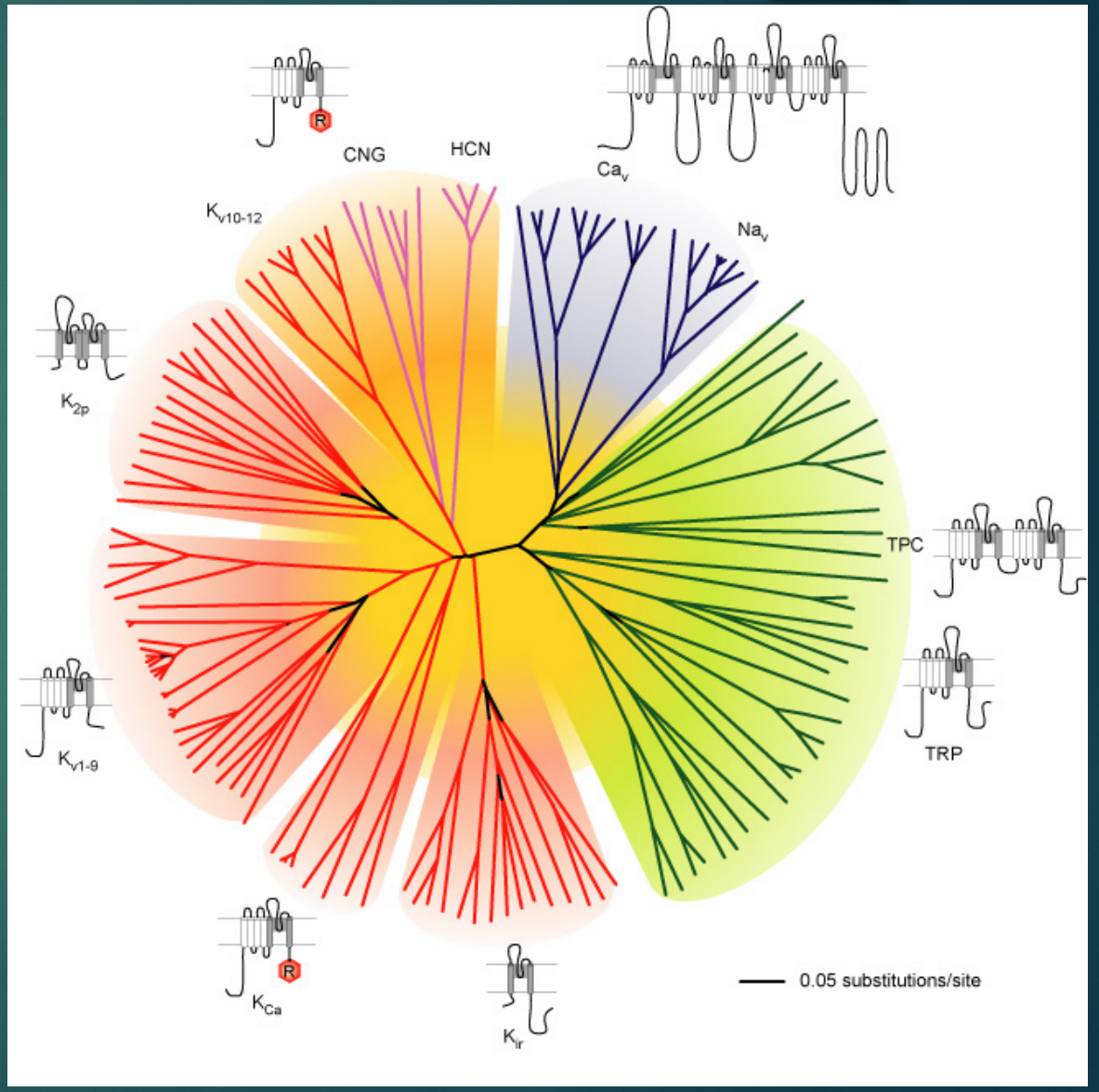
Ion Channels

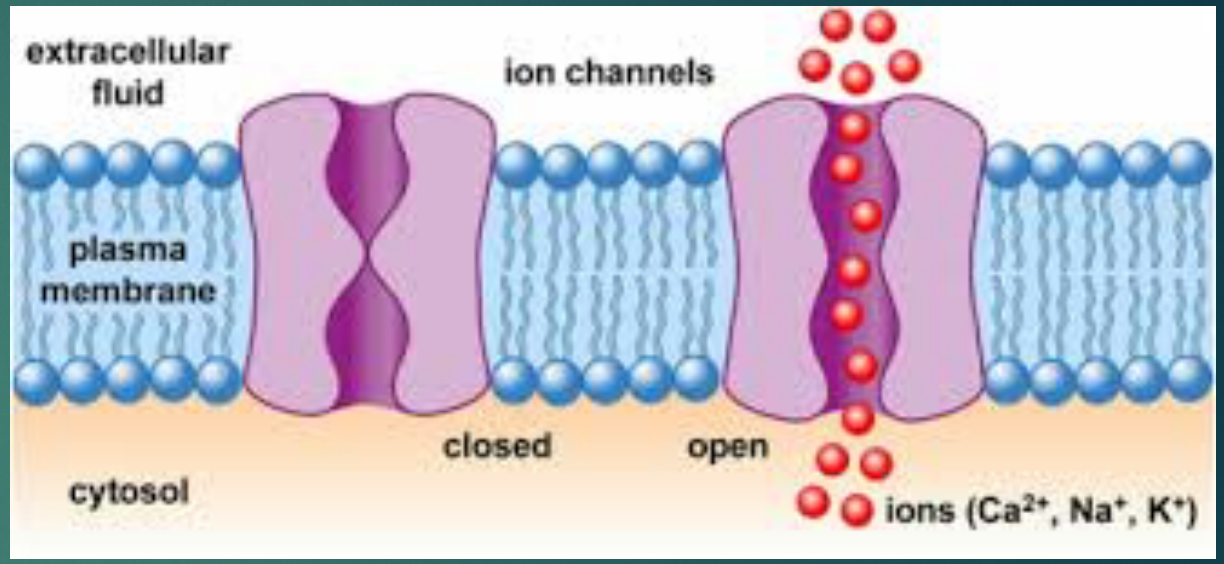
STRUCTURE AND FUNCTION



- 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:

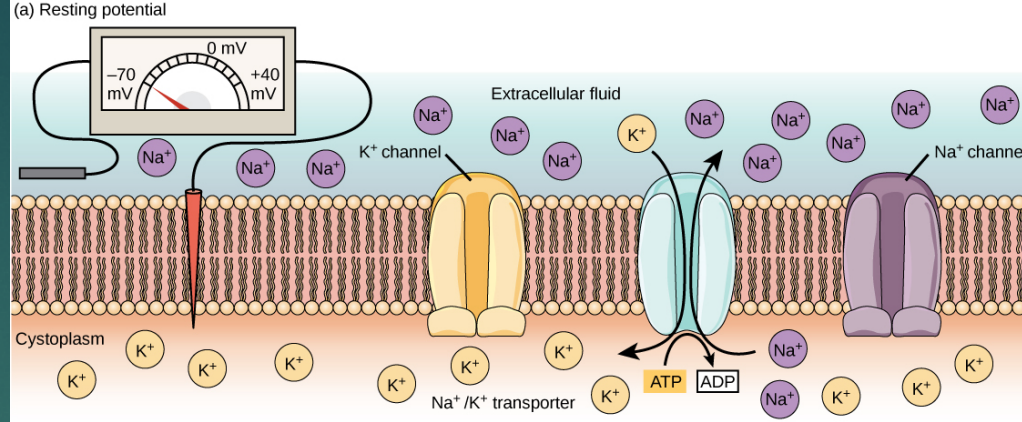
OPEN = allows ion fluxes

CLOSE = very low probability of ion permeation

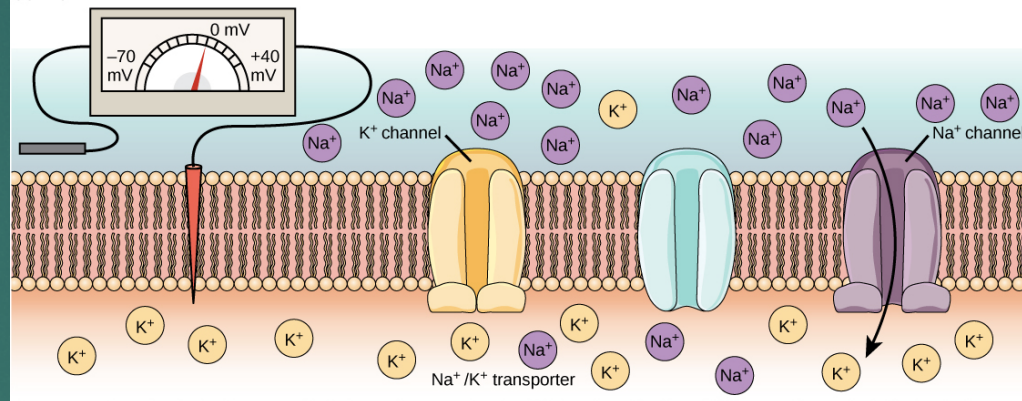


In the open state channels allows highly efficient ion fluxes allowing single channels current measurements which is very difficult for Transporters

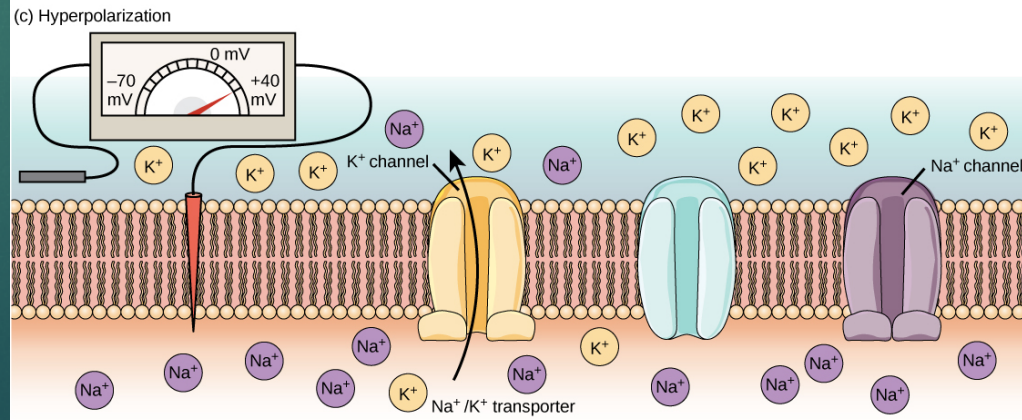
- The ion fluxes through ion channels significantly change Vm. Therefore In channels play a significant role in cell excitability



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.



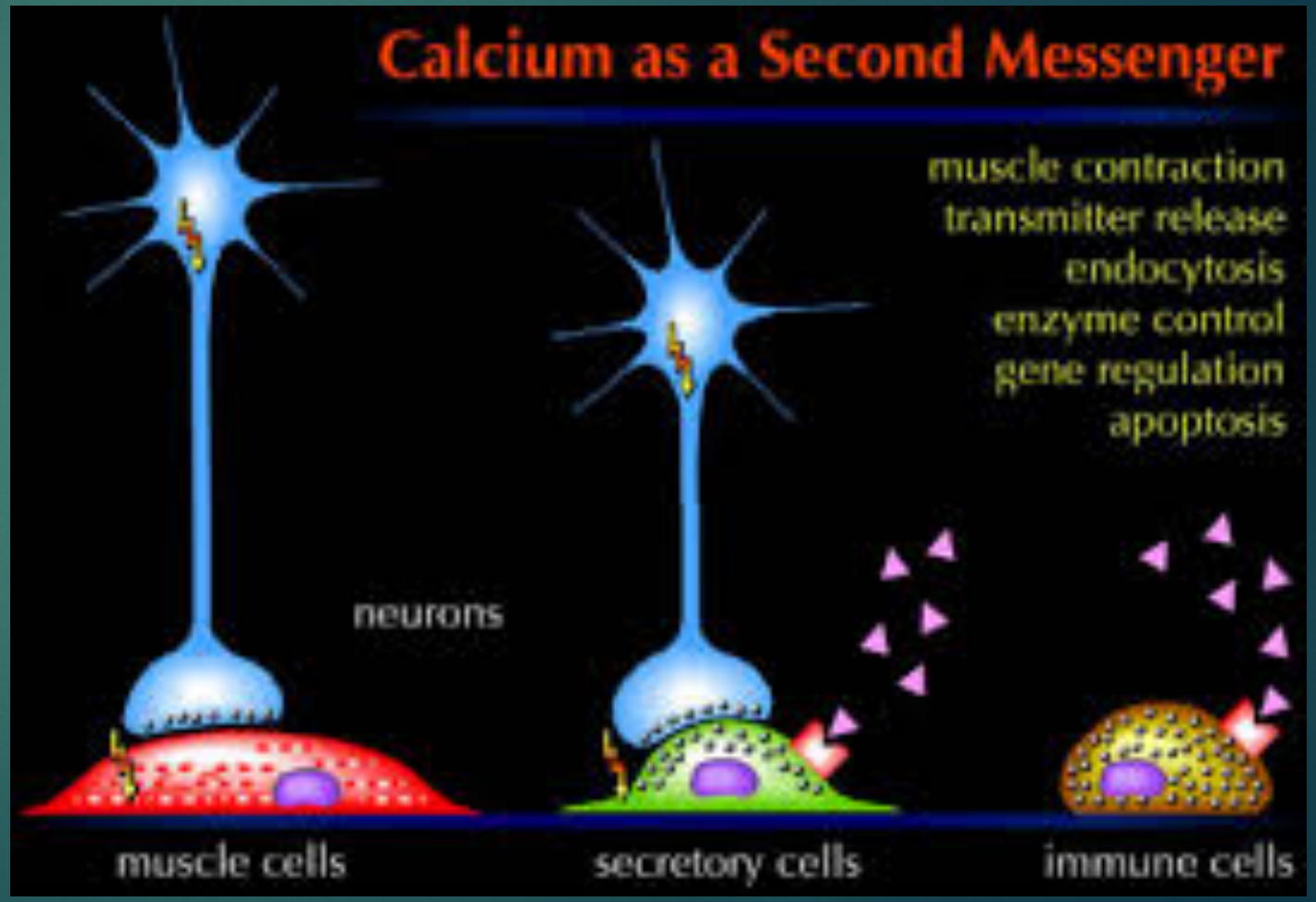
In response to a depolarization, some Na^+ channels open, allowing Na^+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na^+ channels open.

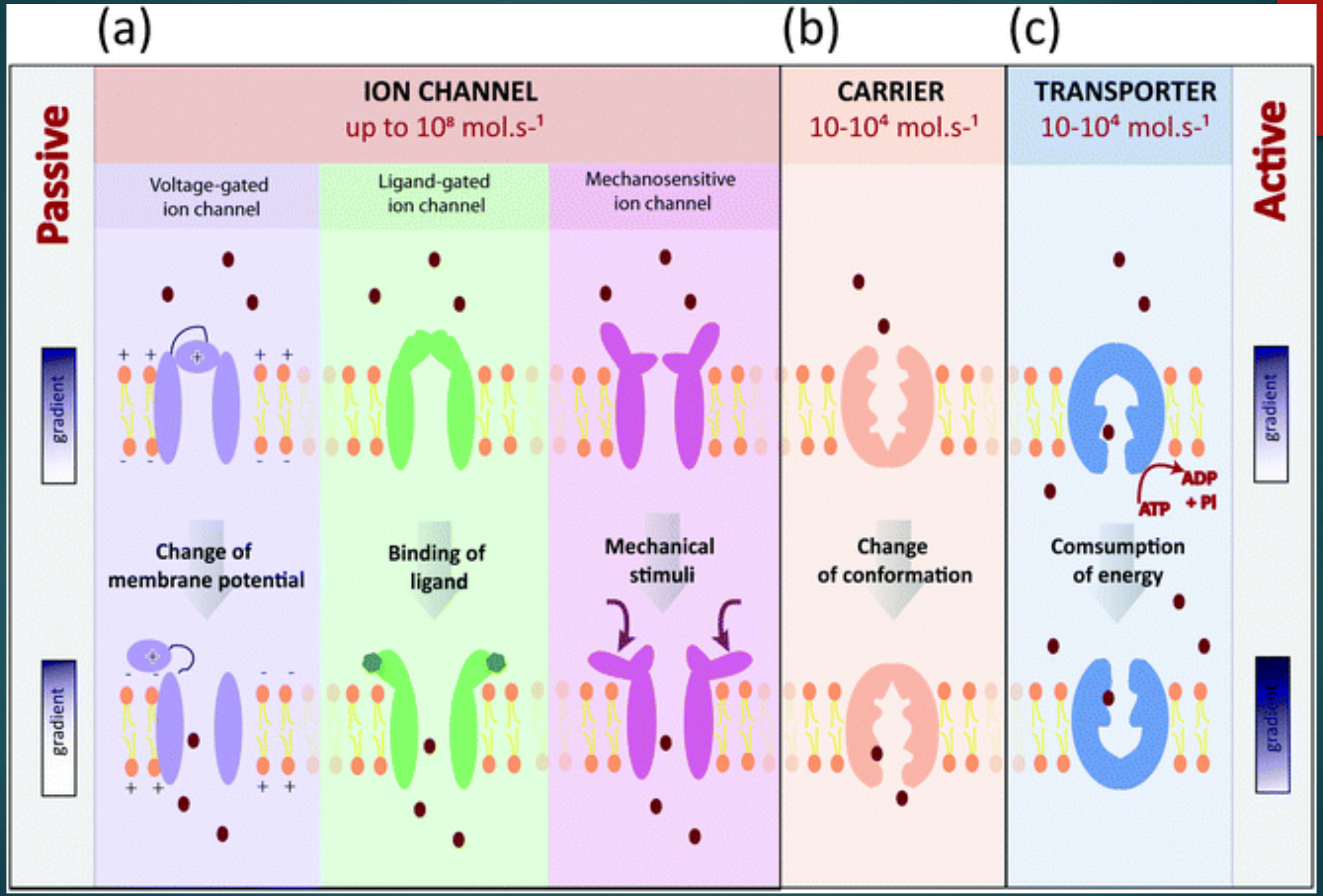


At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

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

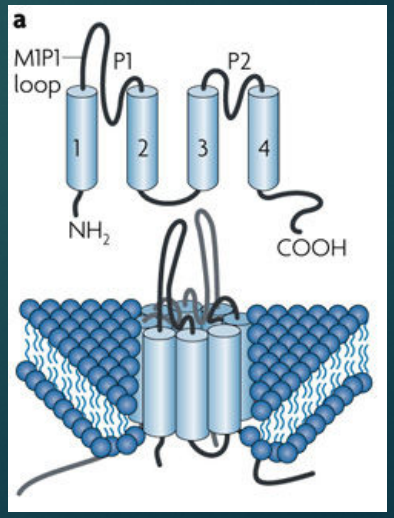
ION CHANNELS classification: basic types of ion channels

- **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).

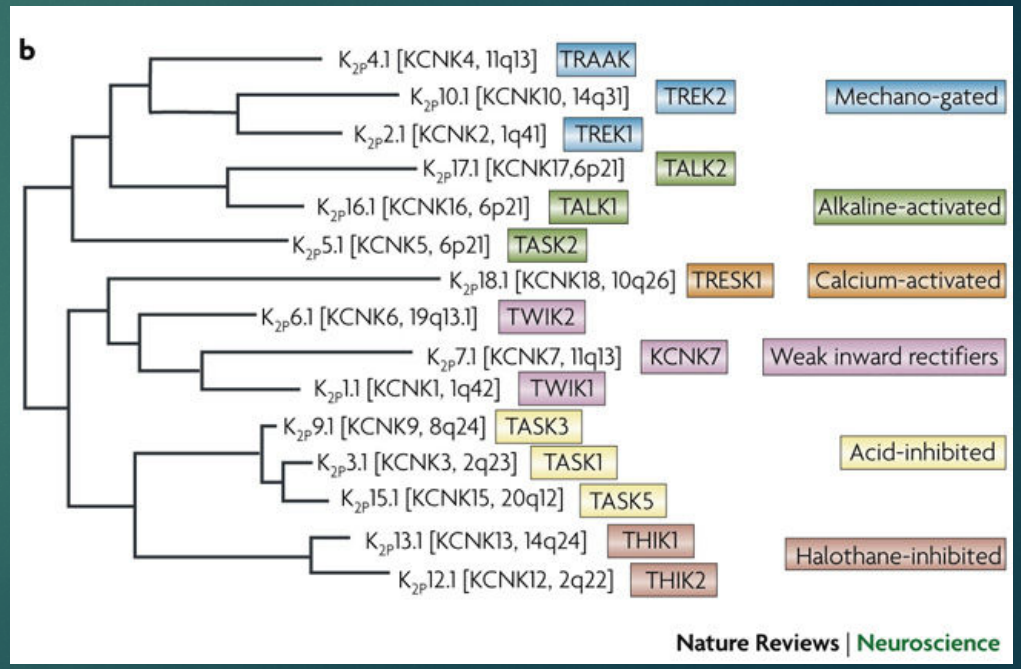
The resting activity of these K+ channels drives the membrane potential (through hyperpolarization) closer to the K+ equilibrium potential of about –90 mV, and therefore tends to reduce excitability.



ION CHANNELS classification: basic types of ion channels

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

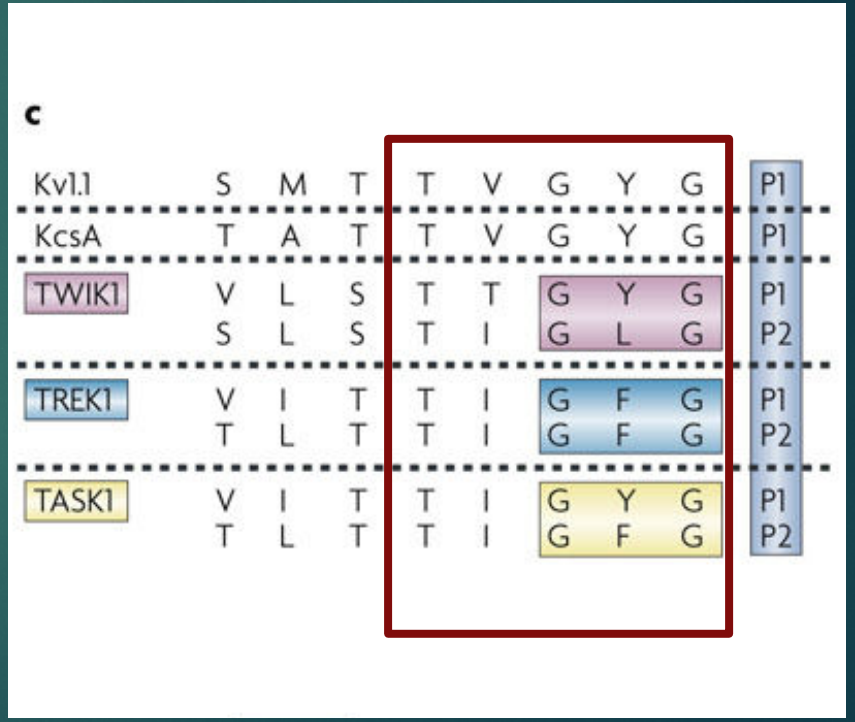
This family has 15 members that are subdivided in six distinct subfamilies, TWIK, TRAAK (TWIK Related Arachidonic acid Activated K+ channel), TREK (TWIK RElated K+channels), TASK (TWIK related Acid-Sensitive K+ channels), TALK (TWIK related ALkaline pH-activated K+ channels), THIK (Tandem pore domain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

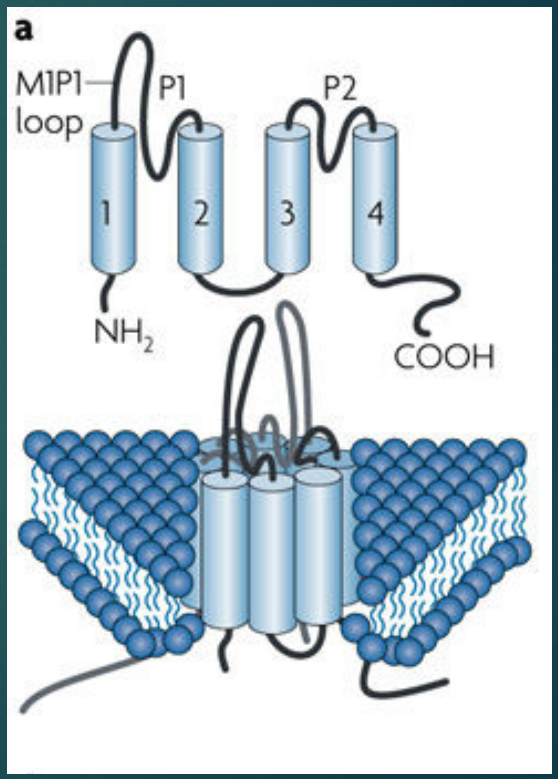
Two pore family of K+ leak channels (K2P).

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.

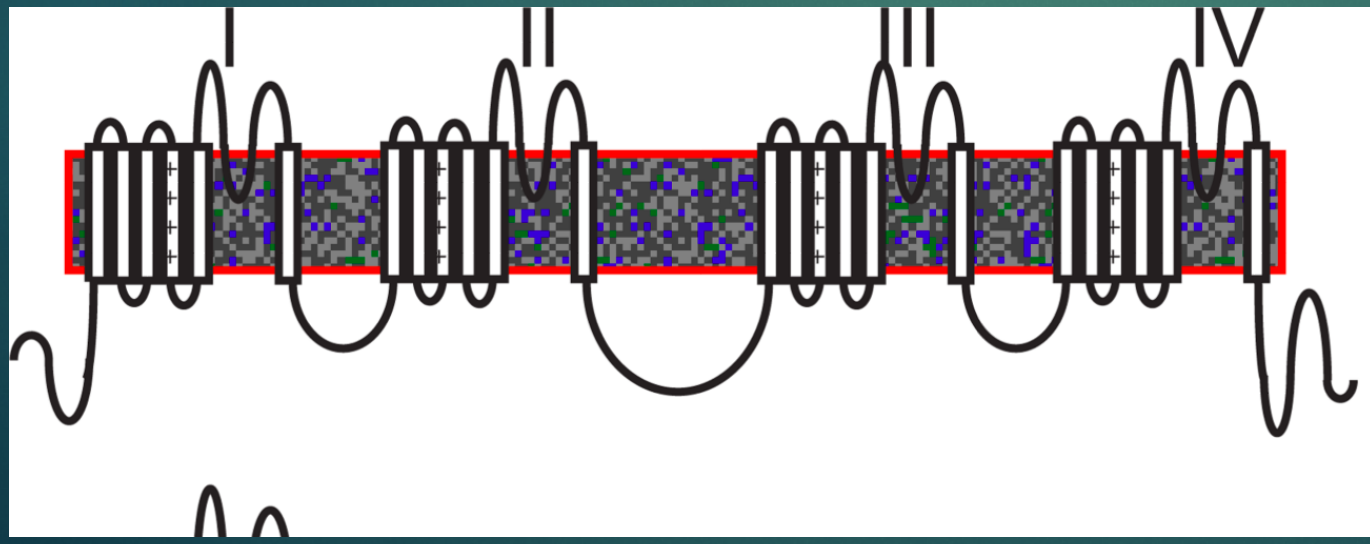
A tonic leak of other ions such as Ca2+, Mg2+ and H+ can hypothetically achieve the same goal, but excessive leak of these ions into neurons can be damaging to the cells because of the cellular metabolism's high sensitivity to the intracellular concentrations of the ions.

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 a 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

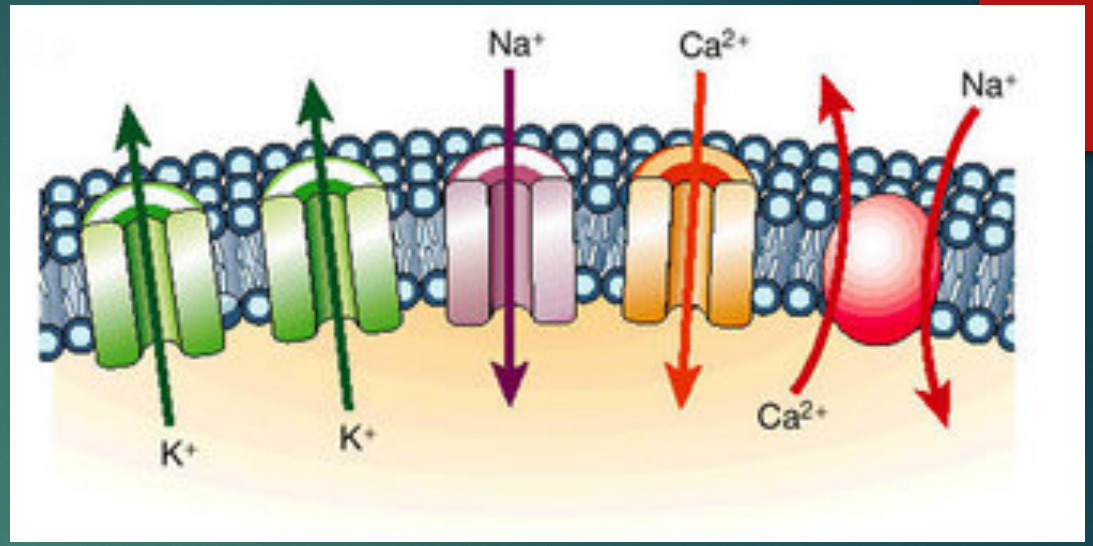
Direction of movement of one ion is dictated by the electrochemical driving force:

(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

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

NERNST equation

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

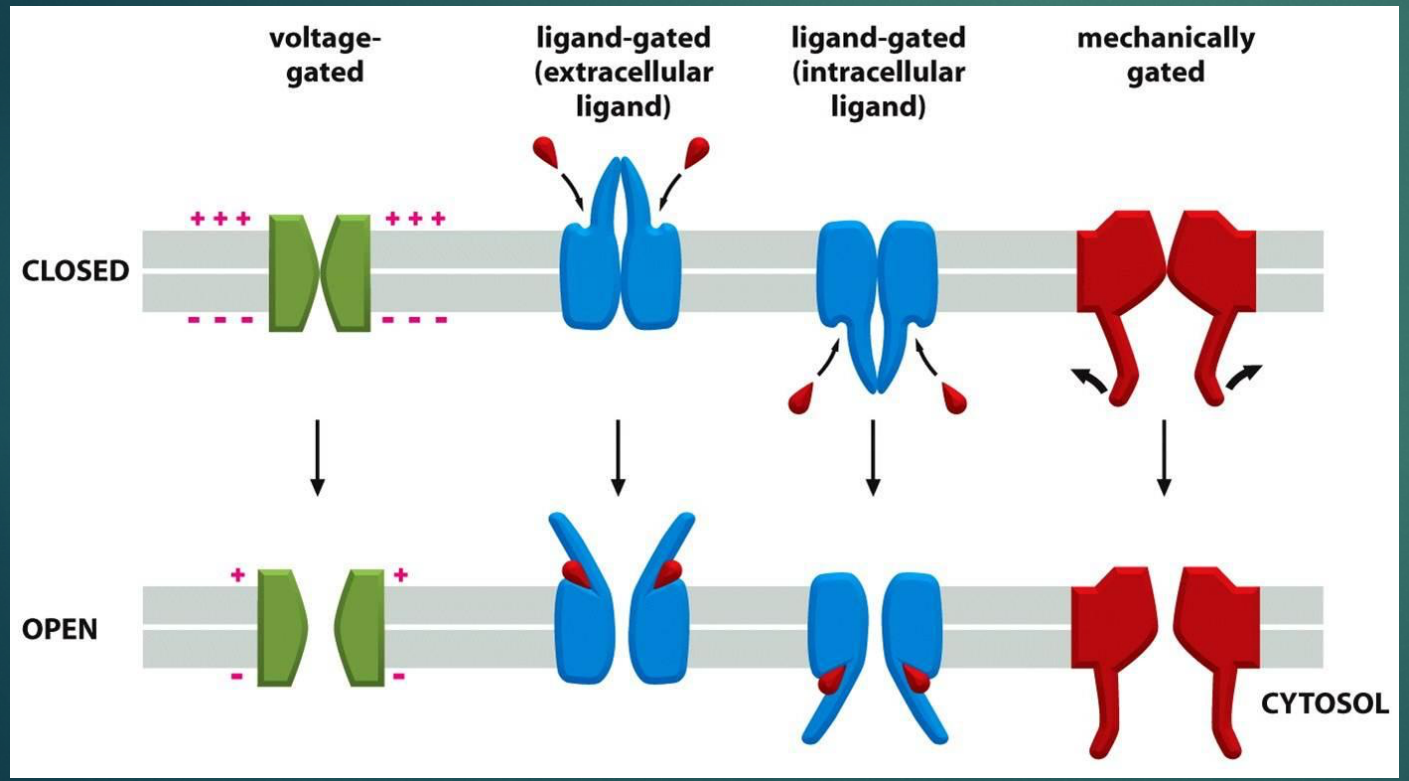
Equilibrium potential (E) for important ions in a neuron.

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

ION CHANNELS classification: basic types of ion channels

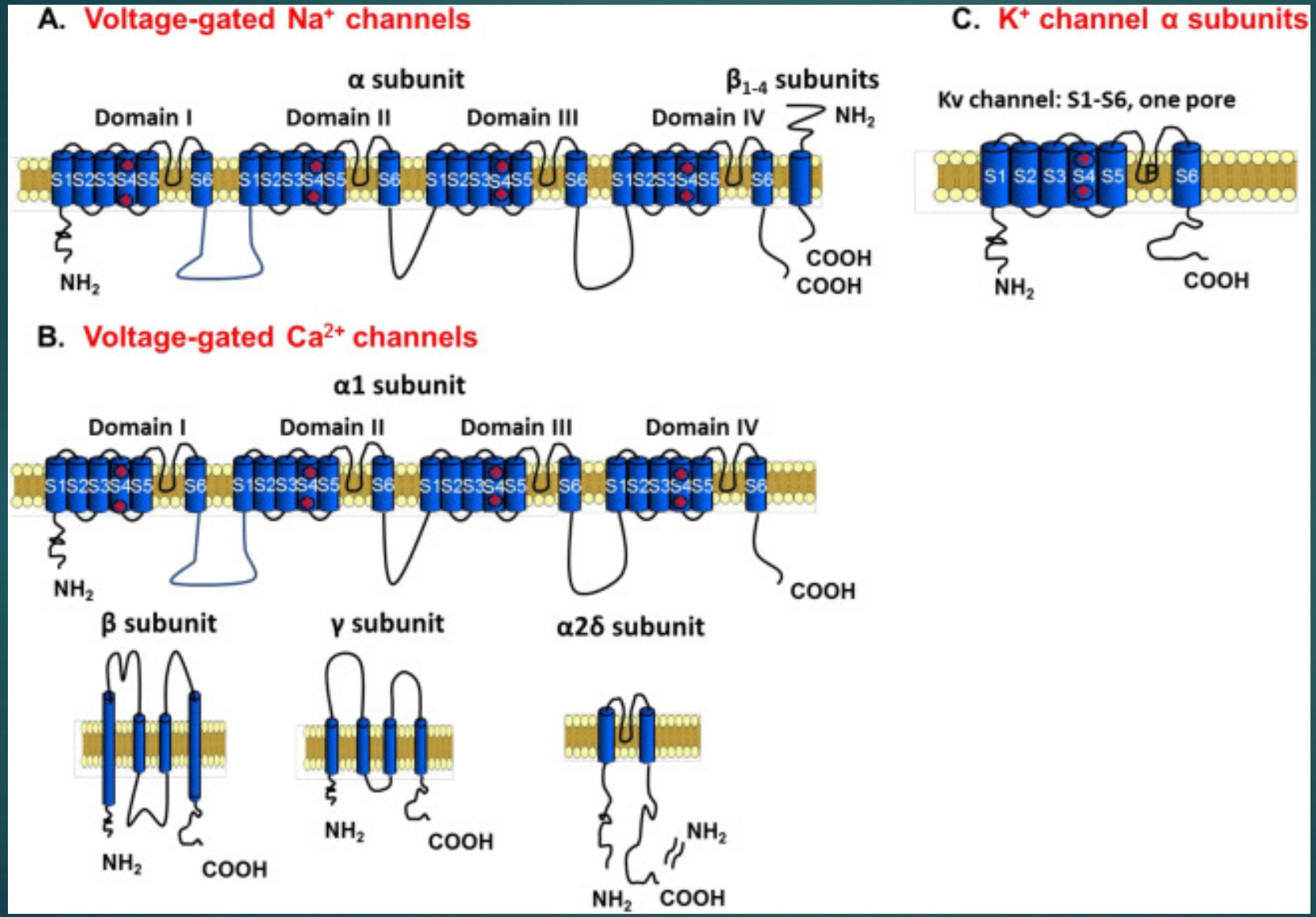
- **Leakage channels**: constitutively open channels.
- **Gated channels**: open/close in response to a stimulus

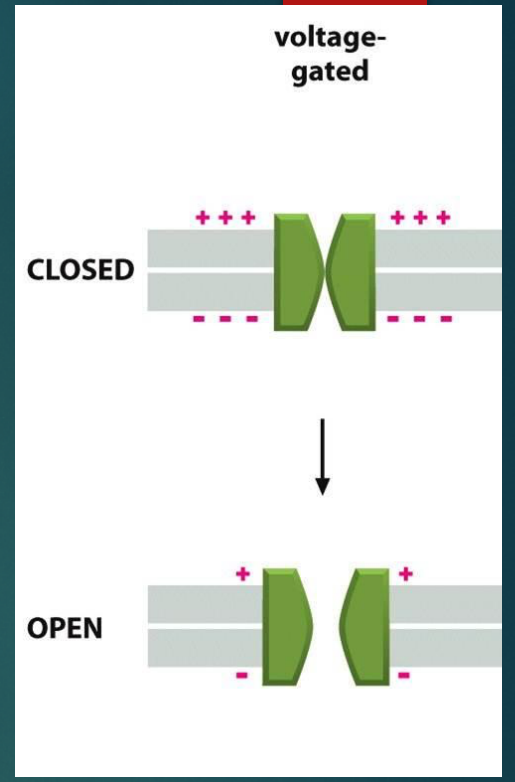
- **GATING**: mechanism that controls conformational transitions between open and closed state and therefore control OPENING and CLOSING of the channel



3 main mechanisms of gating

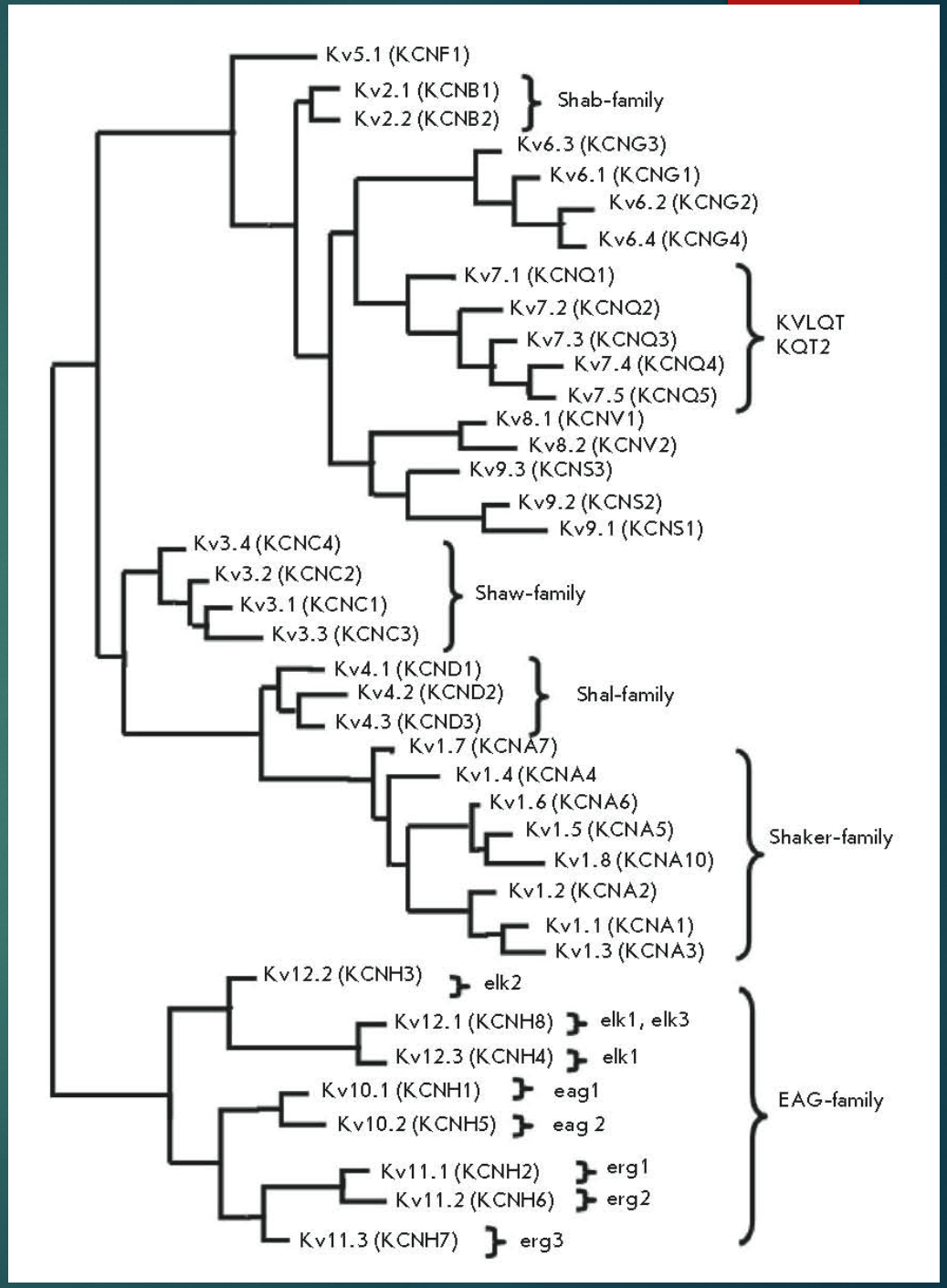
Voltage gated ion channels





Voltage gated K+ channels

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

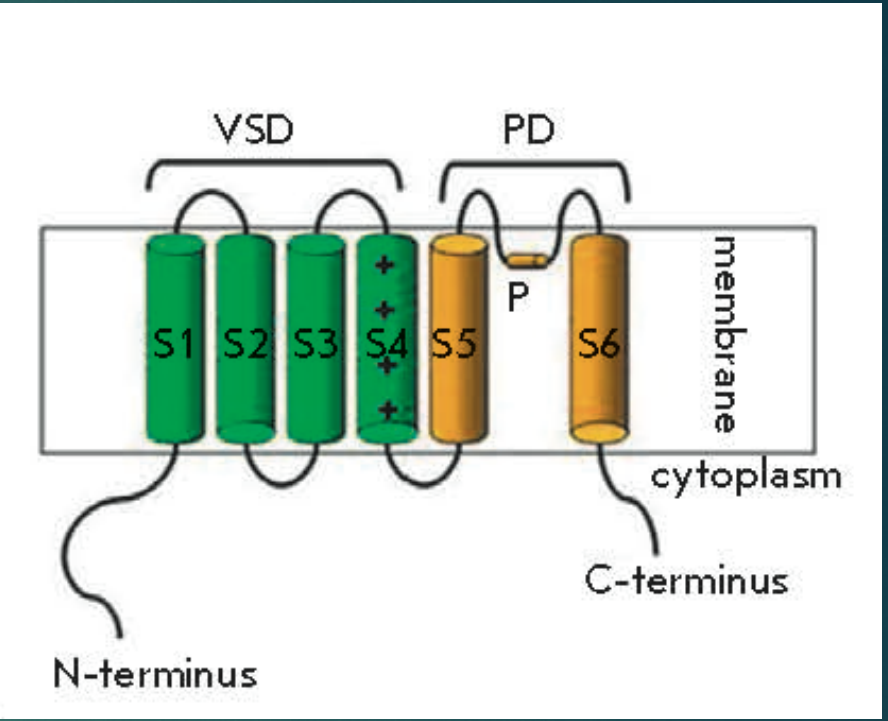


Grizel et al., Acta Nature, 2014

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 contributing to the central pore.

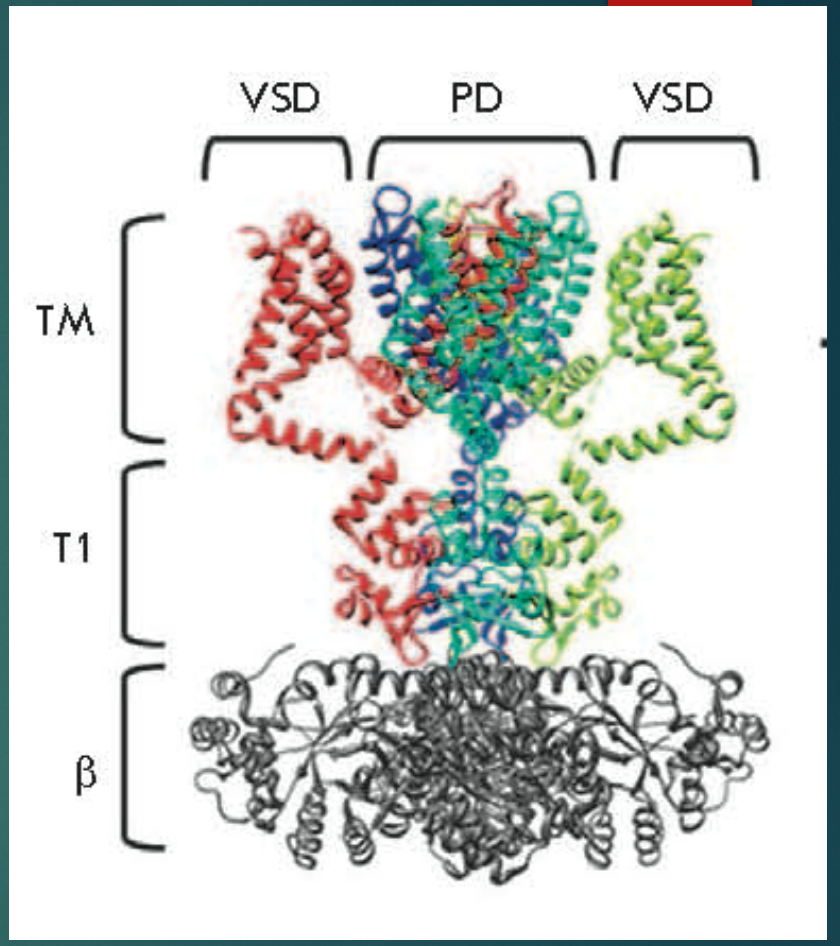
Each Kv channel gene encodes one α-subunit (Kvα).



Grizel et al., Acta Nature, 2014

Voltage gated K+ channels

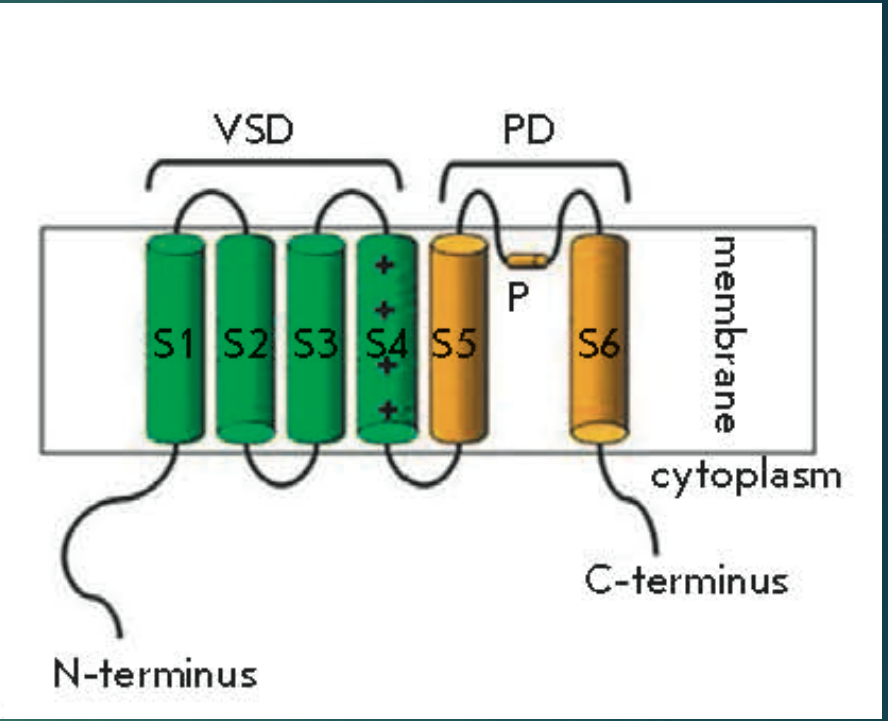
Four α-subunits are required to form a functional channel. Kv channels usually have a homotetrameric structure (with all Kvα being identical); however, some channels can be heterotetrameric (with two or more non-identical Kvα subunits).



Grizel et al., Acta Nature, 2014

Voltage gated K+ channels

The transmembrane domain of the Kv channel α-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.



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