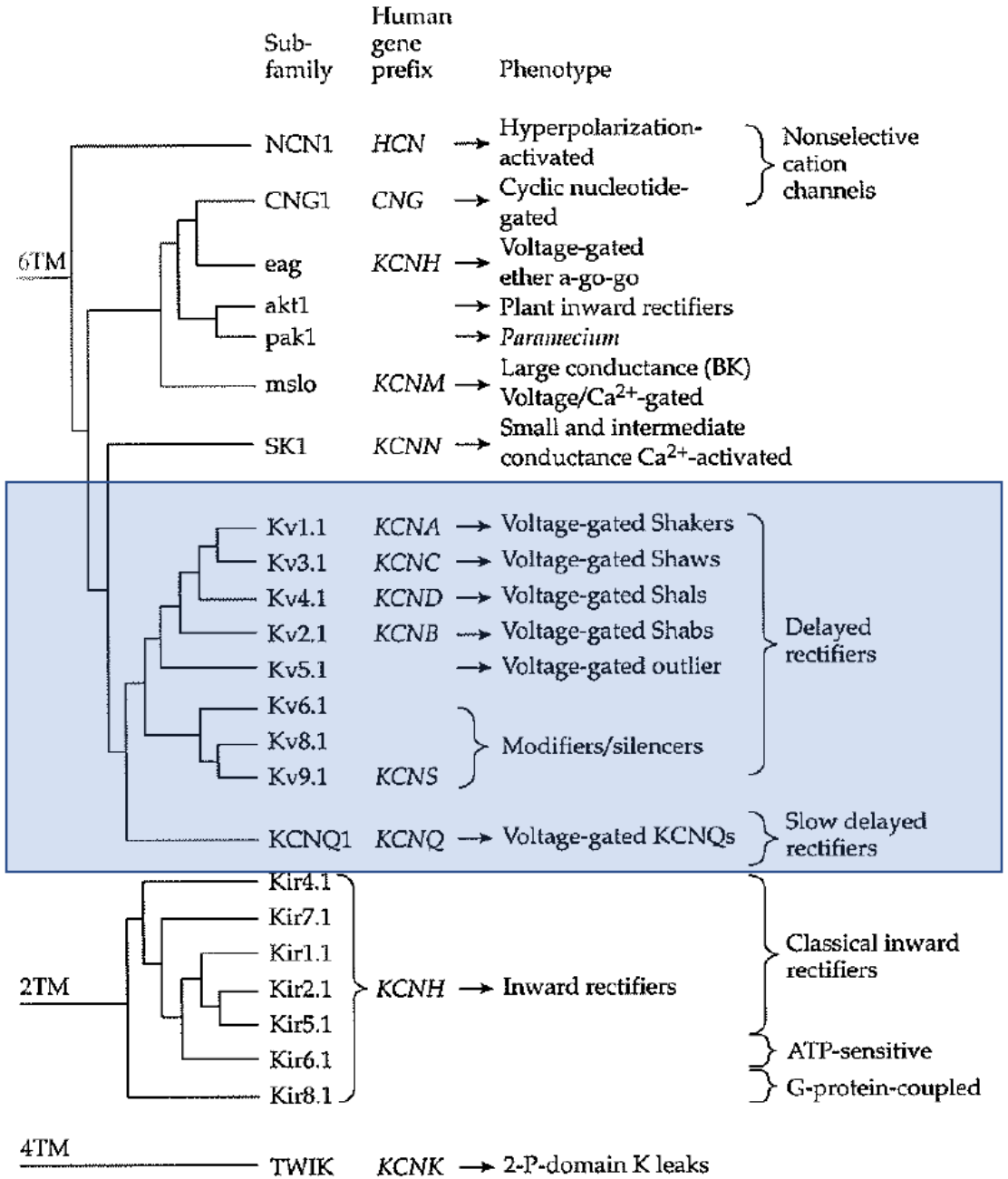






Voltage gated K+ channels

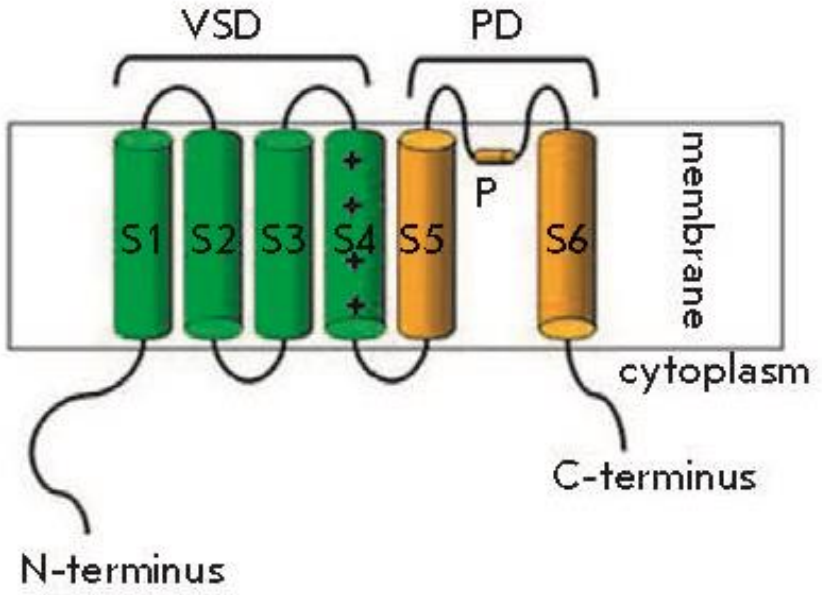
Kv channels form the most diverse group, represented by 12 families (Kv1-Kv12).



Voltage gated K+ channels

The voltage-gated K+ channels are the prototypical voltage-gated channels. At their simplest, they are homotetrameric channels, with each subunit containing a voltage sensor and a portion contributing to the central pore.

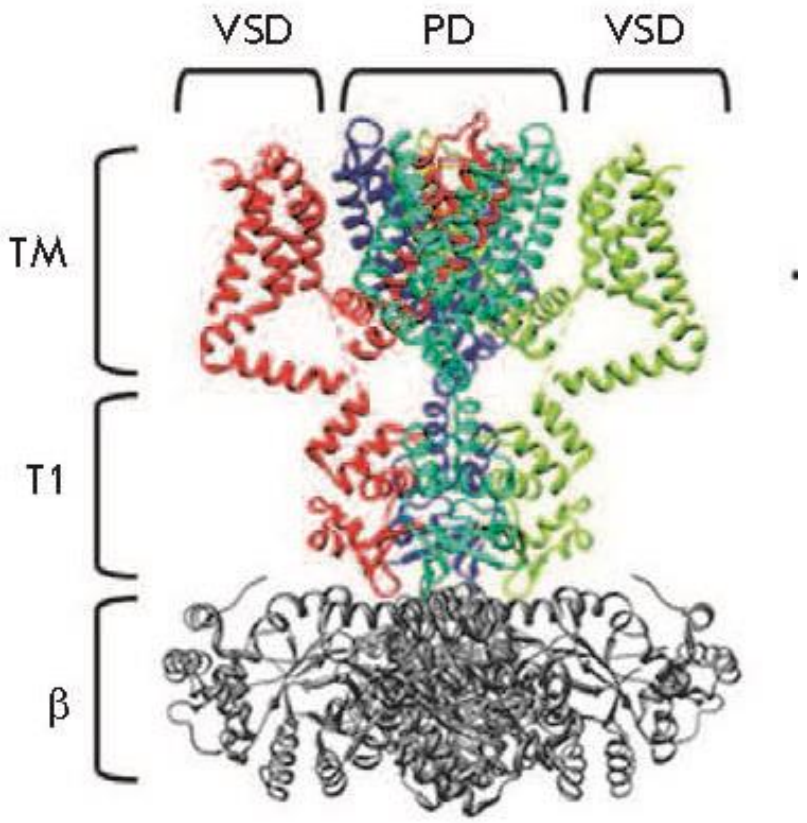
Each Kv channel gene encodes one ⟨-subunit (Kv⟨).



Grizel et al., Acta Nature, 2014

Voltage gated K+ channels

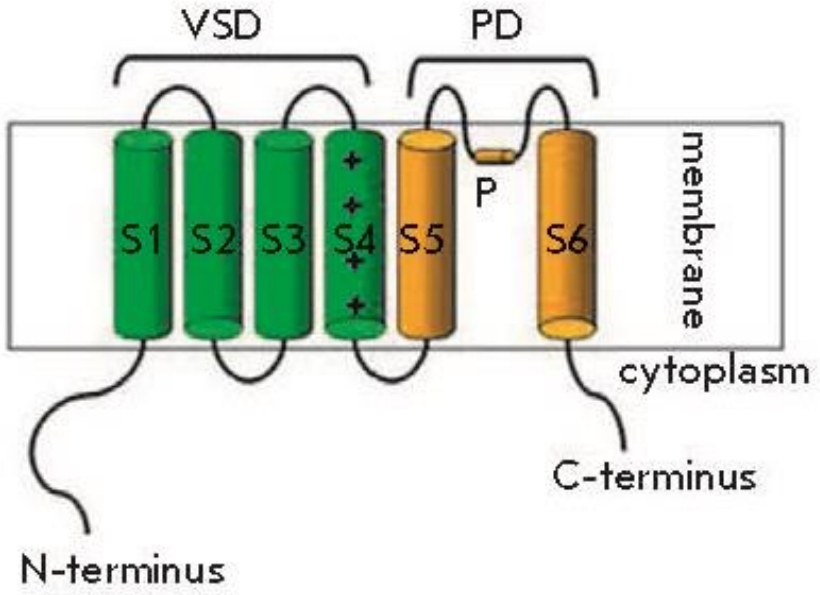
Four ⟨-subunits are required to form a functional channel. Kv channels usually have a homotetrameric structure (with all Kv⟨ being identical); however, some channels can be heterotetrameric (with two or more non-identical Kv⟨ subunits).



Grizel et al., Acta Nature, 2014

Voltage gated K+ channels

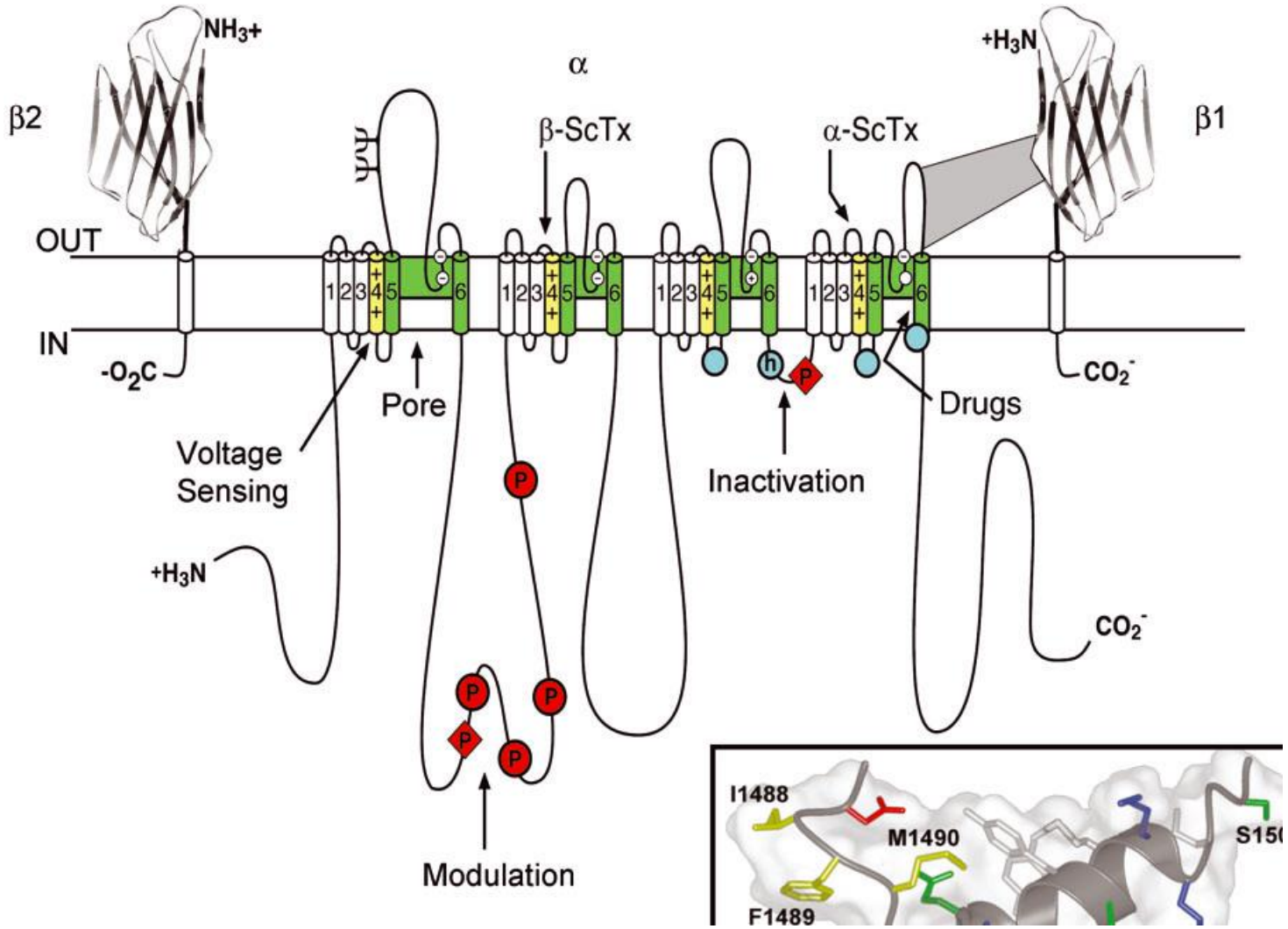
The transmembrane domain of the Kv channel ⟨-subunit consists of six helices: S1–S6. These helices form two structurally and functionally different parts of the tetrameric channel: 1) a potassium ion-conducting domain **(pore domain)** – helices S5–S6 located in the channel center, and 2) a domain sensible to changes in the membrane potential **(voltage-sensing domain, VSD)** – helices S1–S4 located on the channel periphery.



Grizel et al., Acta Nature, 2014

Voltage gated Na+ channels

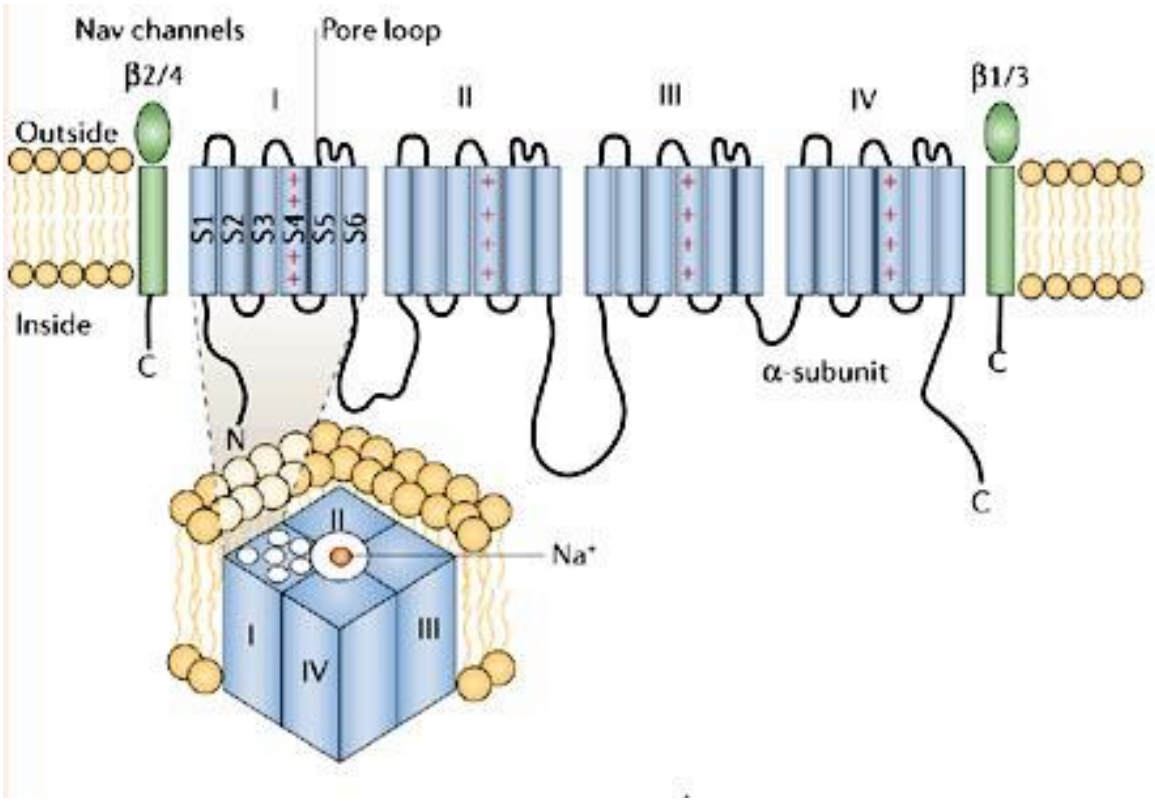
Sodium channel (subunits are composed of approximately 2000 amino acid residues organized in four homologous domains, each containing six transmembrane segments. Later biochemical analyses and cDNA cloning showed that sodium channel *β* subunits are composed of an N-terminal extracellular immunoglobulin-like fold, a single transmembrane segment, and a short intracellular segment.



Catterall W, J Physiol 2012

Voltage gated Na+ channels

These subunits are thought to form heterodimeric and heterotrimeric complexes composed of a single ⟨ subunit and one or two *β* subunits in excitable cell membranes, and co-expression of *β* subunits modulates the kinetics and voltage dependence of sodium channel activation and inactivation.



Catterall W, J Physiol 2012

Voltage gated Na+ channels

β subunits have been identified by genomic analyses and cDNA cloning to give a small family of four NaVβ subunits in total.

β1 and β3 are associated non-covalently with ⟨ subunits and resemble each other most closely in amino acid sequence, whereas β2 and β4 form disulfide bonds with ⟨ subunits and also resemble each other closely.

The structure of Navβ subunits resembles the family of cell adhesion molecules, and increasing evidence supports their role in localization and immobilization of sodium channels in specific locations in excitable cells.

Voltage gated Na+ channels

Sodium channel ⟨ **subunits are encoded by 10 genes**, which are expressed in different excitable tissues.

- NaV1.1, 1.2, 1.3 and 1.6 are the primary sodium channels in the central nervous system.

- NaV1.7, 1.8 and 1.9 are the primary sodium channels in the peripheral nervous system.

- NaV1.4 is the primary sodium channel in skeletal muscle, whereas

- NaV1.5 is primary in heart.

Most of these sodium channels also have significant levels of expression outside of their primary tissues.

- The 10th sodium channel protein is not voltage-gated and is involved in salt sensing.

Table 1. Mammalian sodium channel α subunits

Type	Gene symbol	Chromosomal location	Primary tissues
$Na_v1.1$	*SCN1A*	Mouse 2 Human 2q24	CNS neurons
$Na_v1.2$	*SCN2A*	Mouse 2 Human 2q23–24	CNS neurons
$Na_v1.3$	*SCN3A*	Mouse 2 Human 2q24	CNS neurons
$Na_v1.4$	*SCN4A*	Mouse 11 Human 17q23–25	SkM
$Na_v1.5$	*SCN5A*	Mouse 9 Human 3p21	Uninnervated SkM, heart
$Na_v1.6$	*SCN8A*	Mouse 15 Human 12q13	CNS neurons
$Na_v1.7$	*SCN9A*	Mouse 2 Human 2q24	PNS neurons
$Na_v1.8$	*SCN10A*	Mouse 9 Human 3p22–24	DRG neurons
$Na_v1.9$	*SCN11A*	Mouse 9 Human 3p21–24	DRG neurons
Na_x	*SCN7A* *SCN6A*	Mouse 2 Human 2q21–23	uterus, astrocytes, hypothalamus

Catterall W, J Physiol 2012

Voltage gated Ca+ channels

Ca2+ entering the cell through voltage-gated Ca2+ channels serves as the second messenger of electrical signaling, initiating many different cellular events:

- In cardiac and smooth muscle cells, activation of Ca2+ channels initiates contraction directly by increasing cytosolic Ca2+ concentration and indirectly by activating calcium-dependent calcium release by ryanodine-sensitive Ca2+ release channels in the sarcoplasmic reticulum.
- In skeletal muscle cells, voltage-gated Ca2+ channels in the transverse tubule membranes interact directly with ryanodine-sensitive Ca2+ release channels in the sarcoplasmic reticulum and activate them to initiate rapid contraction.

Voltage gated Ca+ channels

- In endocrine cells, voltage-gated Ca2+ channels mediate Ca2+ entry that initiates secretion of hormones.
- In neurons, voltage-gated Ca2+ channels initiate synaptic transmission.
- In many different cell types, Ca2+ entering the cytosol via voltage-gated Ca2+ channels regulates enzyme activity, gene expression, and other biochemical processes

Voltage gated Ca+ channels

Table 1. Subunit composition and function of Ca^{2+} channel types

Ca^{2+} current type	α1 Subunits	Specific blocker	Principal physiological functions	Inherited diseases
L	$Ca_v1.1$	DHPs	Excitation-contraction coupling in skeletal muscle, regulation of transcription	Hypokalemic periodic paralysis
	$Ca_v1.2$	DHPs	Excitation-contraction coupling in cardiac and smooth muscle, endocrine secretion, neuronal Ca^{2+} transients in cell bodies and dendrites, regulation of enzyme activity, regulation of transcription	Timothy syndrome: cardiac arrhythmia with developmental abnormalites and autism spectrum disorders
	$Ca_v1.3$	DHPs	Endocrine secretion, cardiac pacemaking, neuronal Ca^{2+} transients in cell bodies and dendrites, auditory transduction	
	$Ca_v1.4$	DHPs	Visual transduction	Stationary night blindness
N	$Ca_v2.1$	ω-CTx-GVIA	Neurotransmitter release, Dendritic Ca^{2+} transients	
P/Q	$Ca_v2.2$	ω-Agatoxin	Neurotransmitter release, Dendritic Ca^{2+} transients	Familial hemiplegic migraine, cerebellar ataxia
R	$Ca_v2.3$	SNX-482	Neurotransmitter release, Dendritic Ca^{2+} transients	
T	$Ca_v3.1$	None	Pacemaking and repetitive firing	
	$Ca_v3.2$		Pacemaking and repetitive firing	Absence seizures
	$Ca_v3.3$			

Abbreviations: DHP, dihydropyridine; ω-CTx-GVIA, ω-conotoxin GVIA from the cone snail *Conus geographus*; SNX-482, a synthetic version of a peptide toxin from the tarantula *Hysterocrates gigas*.

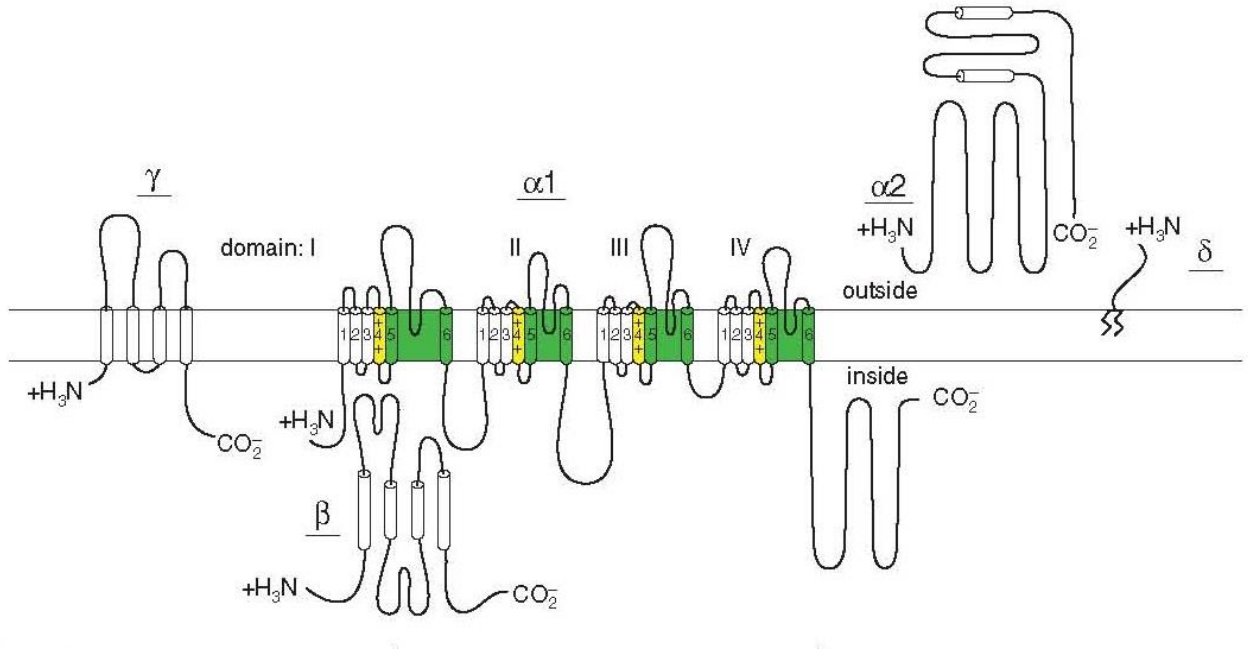
Catterall W, CSH persp, 2011

Voltage gated Ca+ channels

Ca2+ channels purified from skeletal muscle transverse tubules are complexes of $\alpha 1$, $\alpha 2$, β, γ, and δ subunits.

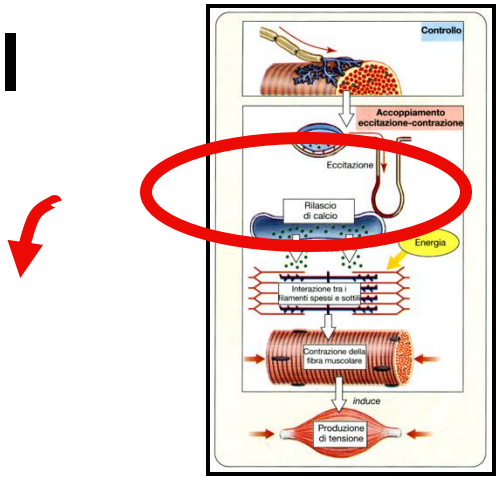
The principal transmembrane $\alpha 1$ subunit of 190 kDa in association with a disulfide-linked $\alpha 2\delta$ dimer of 170 kDa, an intracellular β subunit of 55 kDa, and a transmembrane γ subunit of 33 kDa.

The $\alpha 1$ subunit is a protein of about 2000 amino acid residues in length with an amino acid sequence and predicted **transmembrane structure like the previously characterized, pore-forming a subunit of voltage-gated sodium channels**

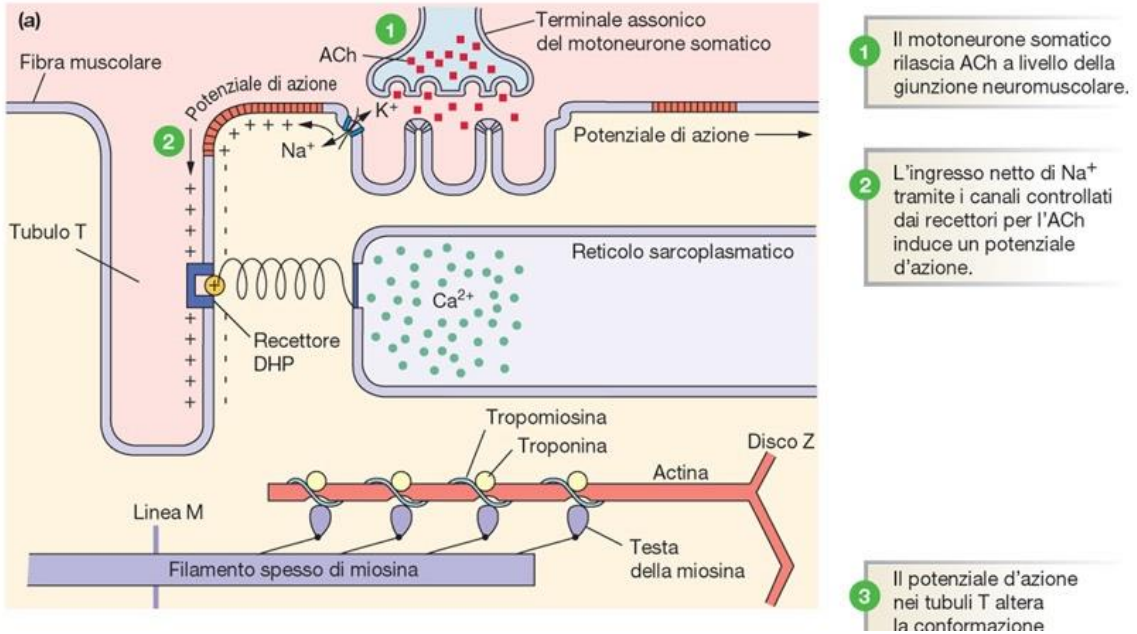


Catterall W, CSH persp, 2011

Excitation-contraction coupling in skeletal muscle

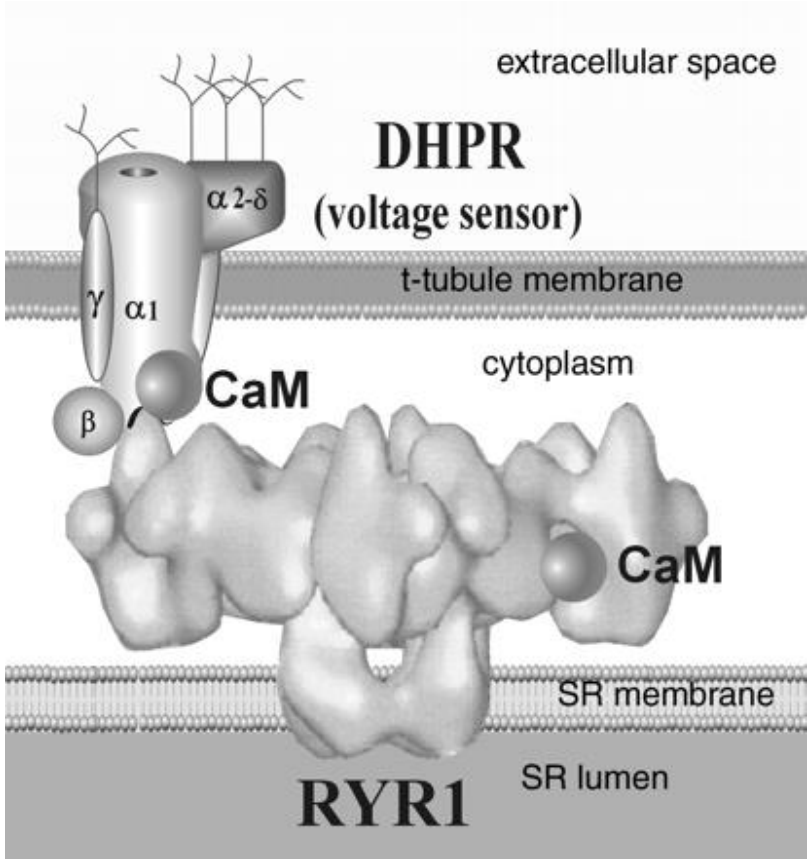


CaV1.1 channels in the transverse tubules are thought to interact directly with the ryanodine-sensitive Ca2+ release channels (RyR1) of the sarcoplasmic reticulum, as observed in high-resolution electron microscopy, and the voltage-driven conformational changes in their voltage-sensing domains are thought to directly induce activation of RyR1.



In skeletal muscle, entry of external Ca2+ is not required for initiation of contraction

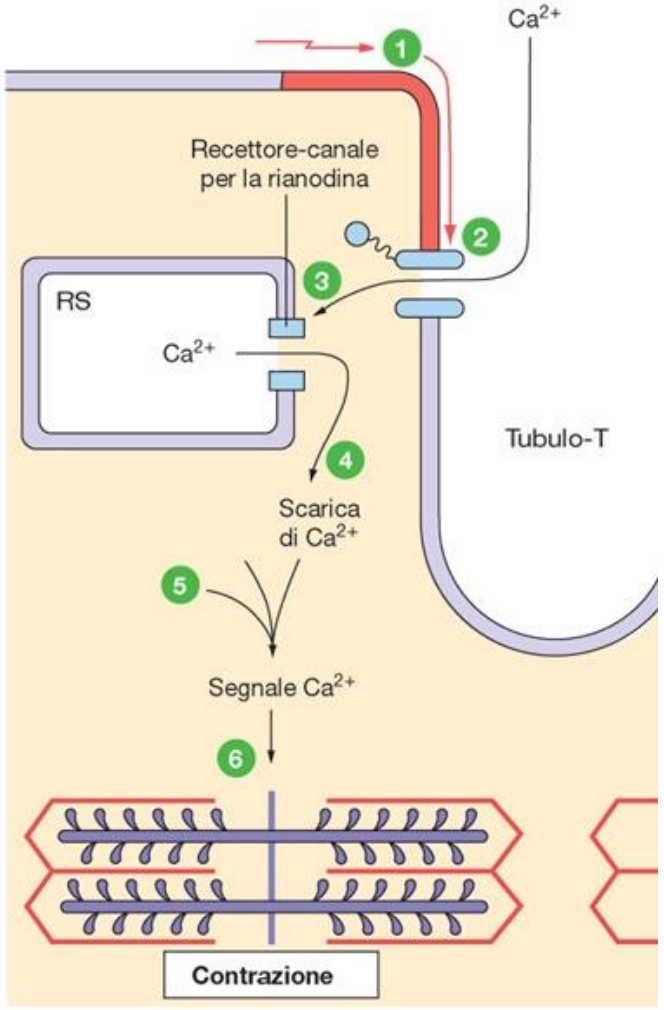
This is because the cytoplasmic domain of these channels is physically coupled to ryanodine receptor (RyR1) Ca2+ release channels on internal membranes. Even though Cav1.1 proteins can act as *bona fide Ca2+ channels, they also function as* voltage sensors that directly produce conformational changes in the ryanodine receptor/Cav1.1 complex, resulting in the release of Ca2+ from internal stores.



Excitation-contraction coupling in cardiac muscle

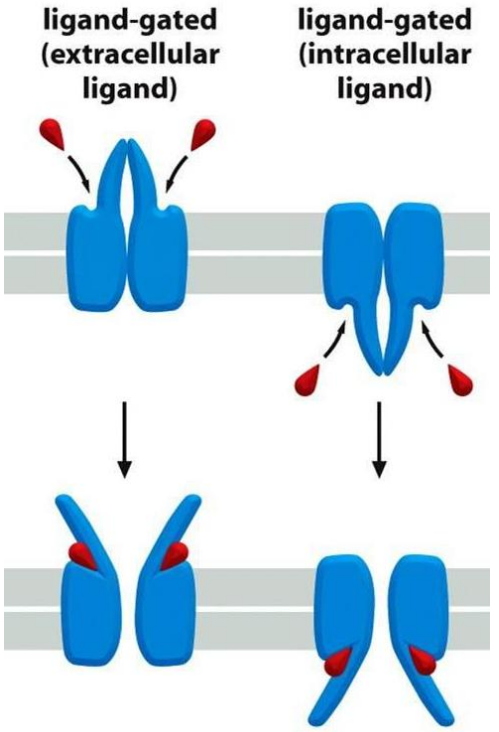
In contrast to skeletal muscle, entry of **Ca2+ is required for excitation-contraction coupling in cardiac myocytes**, and Ca2+ entry via CaV1.2 channels triggers activation of the RyR2 and initiates Ca2+-induced Ca2+-release, activation of actomyosin, and contraction

Release of Ca2+ from the sarcoplasmic reticulum via RyR2 greatly amplifies the cellular Ca2+ transient and is required for effective initiation of contraction. All three steps in the cascade of Ca2+ transport processes—**Ca2+ entry via CaV1.2 channels**, **Ca2+ release via RyR, and Ca2+ uptake into the sarcoplasmic reticulum by SERCA Ca2+ pumps**—are tightly regulated by second messenger signaling networks



1. Un potenziale d'azione invade la membrana cellulare provenendo da una cellula adiacente.
2. I canali voltaggio-dipendenti per il Ca^{2+} si aprono. Il Ca^{2+} entra nella cellula.
3. L'ingresso di Ca^{2+} innesca il rilascio di altro Ca^{2+} dal reticolo sarcoplasmatico attraverso i recettori-canali della rianodina (RyR).
4. Il rilascio localizzato di calcio provoca la «scarica» di Ca^{2+}.
5. Le scariche di Ca^{2+} si sommano per produrre un segnale di Ca^{2+}.
6. Gli ioni calcio si legano alla troponina e inizia la contrazione.

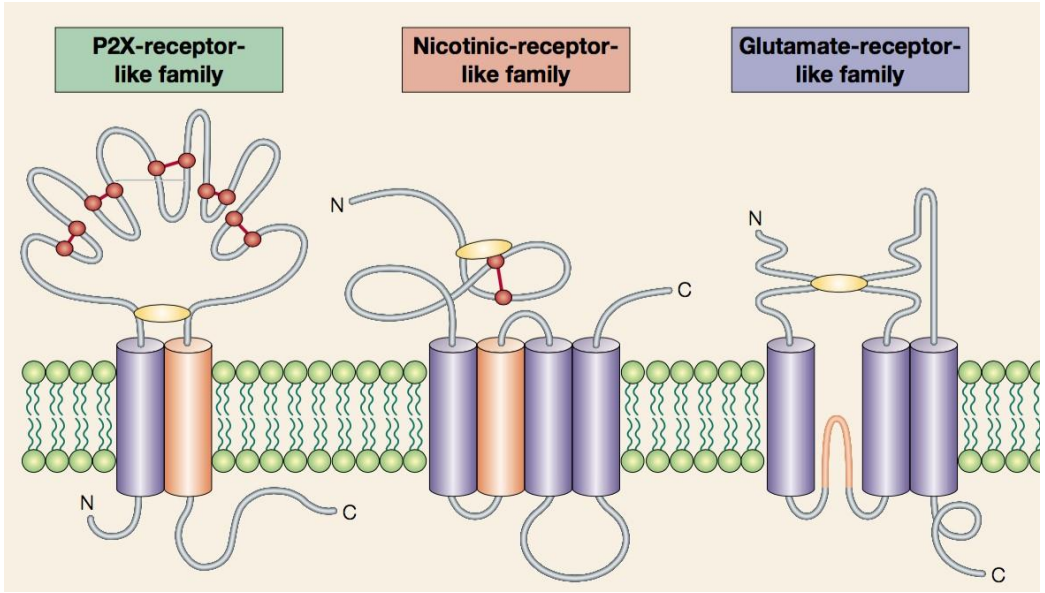
Ligand gated ion channels



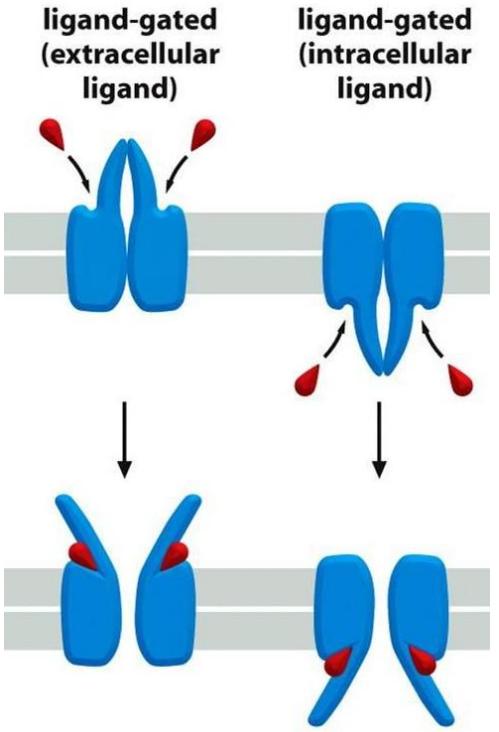
This is a highly heterogenous family of channels that includes several families

- the **extracellular ligand-activated channels** which includes channels such as **glutamate, GABA and glycine receptor channels**, most of which are regulated by ligands that are "neurotransmitters". These channels are often named according to the ligand they bind to. Other examples are: **nicotinic receptors ; P2X receptors**

We will discuss different examples in the course



Ligand gated ion channels

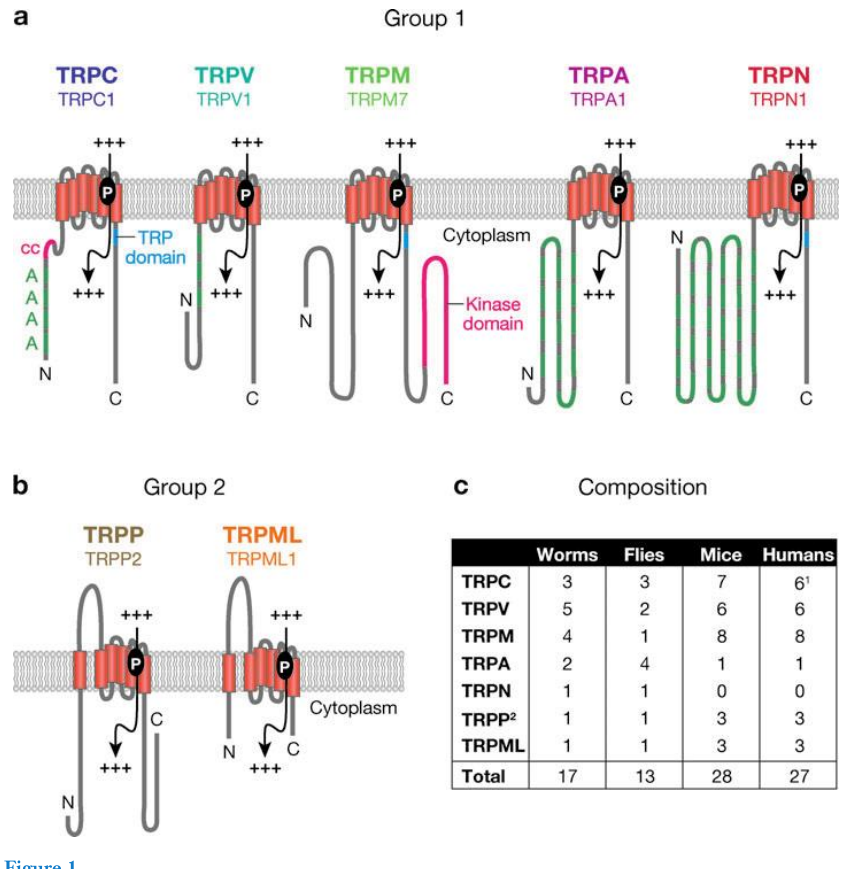


This is a highly heterogenous family of channels that includes several families

- **Intracellular ligand-gated ion channels**. These include **CFTR** and some other ABC family members as well as ion channels involved in sense perception; **TRP channels; CNGC**; **These are often activated indirectly by GCPRs**. Other common intracellular ligands which activate these kinds of channels include calcium ions, **ATP, cyclic AMP and GMP as well as phosphadidyl inositol (PI)**. There are additional systems of nomenclature which have joined the second and third groups into the "chemically activated" or just simply "ligand gated" ion channels.

TRP family of channels

- Cation channels
- Non voltage-dependent
- Diversity in activation mechanisms
- Implication in diverse physiological functions



	Worms	Flies	Mice	Humans
TRPC	3	3	7	6[1]
TRPV	5	2	6	6
TRPM	4	1	8	8
TRPA	2	4	1	1
TRPN	1	1	0	0
TRPP[2]	1	1	3	3
TRPML	1	1	3	3
Total	17	13	28	27

Venkatachalam K & Montell C, *Annual Review of Biochemistry*, 2007

First TRP channel identification

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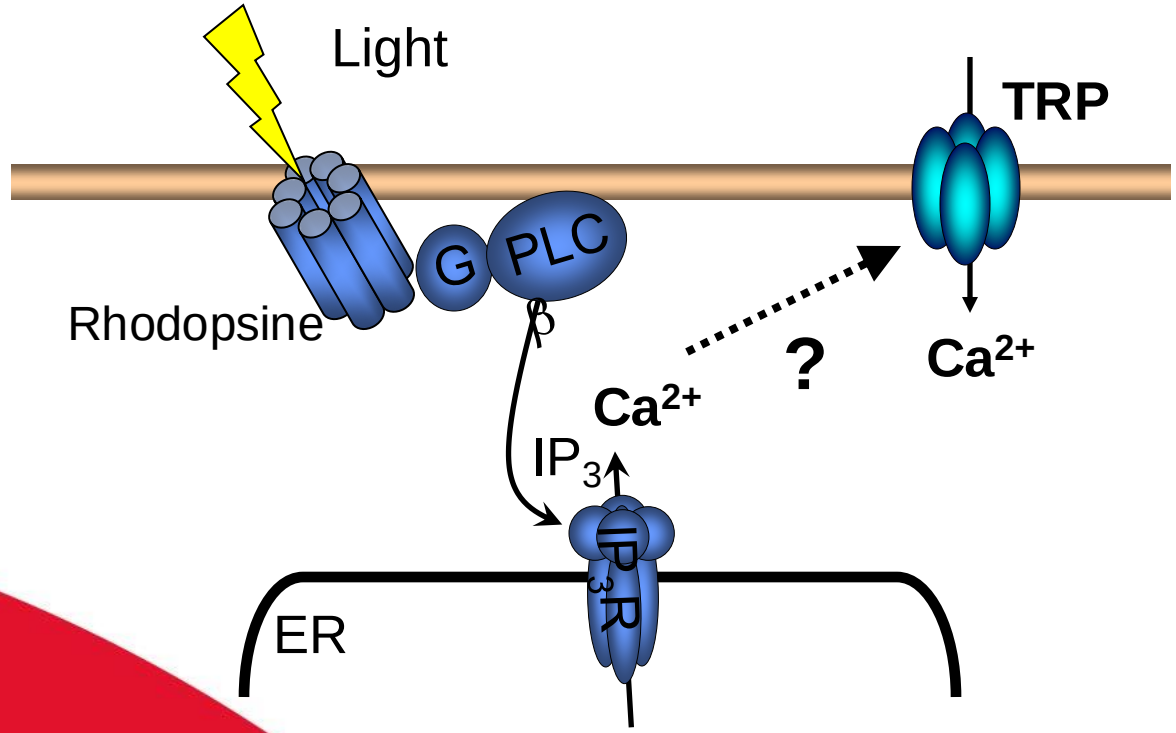
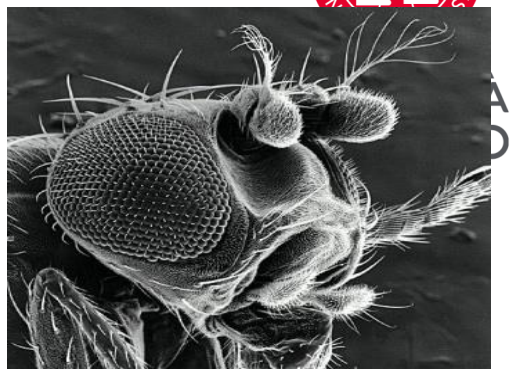
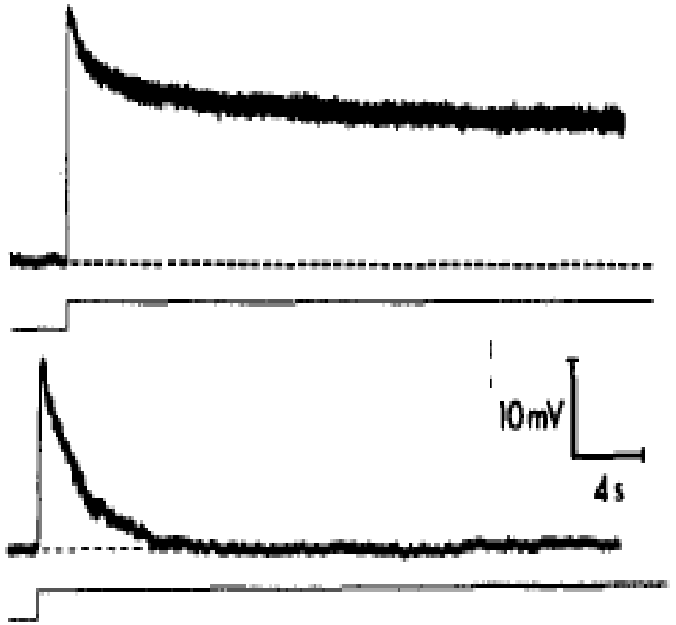
Drosophila melanogaster :

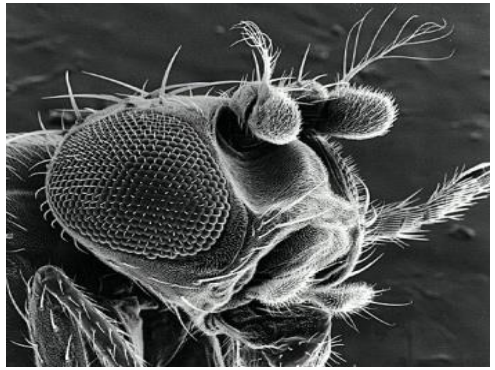


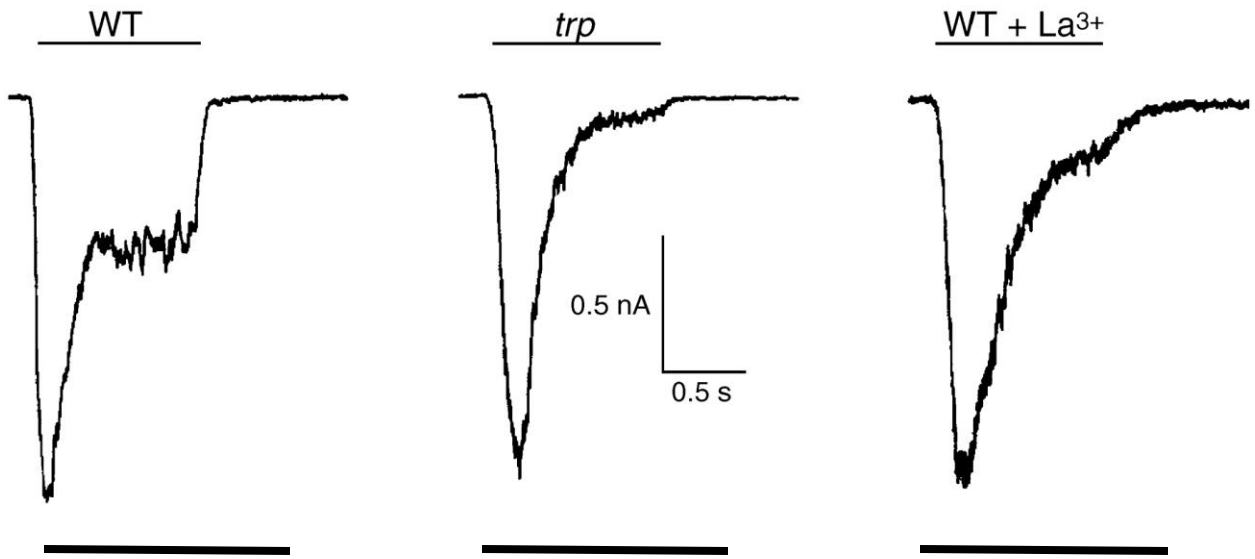




Minke B, Biophys Struct Mech., 1977

Identification du 1er Canal TRP





trp
Transient Receptor Potential → Cationic channel → Conserved from c.Elegans to human

Montell C et al. *Neuron.* **2**, 1313-1323 (1989).

TRP family composition in worms, flies, mice and humans

Subfamily	Worms	Flies	Mice	Humans
TRPC	3	3	7	6[1]
TRPV	5	2	6	6
TRPM	4	1	8	8
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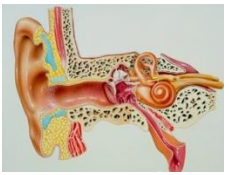
Total	17	13	28	27

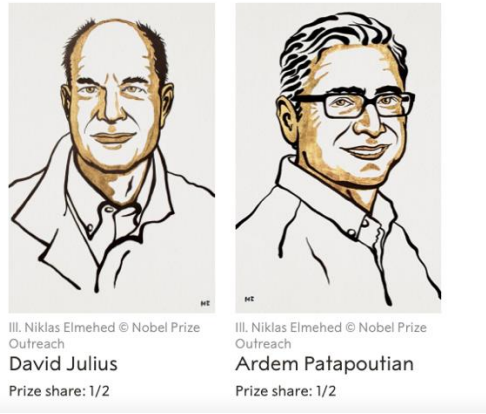
C. Montell, Sci. STKE 2005, re3 (2005)



TRPML
(mucolipin)
hTRPML2
hTRPML3
hTRPML1
TRPP
(polycystin)
hTRPP5
hTRPP3
hTRPP2
TRPM
(melastatin)
hTRPM5
hTRPM4
hTRPM8
hTRPM2
hTRPM7
hTRPM6
hTRPM3
hTRPM1
TRPA
(ankyrin)
hTRPA1
TRPC
(canonical)
hTRPC1
hTRPC4
hTRP5
hTRPC3
hTRPC7
hTRPC6
mTRPC2
TRPV
(vallinoid)
hTRPV1
hTRPV2
hTRPV3
hTRPV4
hTRPV5
hTRPV6

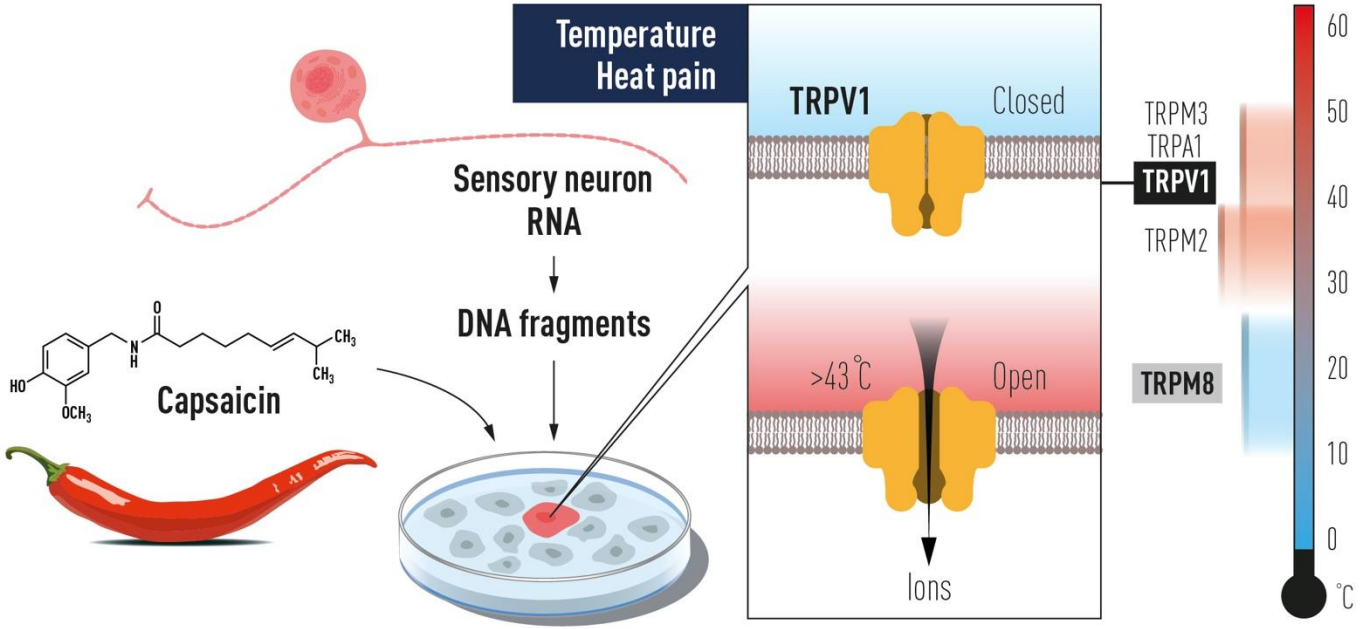
The Nobel Prize in Physiology or Medicine 2021 was awarded jointly to David Julius and Ardem Patapoutian "for their discoveries of receptors for temperature and touch.»

https://www.nobelprize.org/prizes/medicine/2021/press-release/

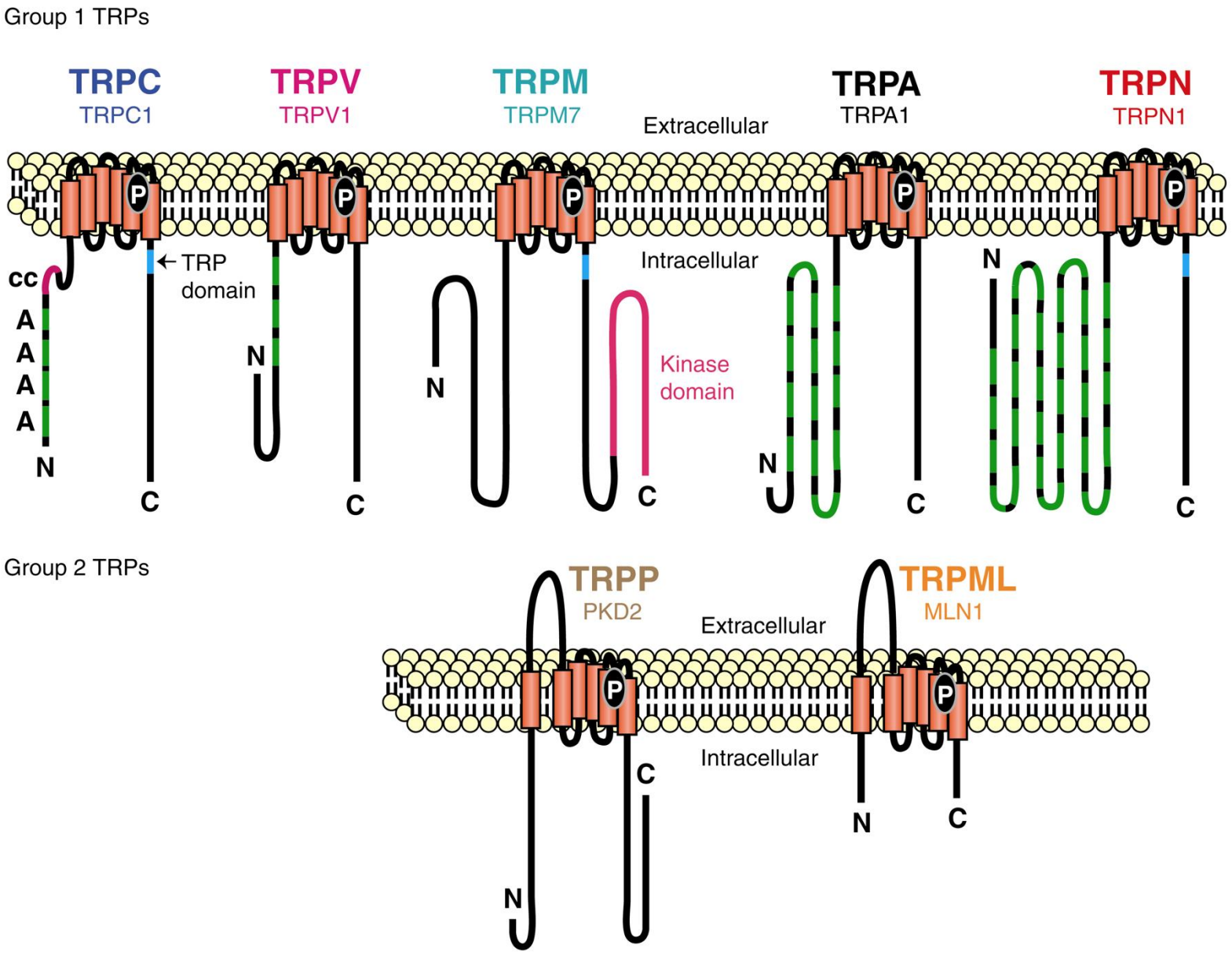


In the latter part of the 1990's, David Julius saw the possibility for major advances in temperature perception by analyzing how the chemical compound **capsaicin** causes the burning sensation we feel when we come into contact with chili peppers. After a laborious search, a single gene was identified that was able to make cells capsaicin sensitive. The identified gene encoded a novel ion channel protein and named TRPV1. When Julius investigated the protein's ability to respond to heat, he realized that he had discovered a heat-sensing receptor that is activated at temperatures perceived as painful.

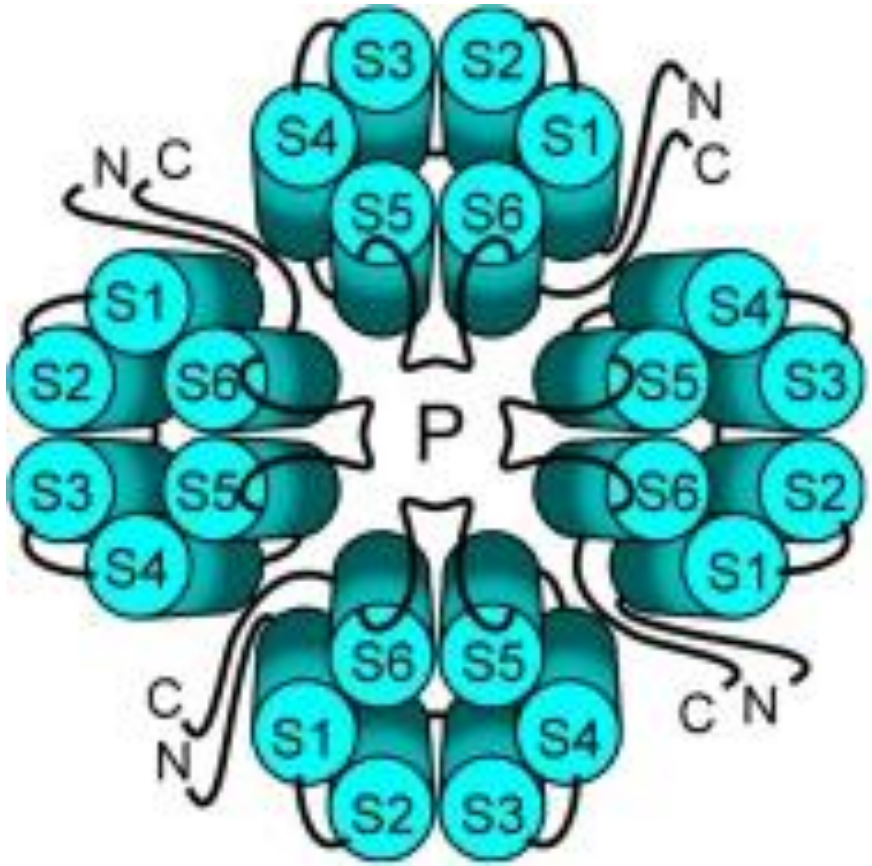
Independently of one another, both David Julius and Ardem Patapoutian used the chemical substance menthol to identify TRPM8, a receptor that was shown to be activated by cold. Additional ion channels related to TRPV1 and TRPM8 were identified and found to be activated by a range of different temperatures.

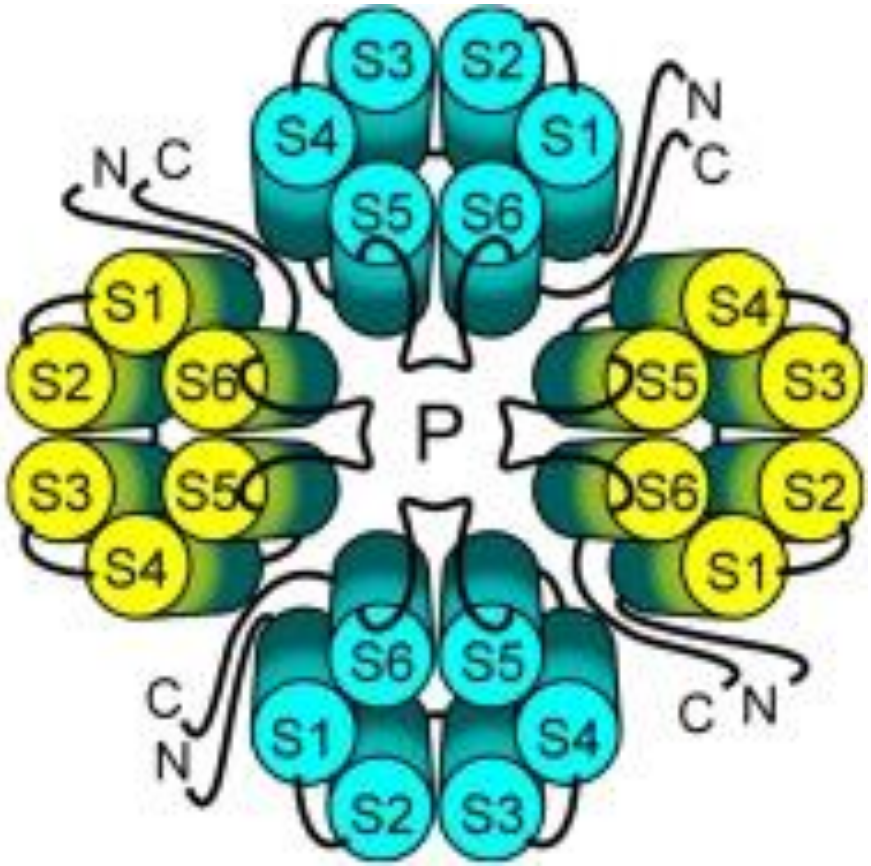


Different topologies of TRP channels

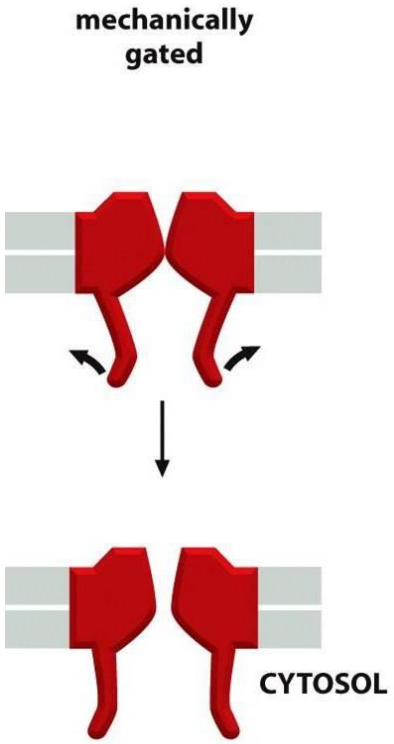


The quartenary structure of TRP channels allows homo- or heteromeric configurations





Mechanically gated ion channels



- Mechanosensitive channels has been detected in nearly every organism. These channels are directly gated by forces to convert mechanical stimuli into electrical signals and thus function as the force transducer in mechanosensory transduction
- Mechanosensitive channels open **very rapidly with short latency**, usually less than 5 milliseconds, which makes it unlikely that second messengers are involved in channel gating.

Mechanically gated ion channels

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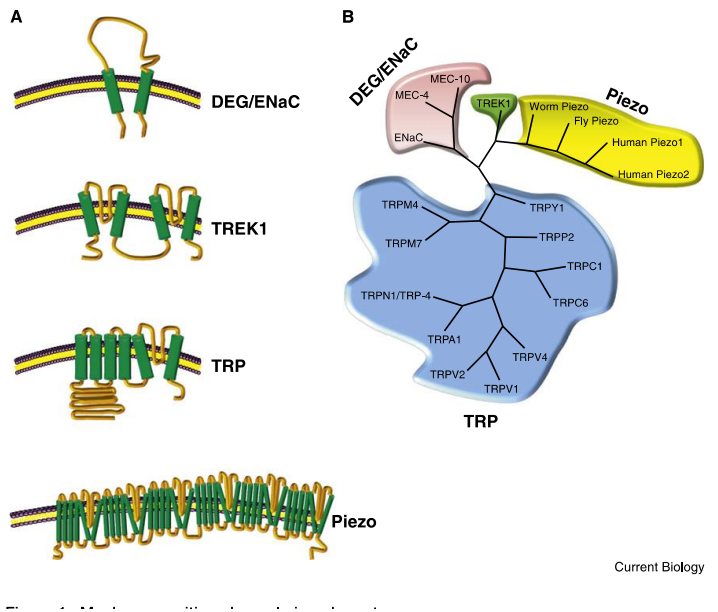
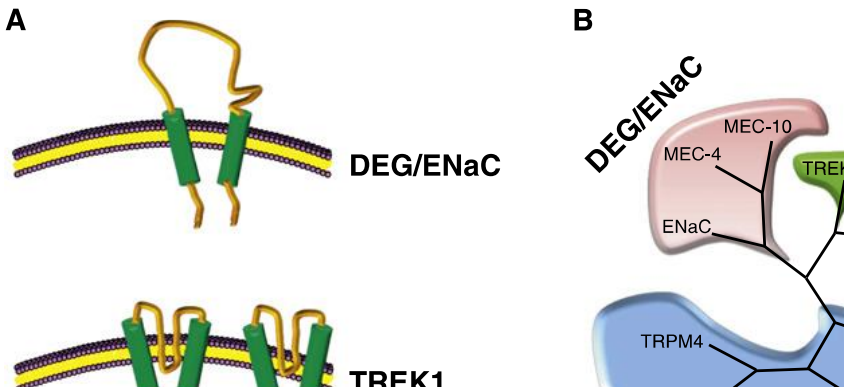
- It is generally believed that the three common mechanical sensory modalities — touch, hearing and proprioception — are mediated by mechanosensitive channels that are directly gated by forces.
- The molecular identities of these channels, however, remain largely elusive, particularly in mammals.

Mechano-sensitive channels in eukaryotes

the biophysical properties of mechanosensitive channels recorded from different cell types show large variation, suggesting that the molecular nature of mechanosensitive channels is highly heterogeneous

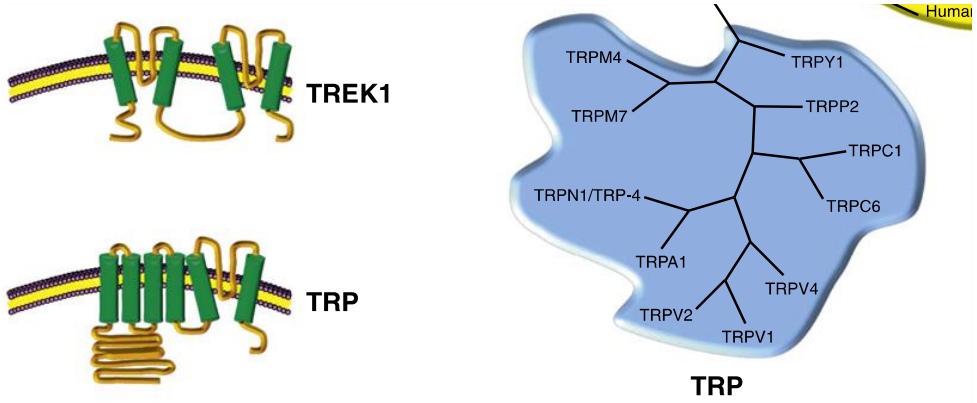


Mechano-sensitive channels in eukaryotes



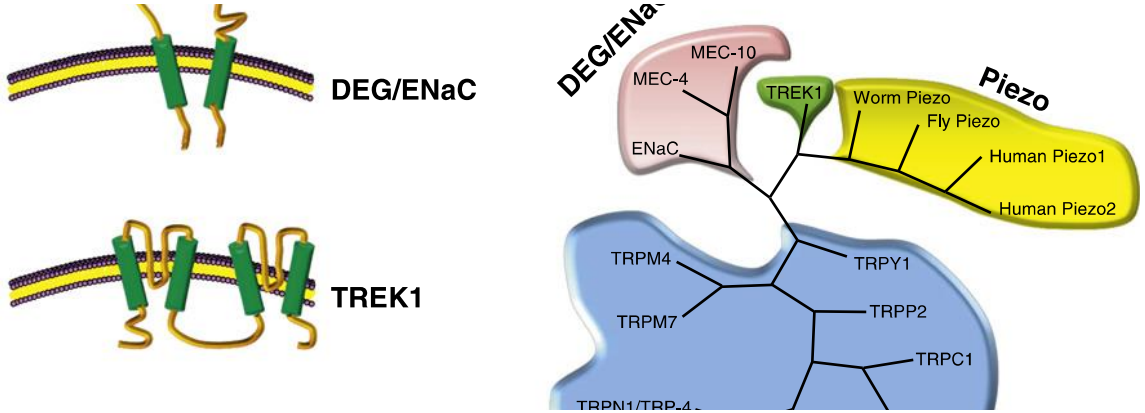
- The first breakthrough came from studies in the genetic model organism Caenorhabditis elegans. Using genetic and electrophysiological approaches, Chalfie and colleagues have identified a mechanosensitive channel complex comprising MEC-4, MEC-10, MEC-2 and MEC-6 that senses gentle body touch in C. elegans. MEC-4 and MEC-10 form the channel pore.
- MEC-4 and MEC-10 belong to the **ENaC/DEG** family of sodium channels that are conserved from worms to humans

Mechano-sensitive channels in eukaryotes



- **TRP family channels** have recently emerged as another class of leading candidates for mechanosensitive channels.

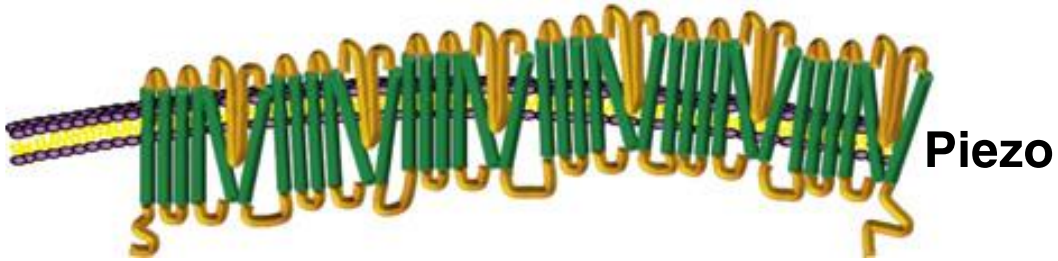
Mechano-sensitive channels in eukaryotes



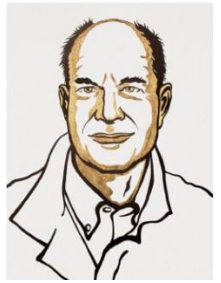
A second, but not mutually exclusive, possibility is that mechanosensitive channels in mammals are encoded by completely different types of genes. Indeed, **the two-pore-domain K+ channel TREK1** has been reported to form a mechanosensitive channel in mammals, but, given that the opening of this K+ channel hyperpolarizes rather than depolarizes a neuron, it cannot be the primary channel mediating touch, hearing and proprioception in mammals.

Mechano-sensitive channels in eukaryotes

Since 2010 a novel class of mechanosensitive channels in mammals has been identified by Patapoutian and colleagues: **PIEZO Channels**



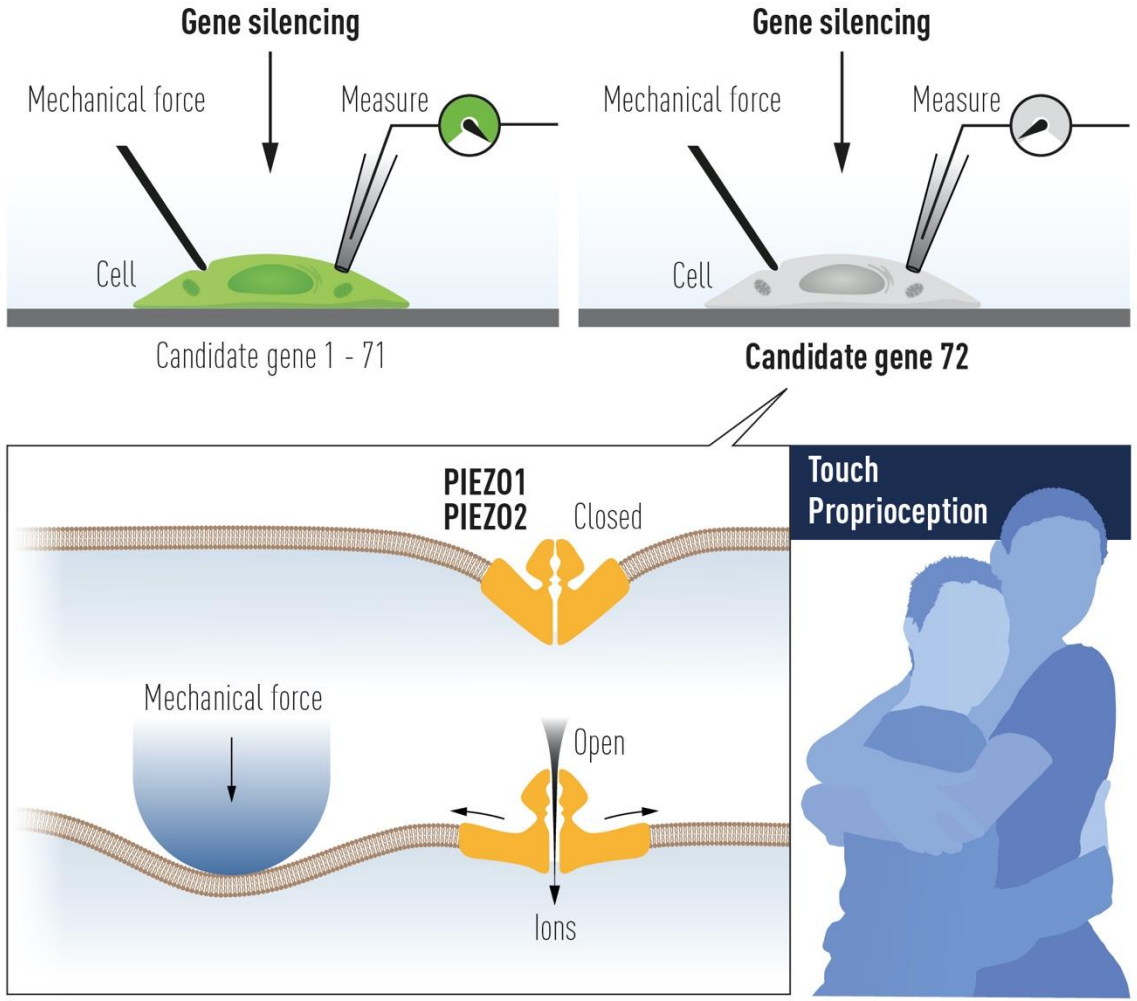
The Nobel Prize in Physiology or Medicine 2021 was awarded jointly to David Julius and Ardem Patapoutian "for their discoveries of receptors for temperature and touch.»



https://www.nobelprize.org/prizes/medicine/2021/press-release/

A new and entirely unknown mechanosensitive ion channel had been discovered and was given the name Piezo1, after the Greek word for pressure (ί; píesi). Through its similarity to Piezo1, a second gene was discovered and named Piezo2. Sensory neurons were found to express high levels of Piezo2 and further studies firmly established that Piezo1 and Piezo2 are ion channels that are directly activated by the exertion of pressure on cell membranes (Figure 3).

The breakthrough by Patapoutian led to a series of papers from his and other groups, demonstrating that the **Piezo2 ion channel is essential for the sense of touch**. Moreover, Piezo2 was shown to play a key role in the critically important sensing of body position and motion, known as proprioception. In further work, Piezo1 and Piezo2 channels have been shown to regulate additional important physiological processes including blood pressure, respiration and urinary bladder control.



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Thank you