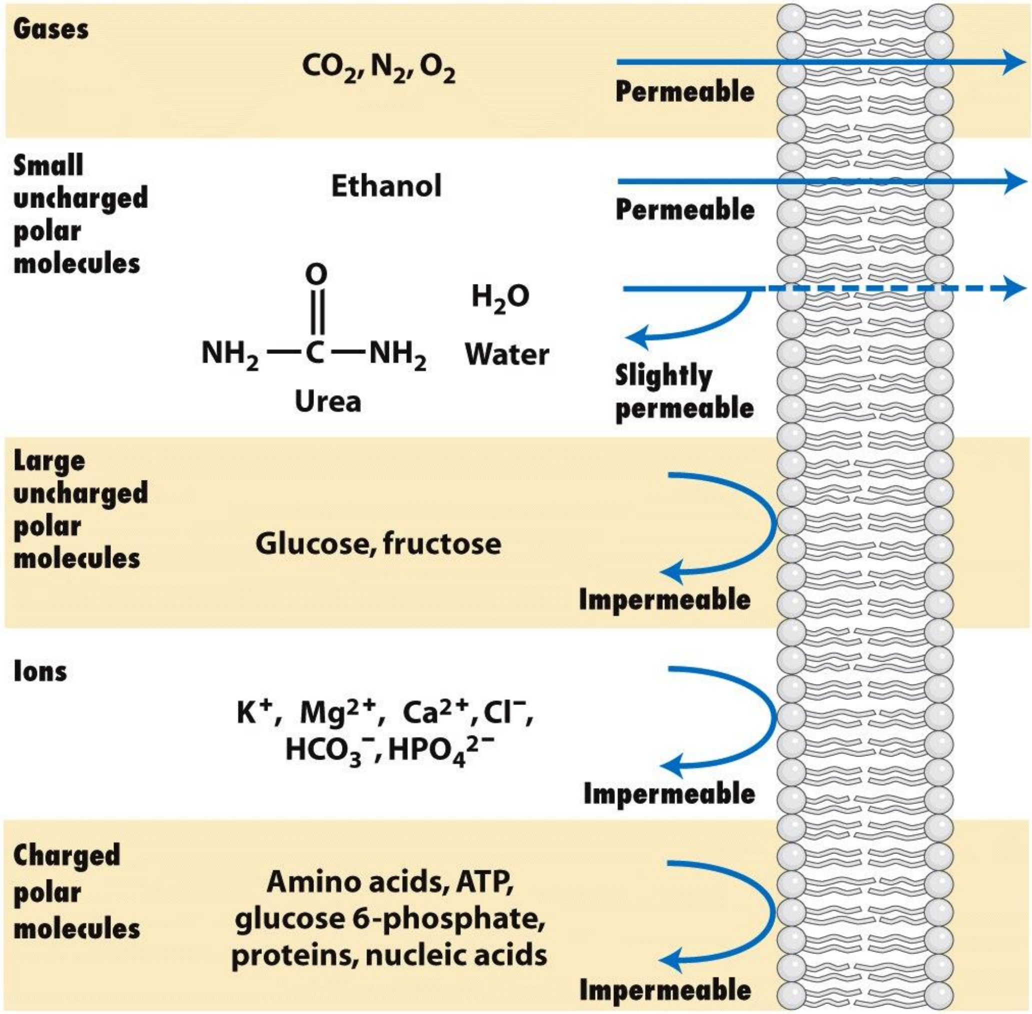
Chapter 5. Ion Channels



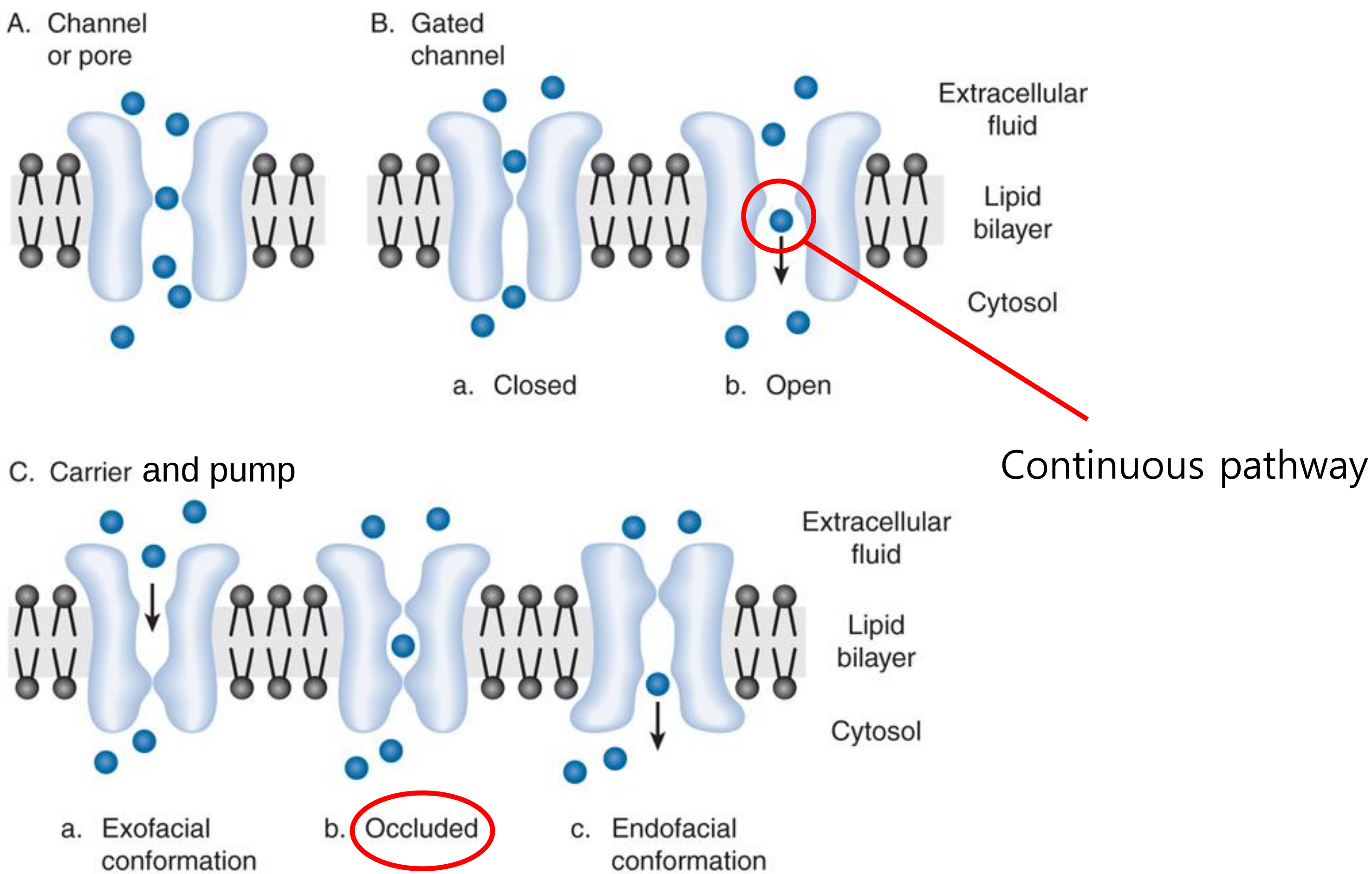
A pure artificial phospholipid bilayer is permeable to <u>small hydrophobic molecules</u> and <u>small uncharged polar molecules</u>.

Ion channels

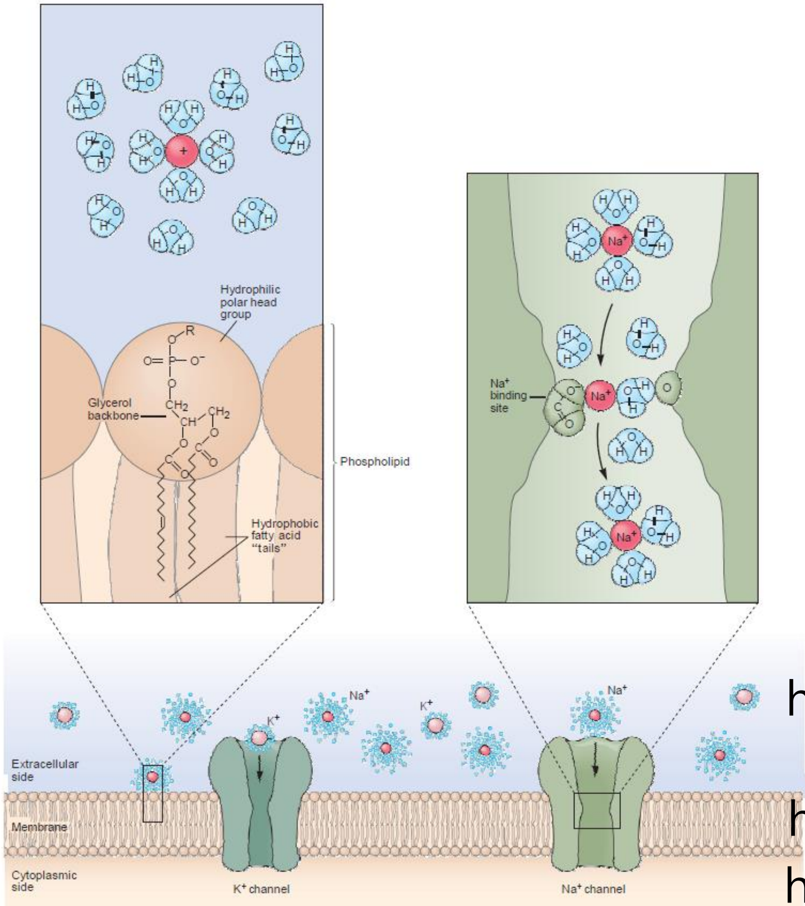
- Integral membrane protein
- select specific ions (selectivity)
- open and close (gating) by electrical, mechanical, or chemical signals
- conduct ions across the membrane

TRANSPORTER	**TURNOVER NUMBER* (PER SEC)**
K^+ channel	30,000,000
Valinomycin (carrier)	30,000
Glucose carrier (GLUT-1)	3,000
Na^+/Ca^{2+} exchanger	2,000
Ca^{2+} pump (SERCA)	200
Na^+ pump	150
enzymes	10-1000

Transport across biological membrane through channel, carrier, and pump protein



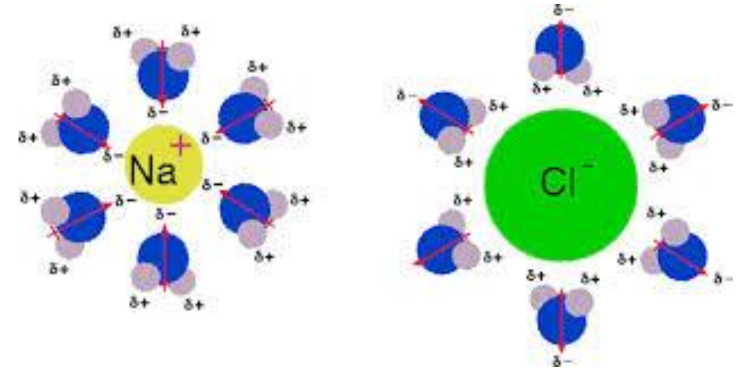
Ion channels provide polar pathways for ions to cross the membrane



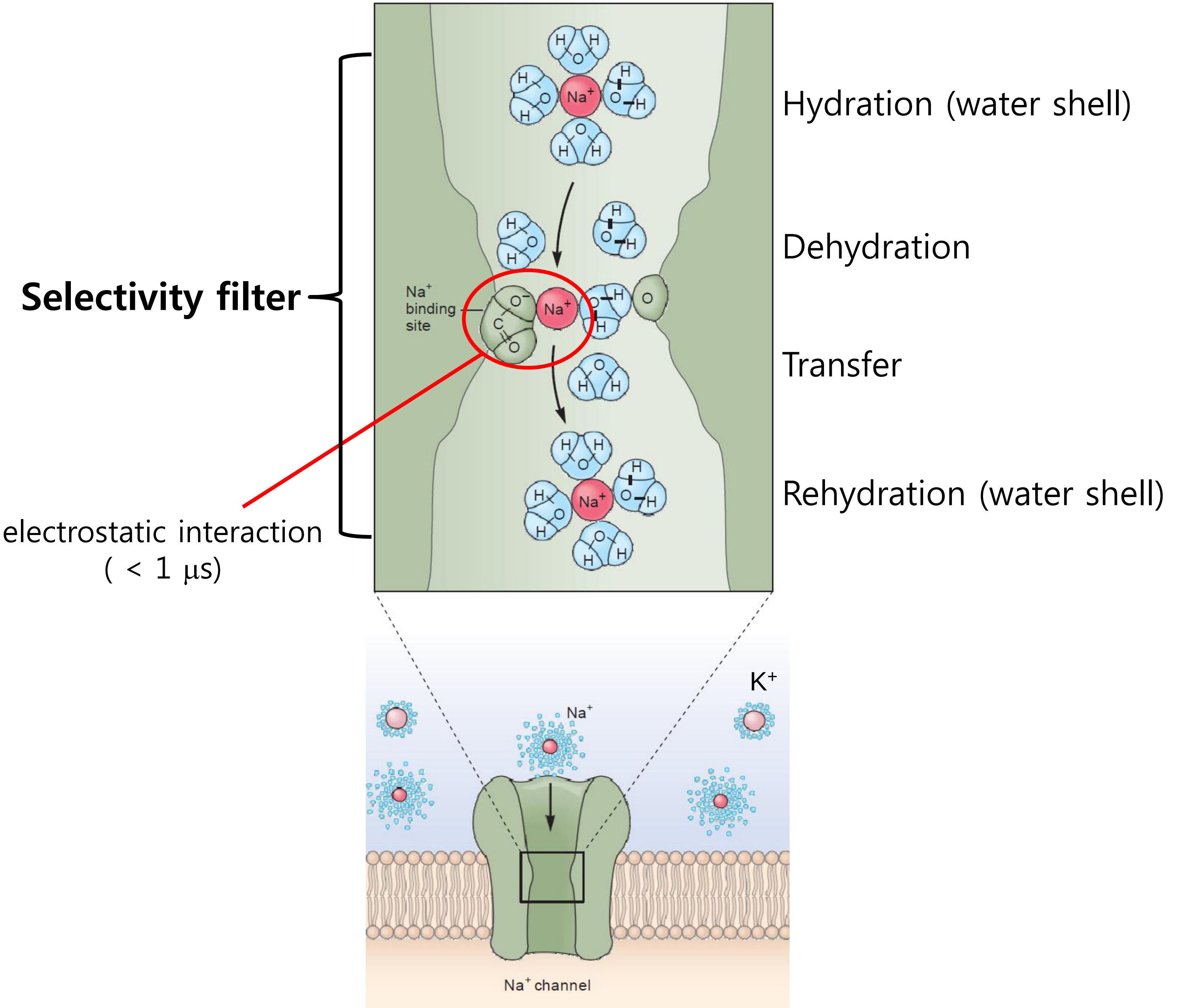
hydrophilic

hydrophobic

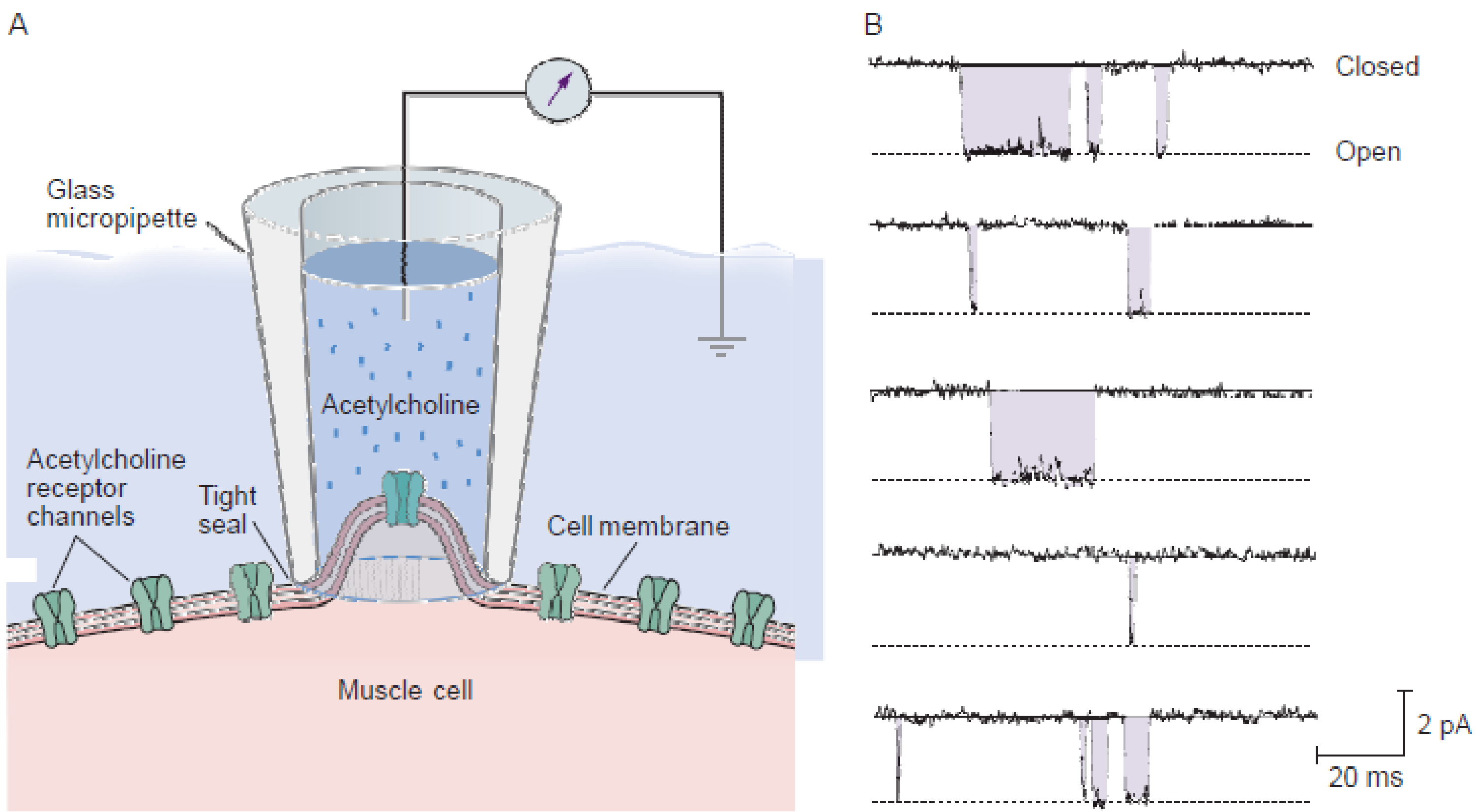
hydrophilic



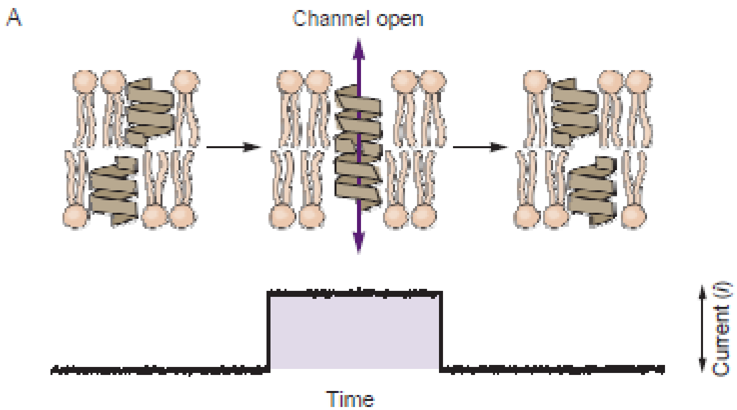
- Relatively fast transport
- Channel density controls membrane permeability to a substance
- Rate of transport through open channels depends on the net driving force
- Transport through some channels is controlled by gating

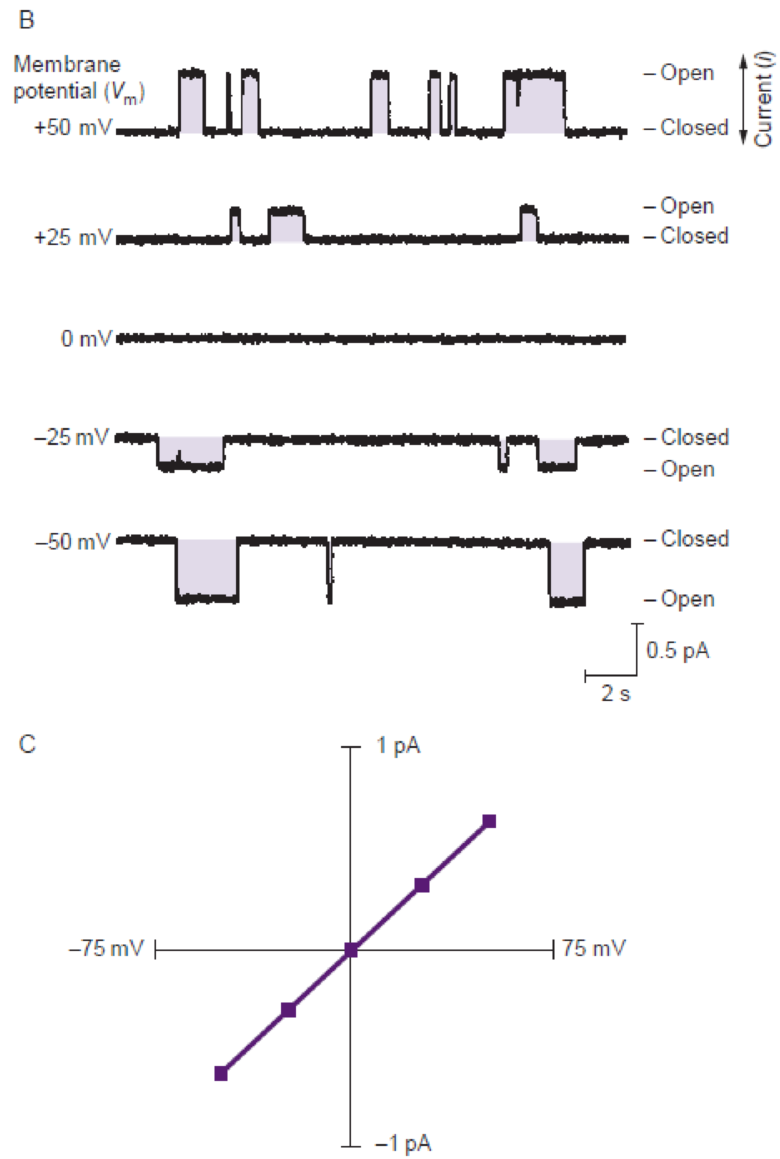

Hydration (water shell)
Dehydration
Transfer
Rehydration (water shell)
Selectivity filter
electrostatic interaction
(< 1 μs)
Na+ binding site
Na+
K+
Na+ channel

Recording Current in Single Ion Channels: The Patch Clamp



Characteristics of the current in a single ion channel





Ohm's law

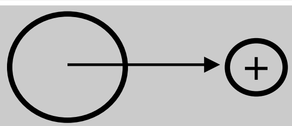
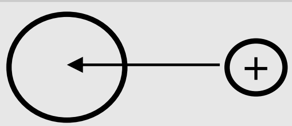
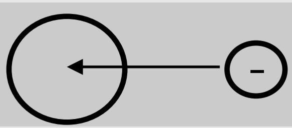
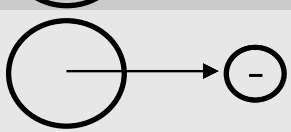
$i = V/R$ or $i = \gamma \times V$

(Conductance; $\gamma = 1/R$)

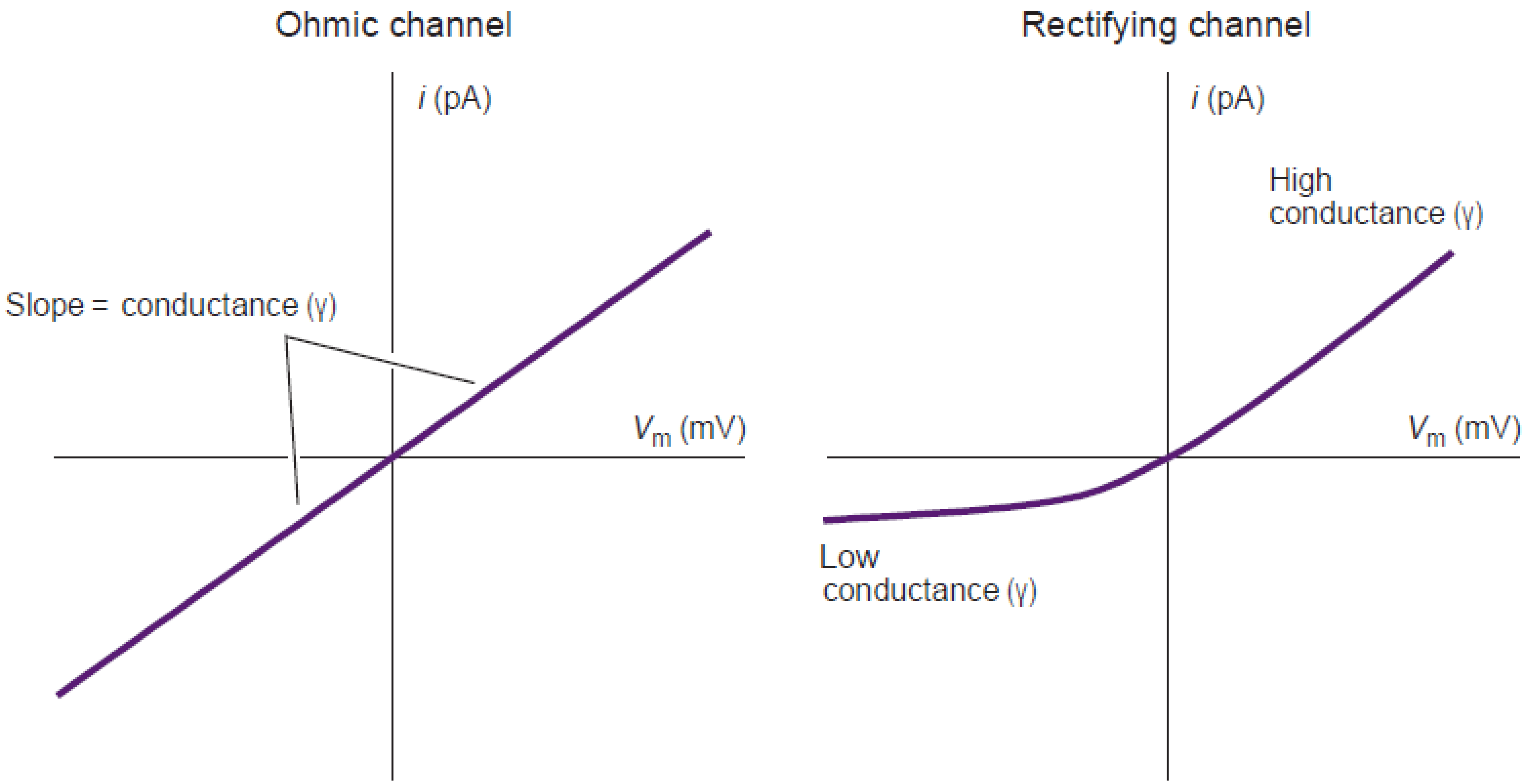
Ionic fluxes and ionic currents

Ionic flux (J)	Ionic current (I)
number of moles of ions moving through a unit area of membrane per unit time	Movement of charges per unit time
[mol/cm^2]/sec	Coulombs/sec, A

$$I = zF \times J \times A_{mem}, \quad \text{where } F=96{,}485 \text{ coulombs/mol}$$

Flow	Direction and Sign of Flux (J)	Direction and Sign of current (I)
	Outward, negative (J<0)	Outward, positive (I>0)
	Inward, positive (J>0)	Inward, negative (I<0)
	Inward, positive (J>0)	Outward, positive (I>0)
	Outward, negative (J<0)	Inward, negative (I<0)

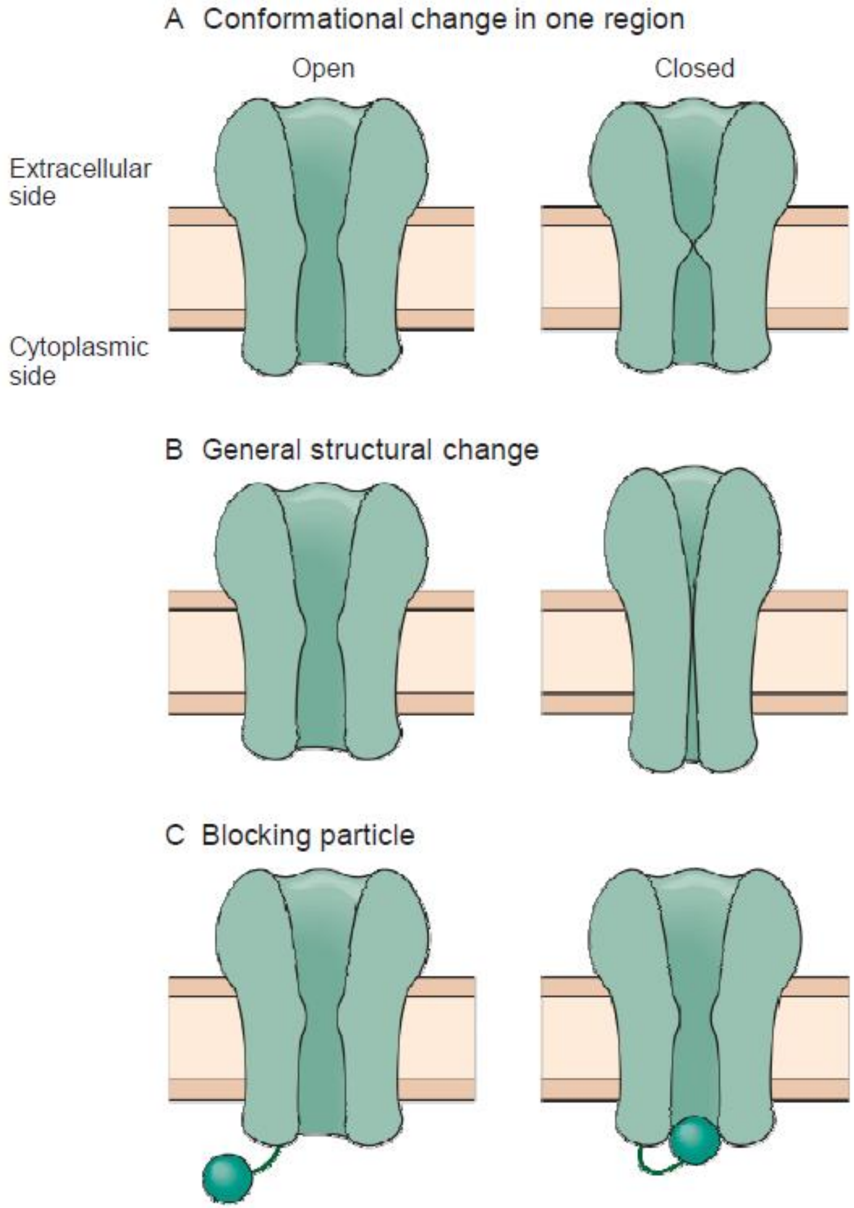
Current–voltage relations



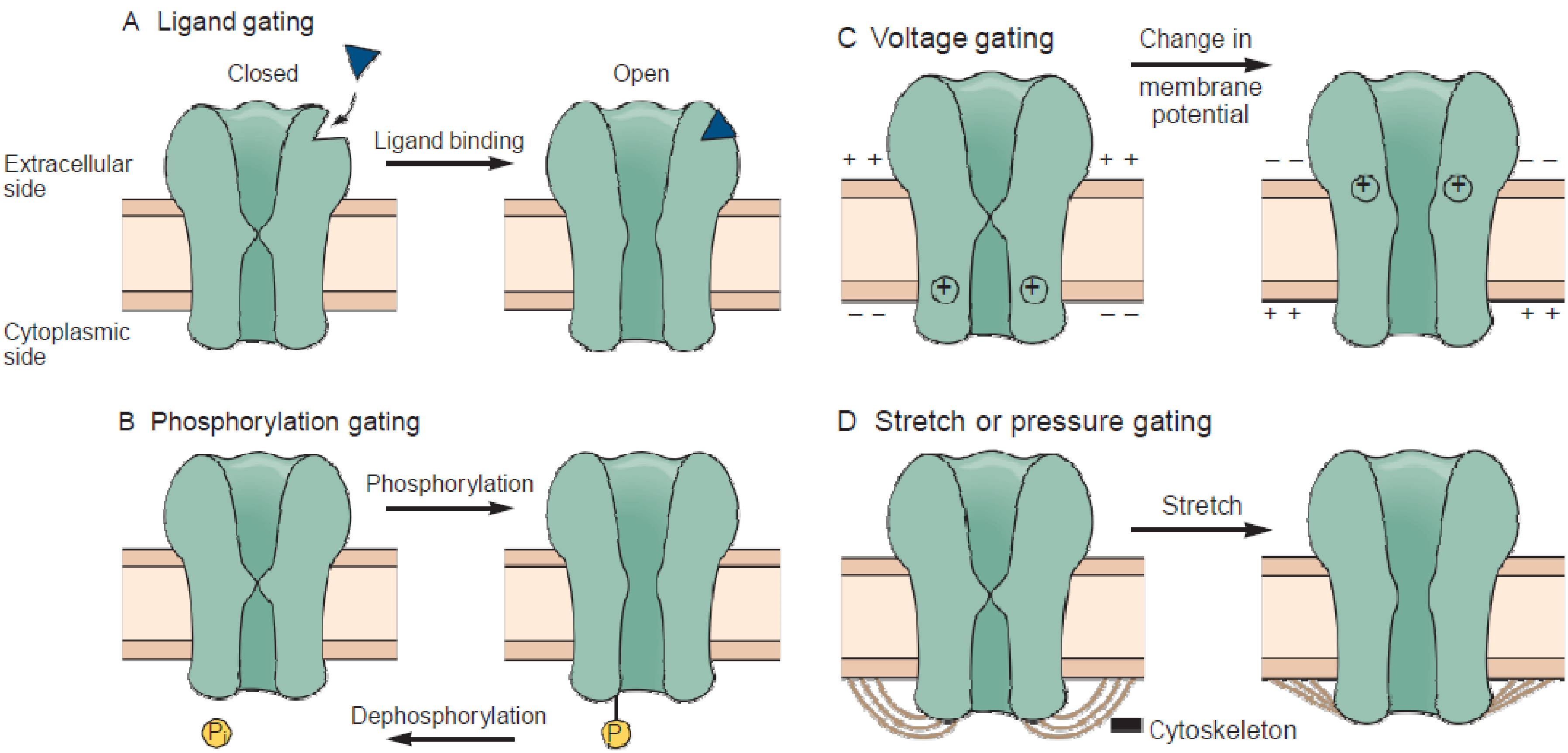
Ohm's law

$i = V/R$ or $i = \gamma \times V$

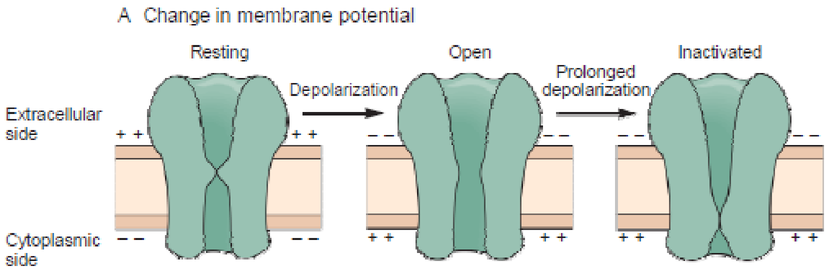
Models for the opening and closing of ion channels



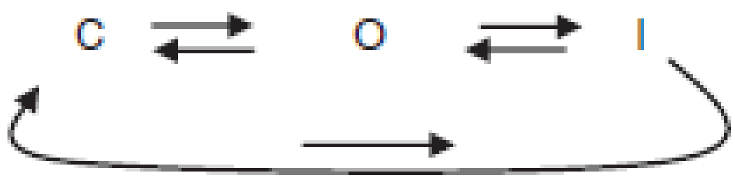
Classification by gating of ion channel

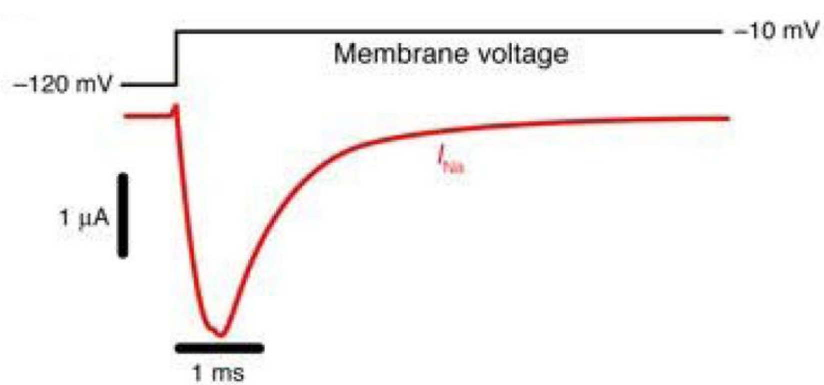


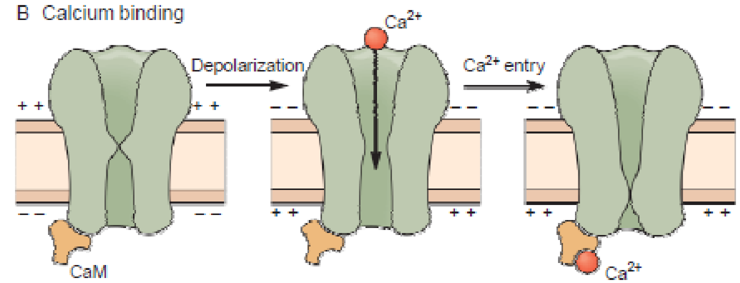
Inactivation mechanisms of voltage-gated ion channels

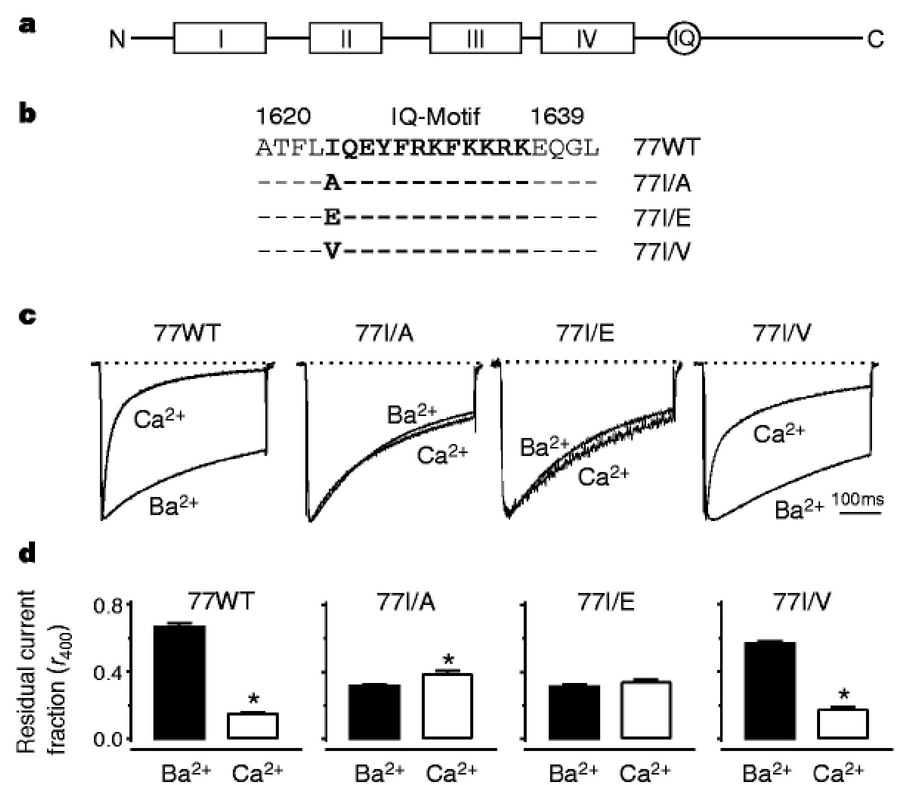


closed activatable | active | closed nonactivatable (refractory)

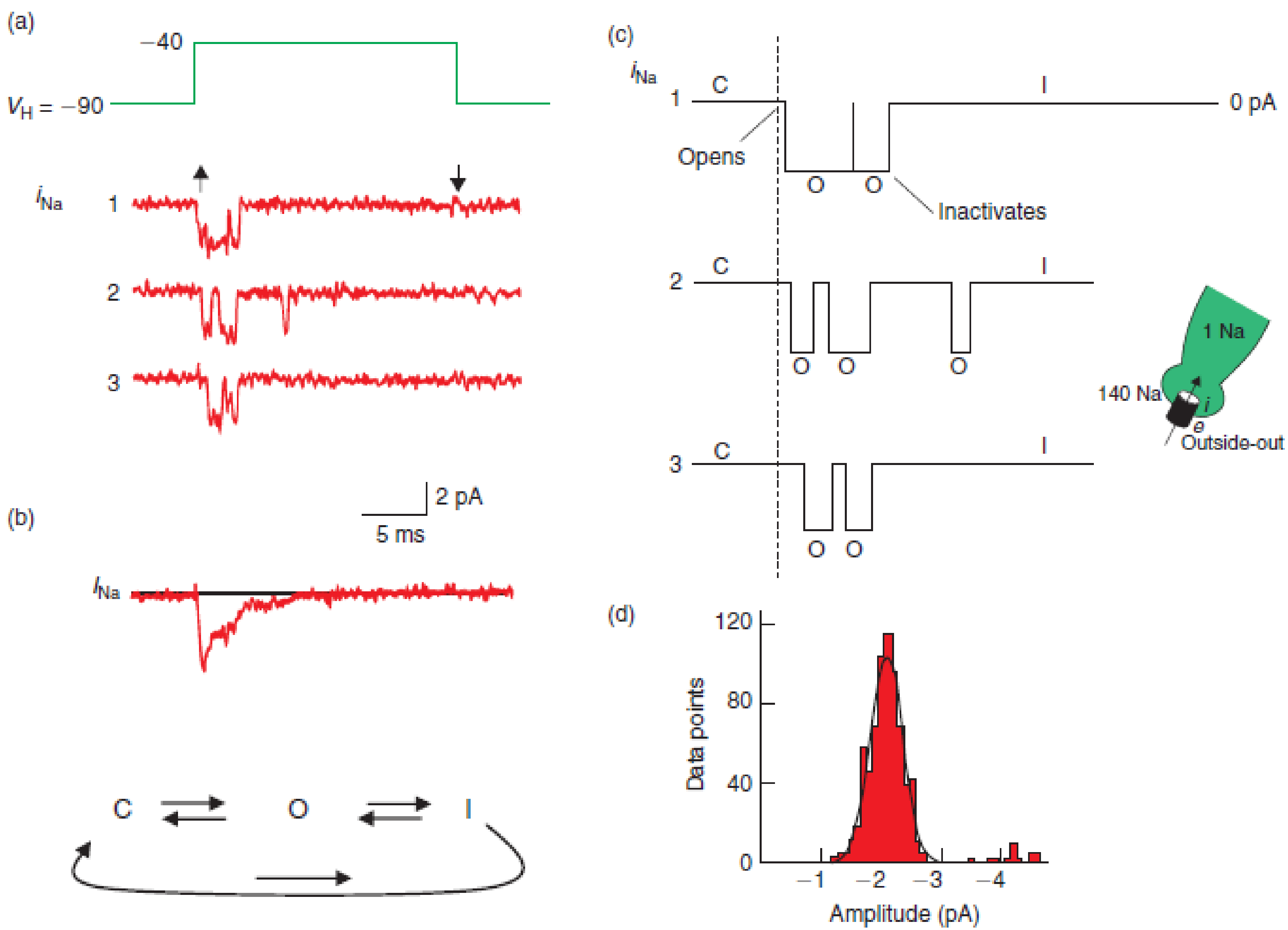




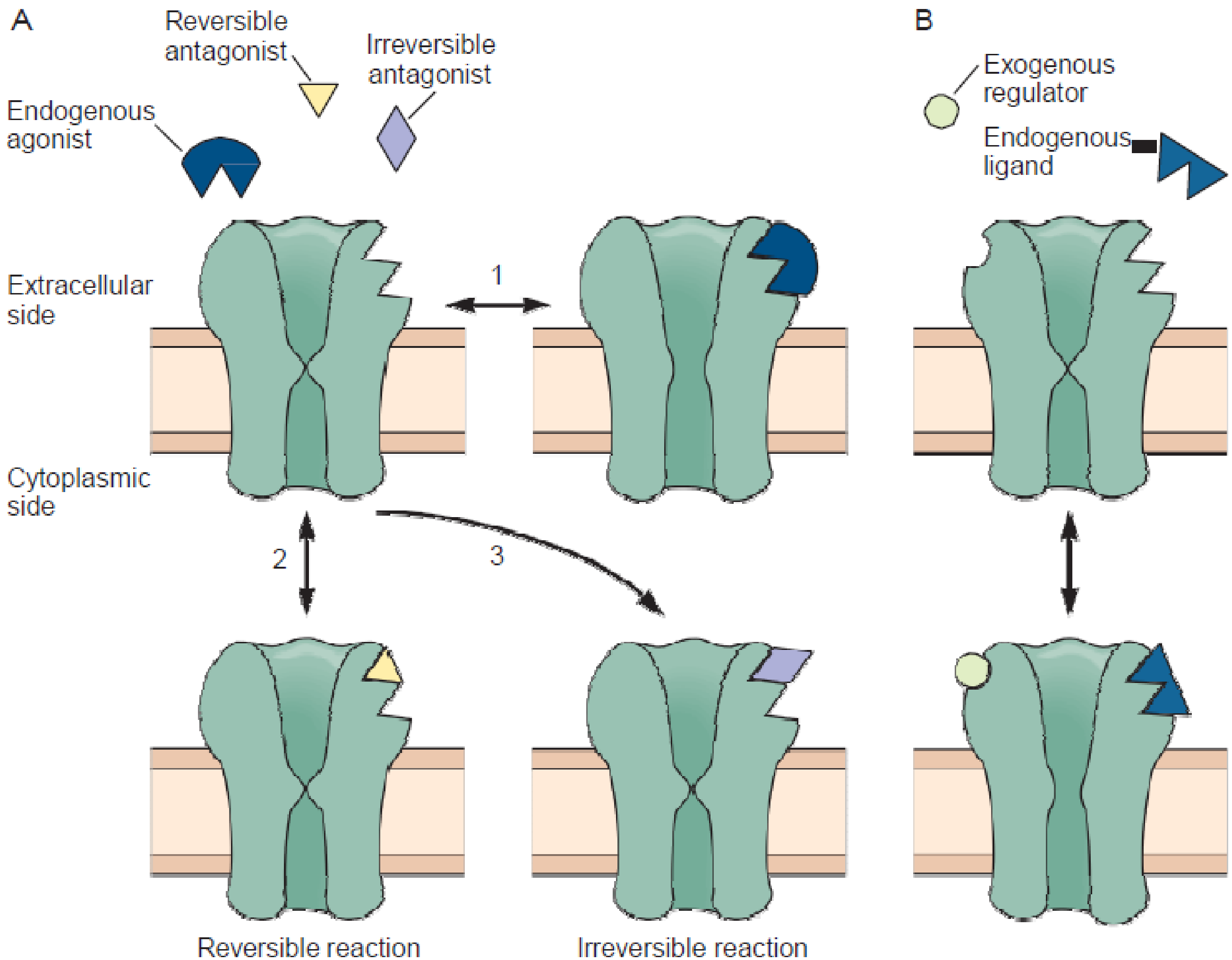




Single channel activity of a voltage-gated Na$^+$ channel

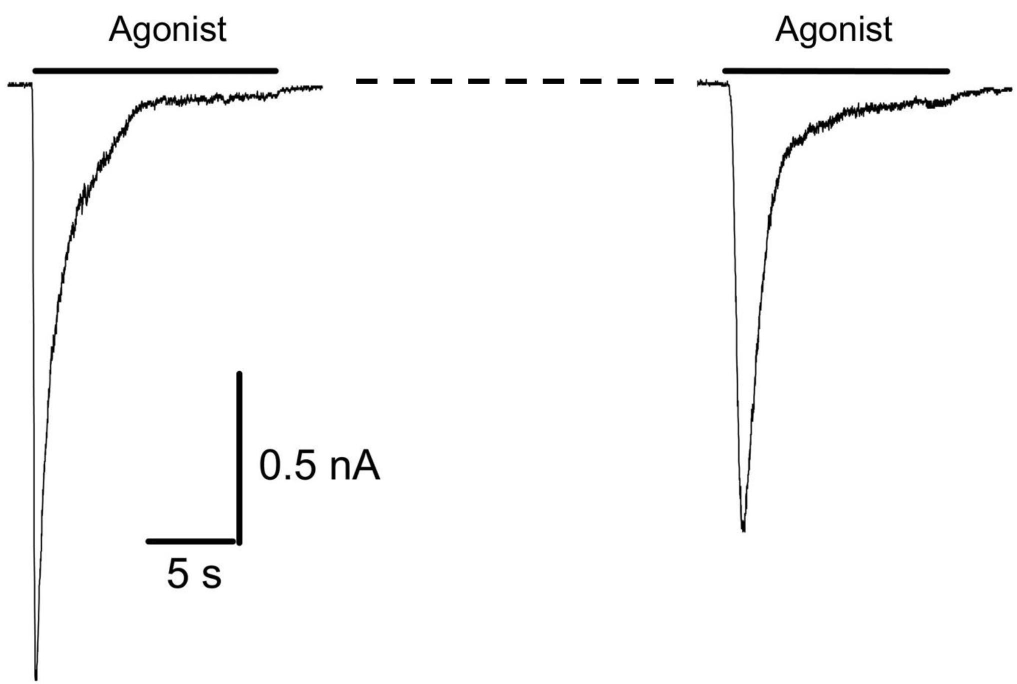


Exogenous ligands affect gating of ion channel

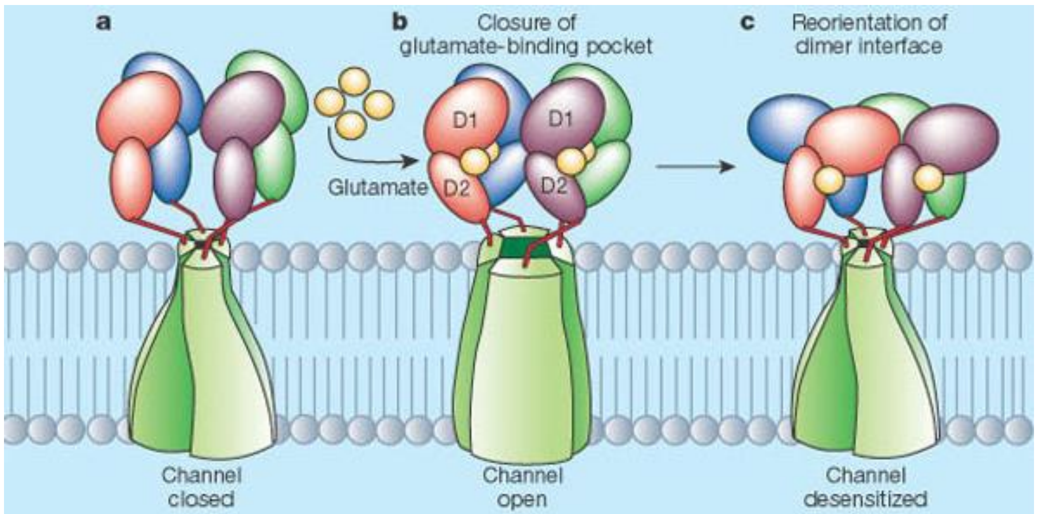


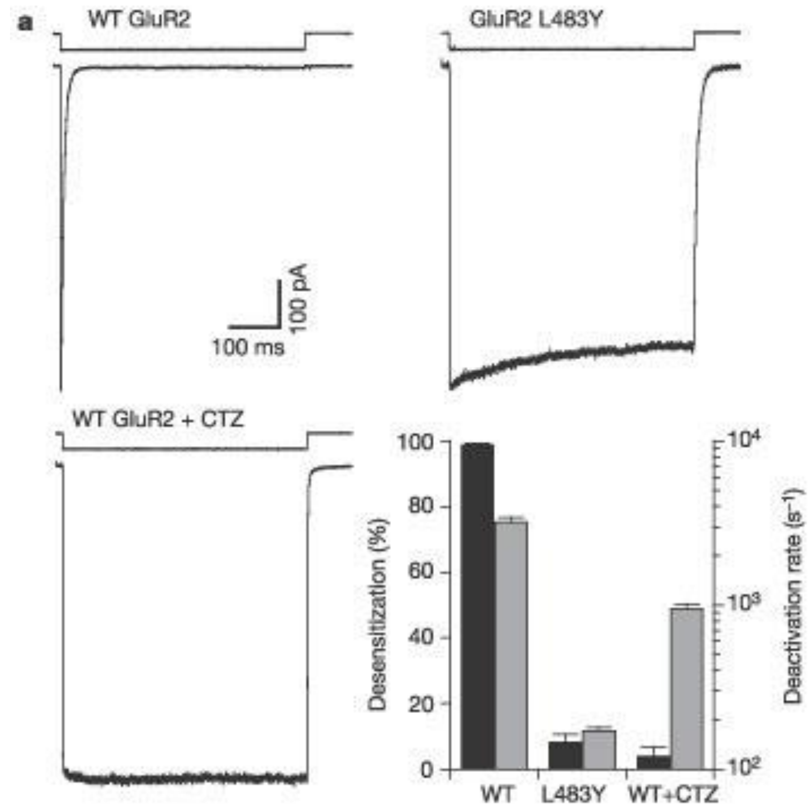
Desensitization

- loss of responsiveness to a continuing dose of agonist
- refractory state
- mechanisms
  - intrinsic property of the interaction between ligand and channel
  - phosphorylation by protein kinase



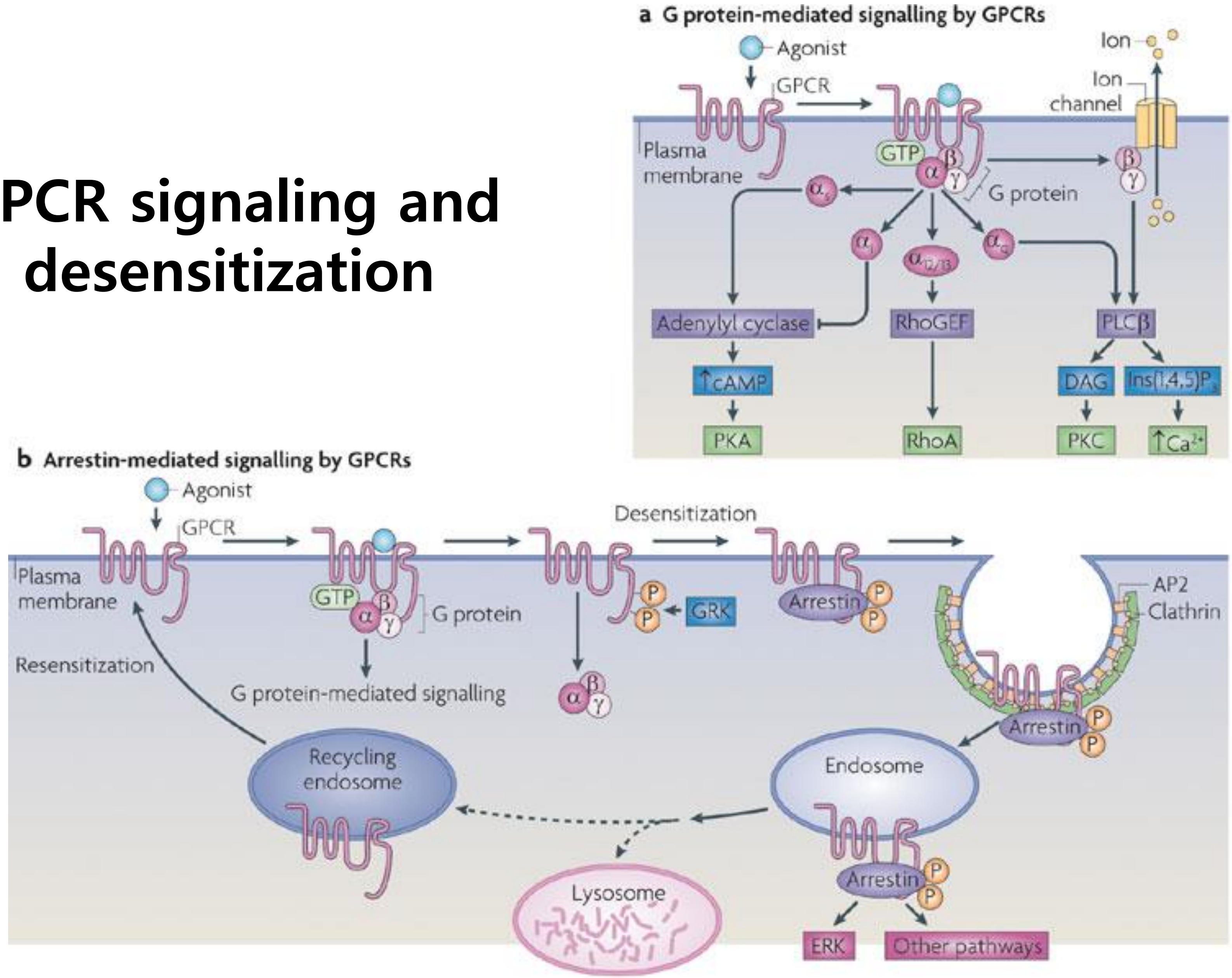
AMPA receptor desensitization





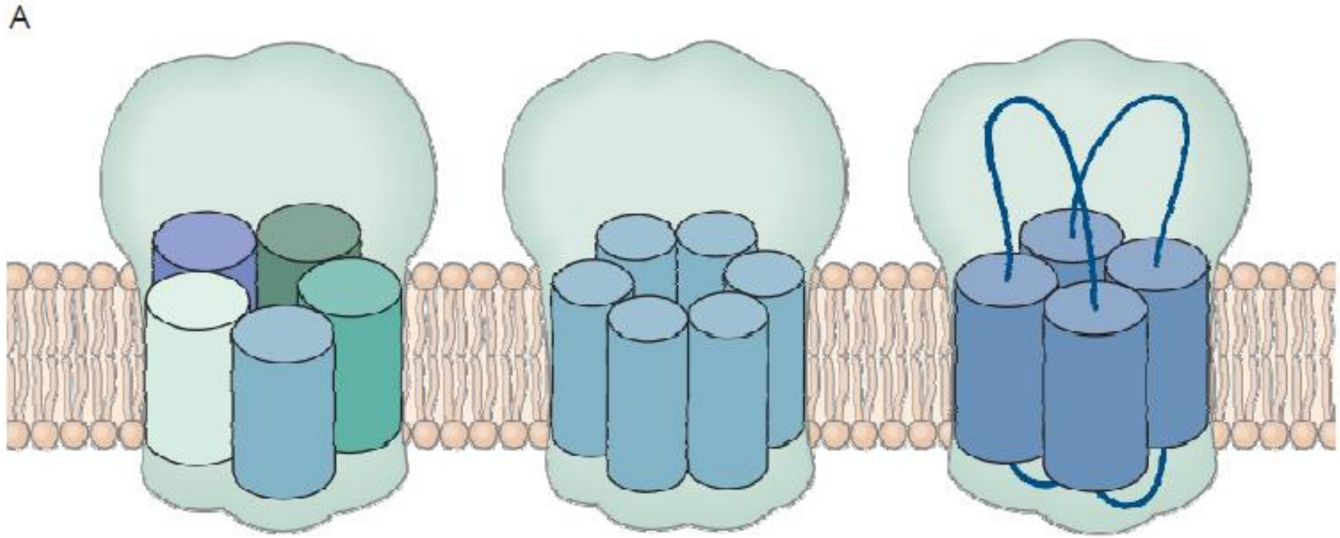
-intrinsic property of the interaction between ligand and channel

GPCR signaling and desensitization

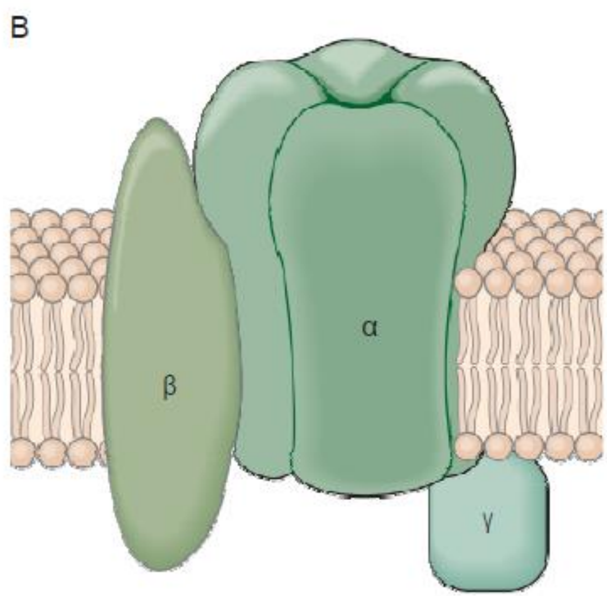


-phosphorylation by protein kinase

Ion channels are integral membrane proteins composed of several subunits

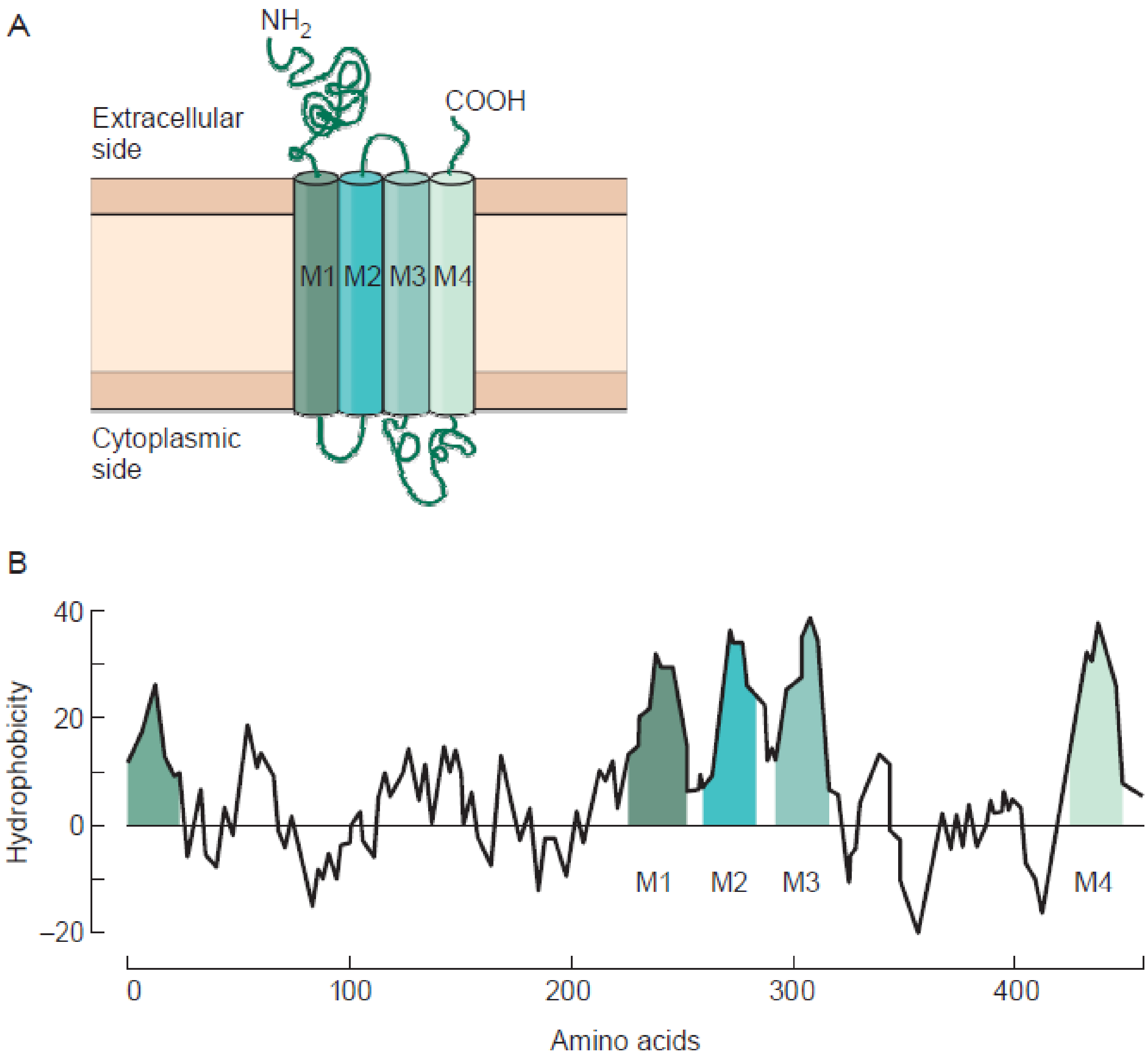


Hetero-oligomer Homo-oligomer Single peptide chain with repeating motifs

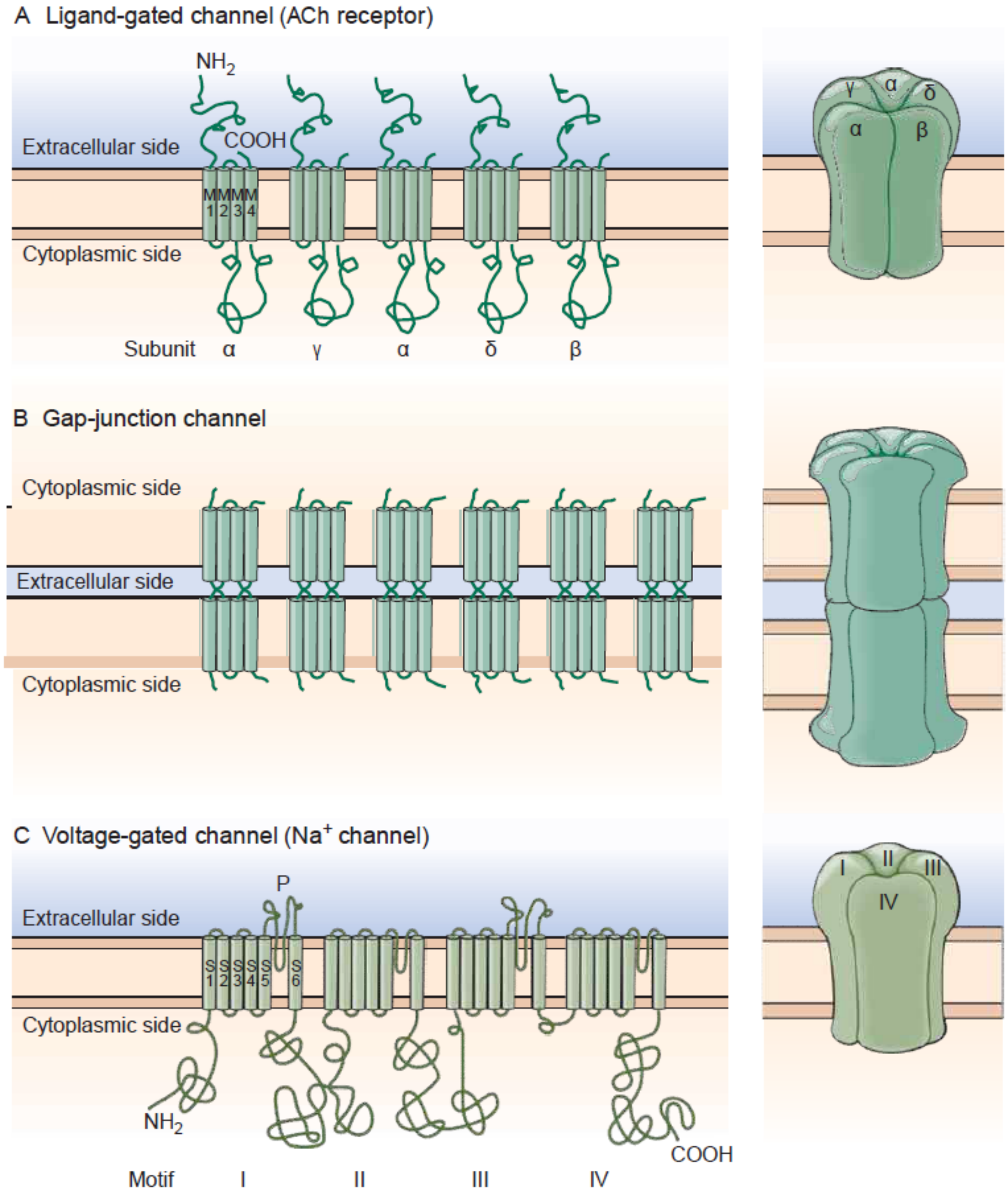


Pore forming subunit (α)
+ auxiliary subunits (β or γ)

The secondary structure of membrane-spanning proteins

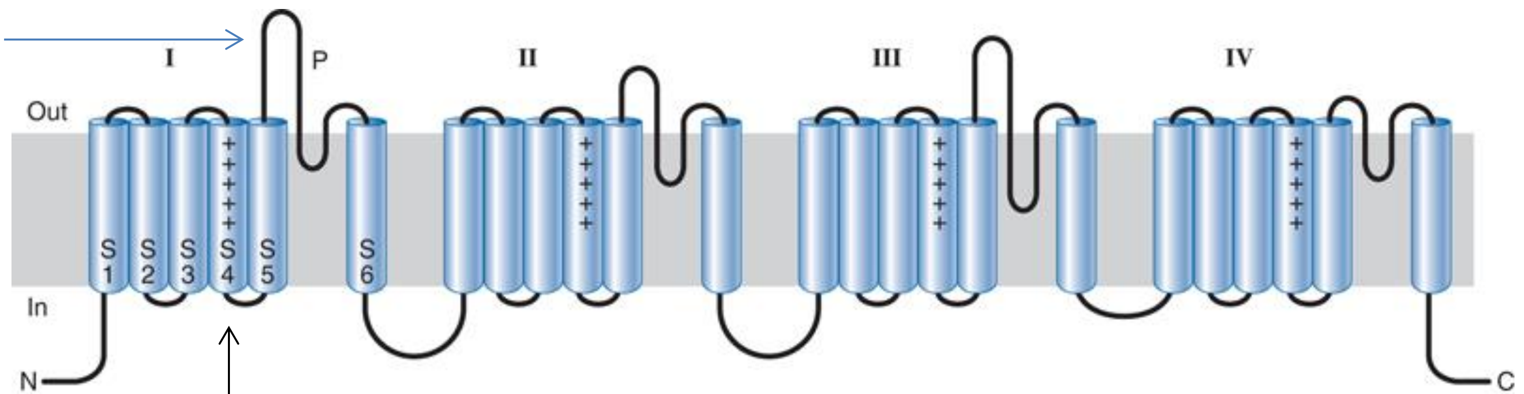


Three superfamilies of ion channel



Voltage-gated Na⁺ channel (α subunit)

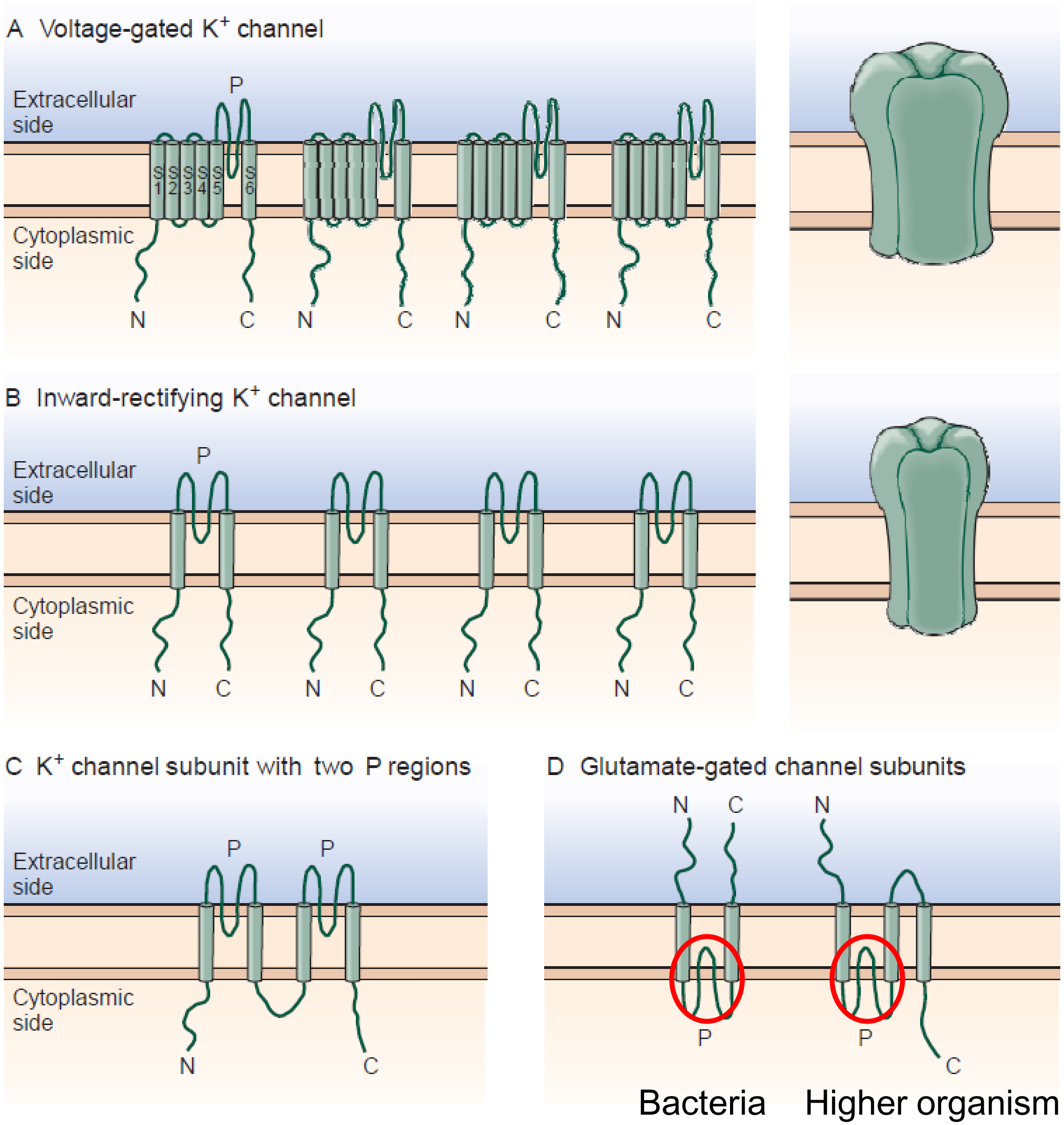
Selectivity filter
(P-region)



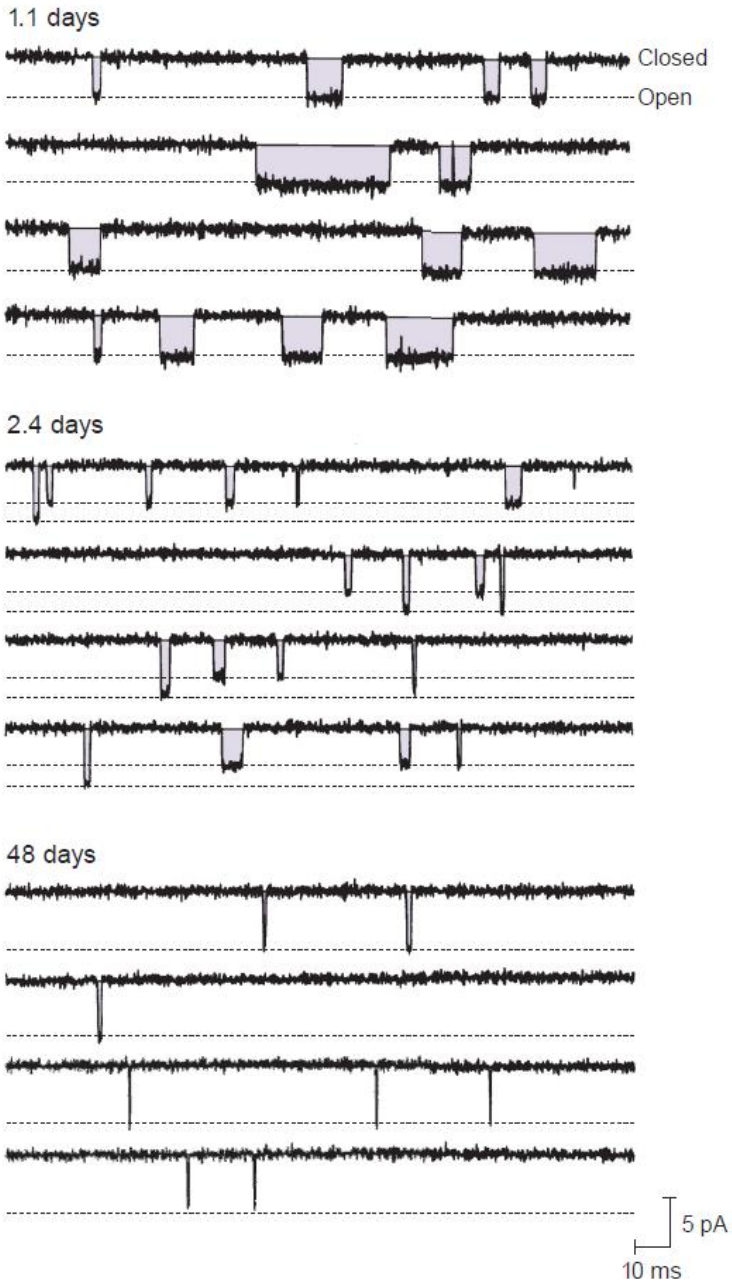
Voltage sensor

-positive amino acids located at every fourth position

Four related families of ion channels with P-regions



nACh receptor channel

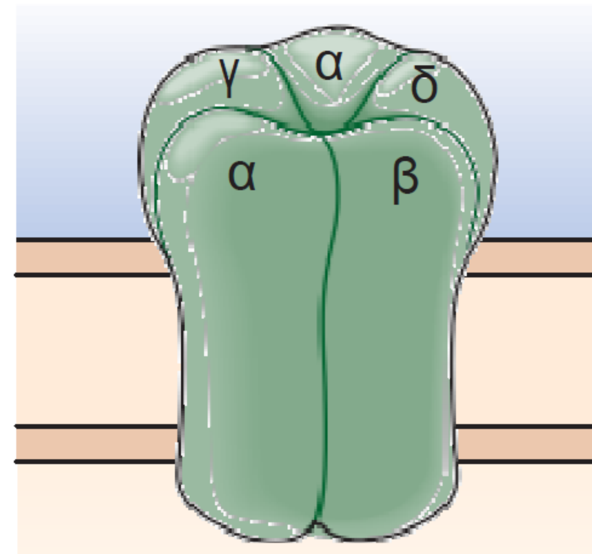


Subunit composition

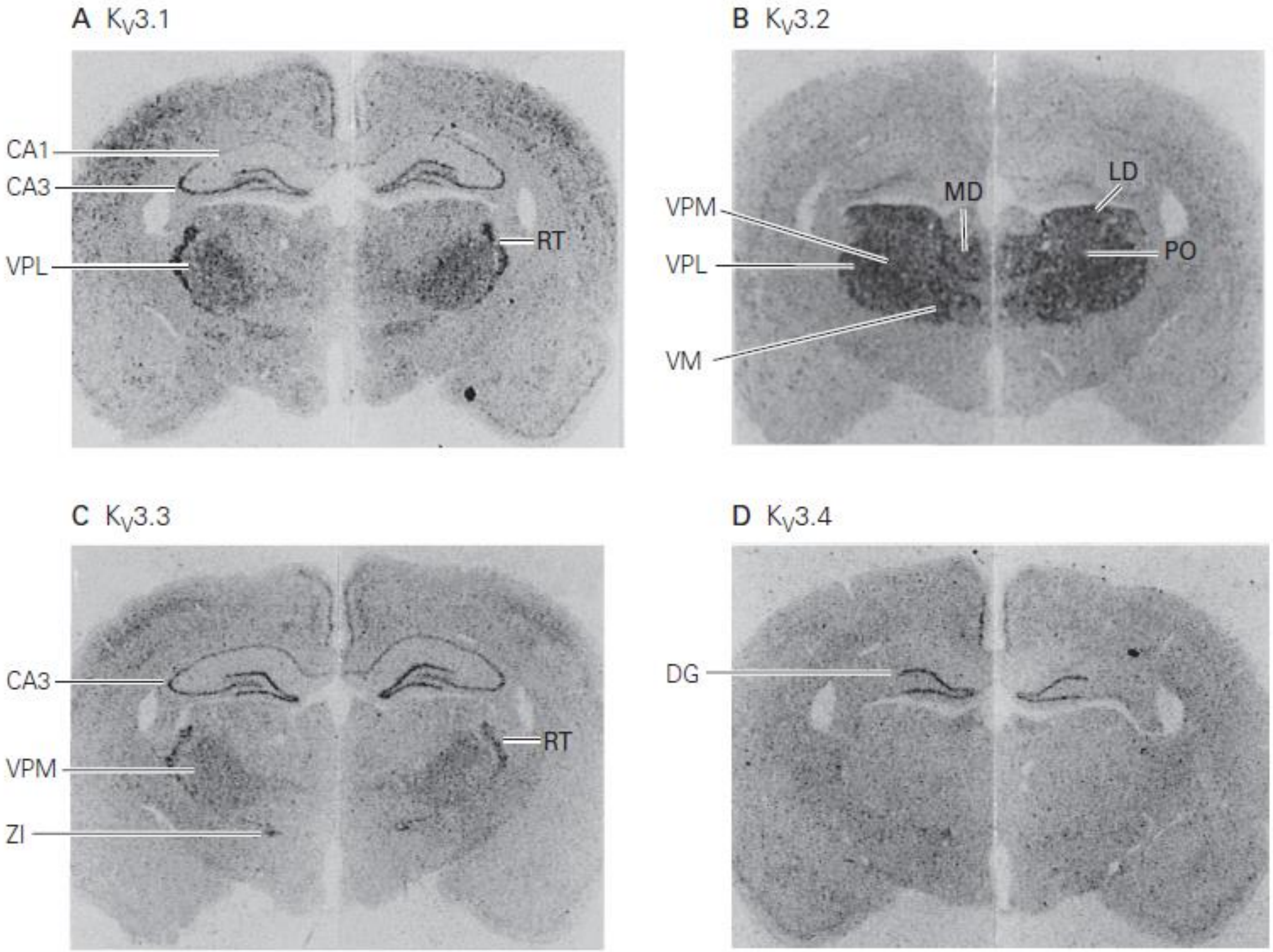
$2\,\alpha\,,\ \beta,\ \gamma\,,\ \delta$

$2\,\alpha\,,\ \beta,\ \gamma\,,\ \delta$
+
$2\,\alpha\,,\ \beta,\ \gamma\,,\ \varepsilon$

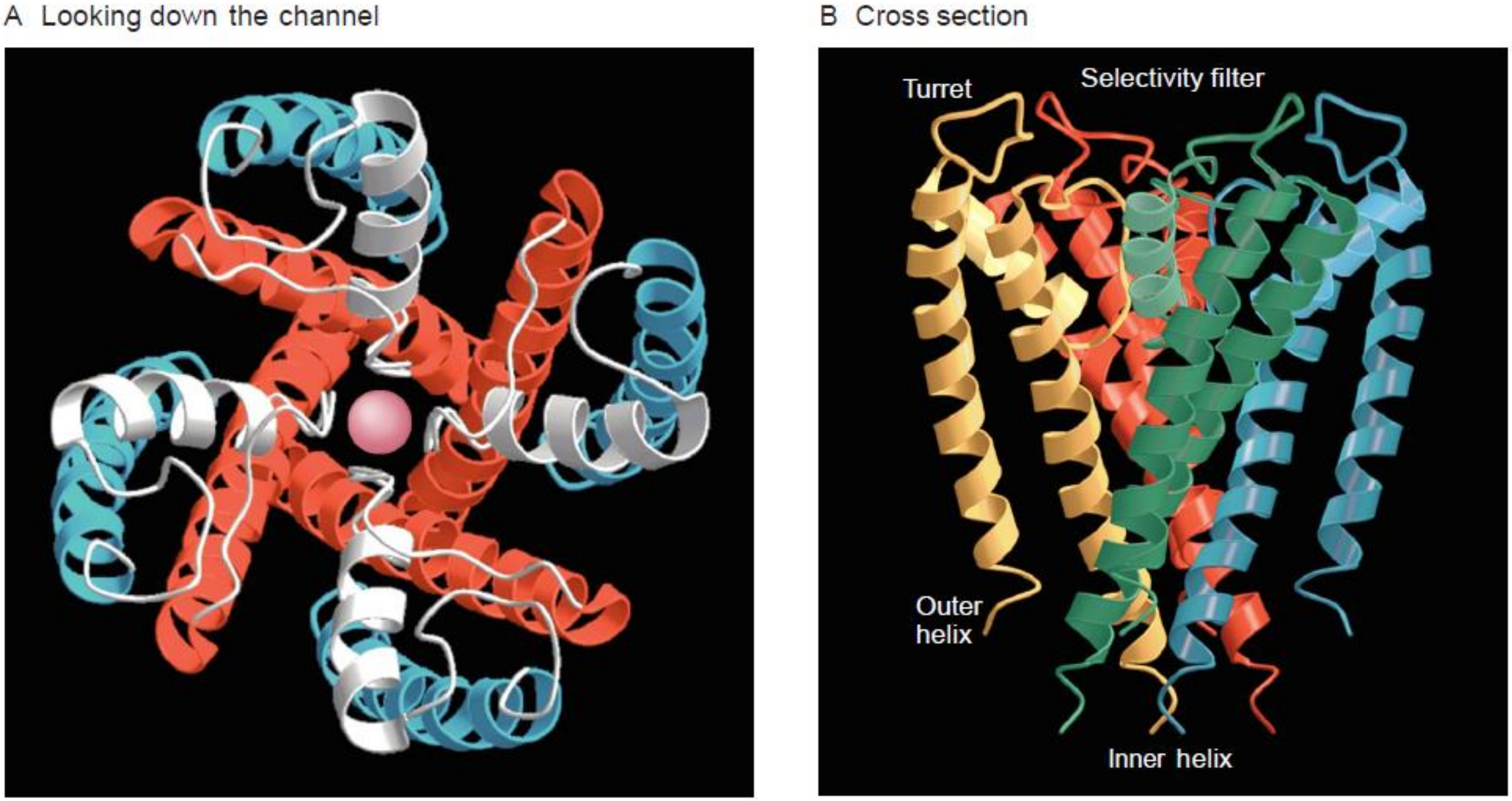
$2\,\alpha\,,\ \beta,\ \gamma\,,\ \varepsilon$

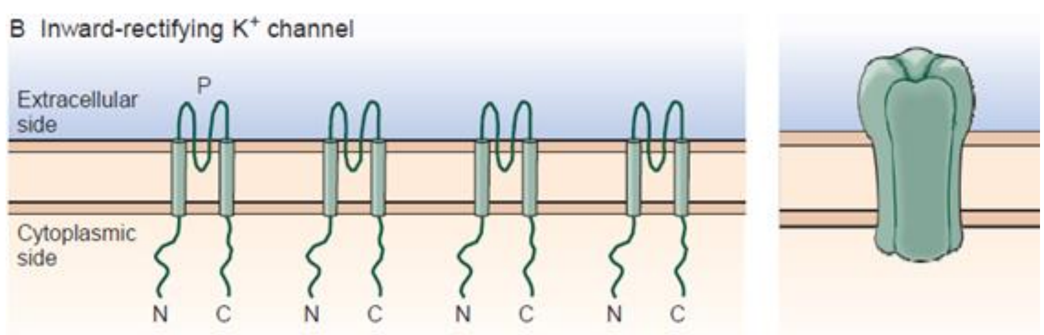


Brain expression patterns of Kv3 channel variants

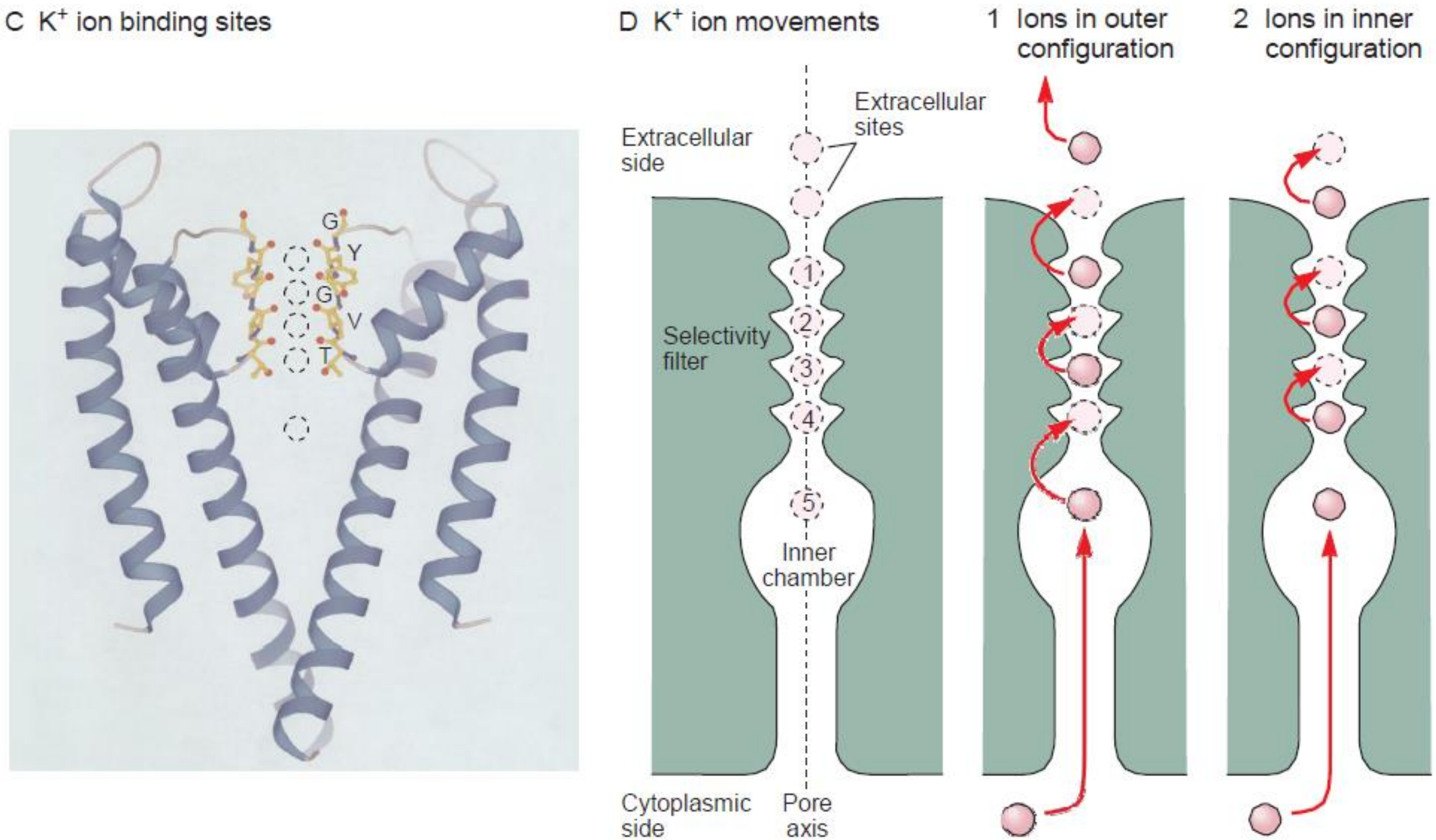


The X-ray crystal structure of a bacterial potassium (KcsA K⁺) channel

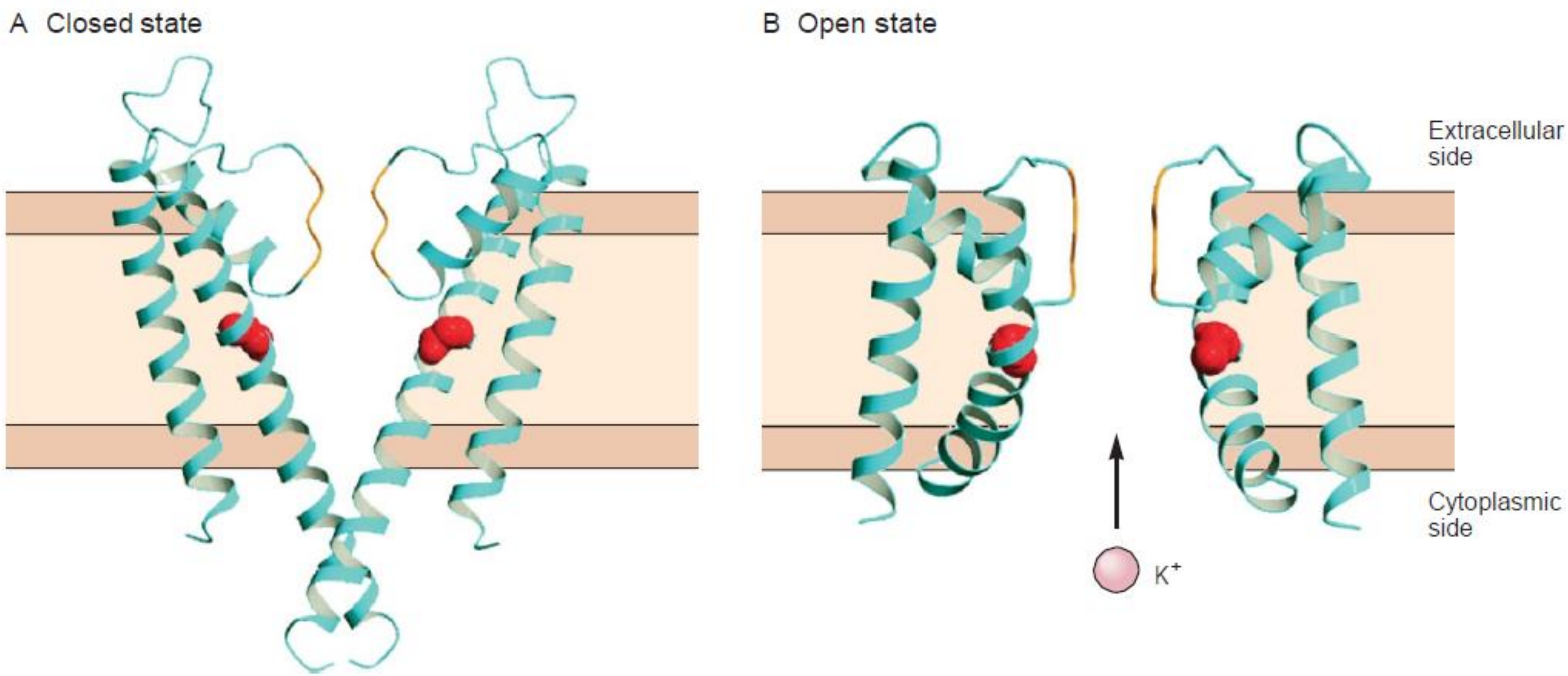




Ion permeation through the KcsA K^+ channel

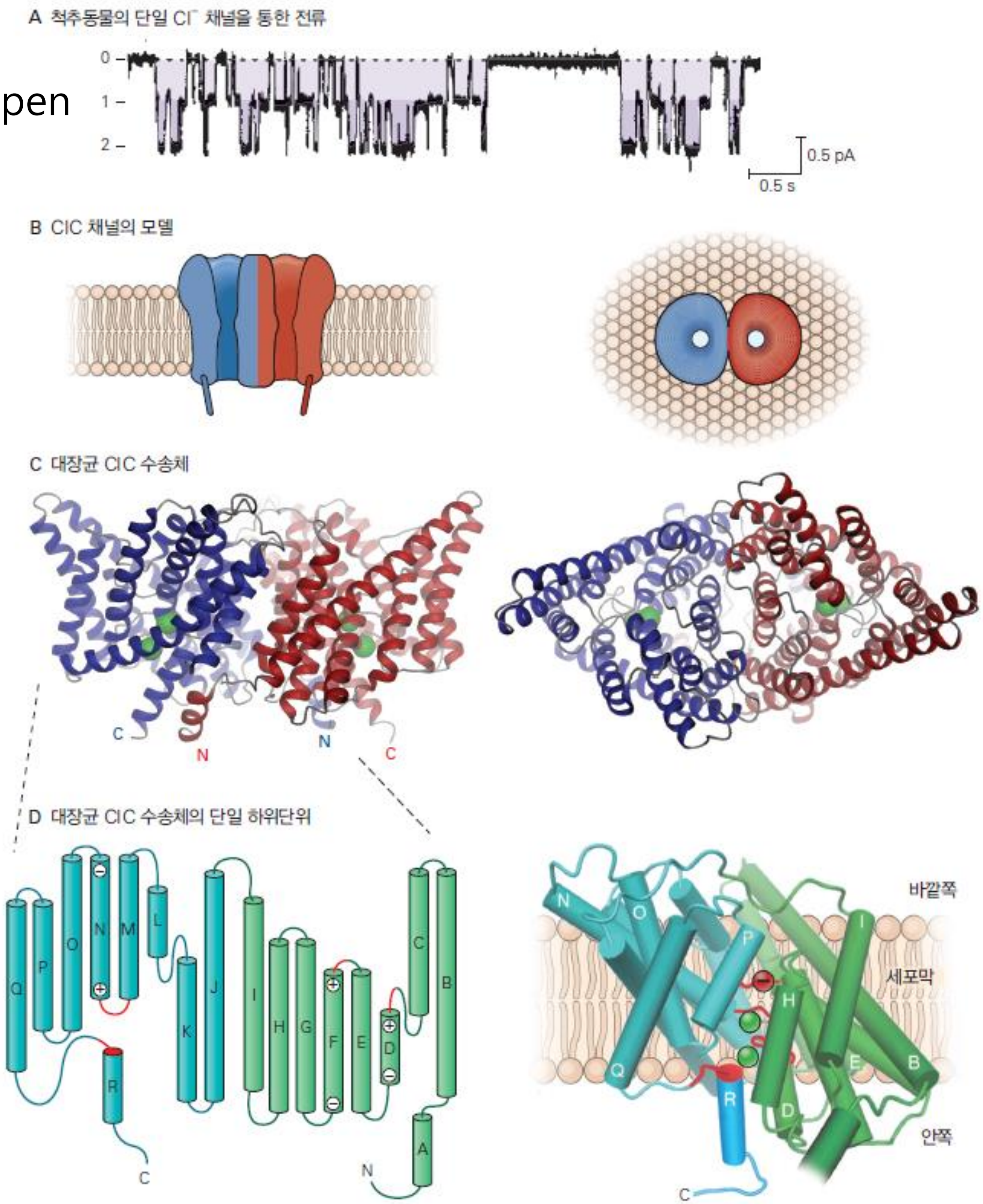


Gating of bacterial potassium (MthK) channels

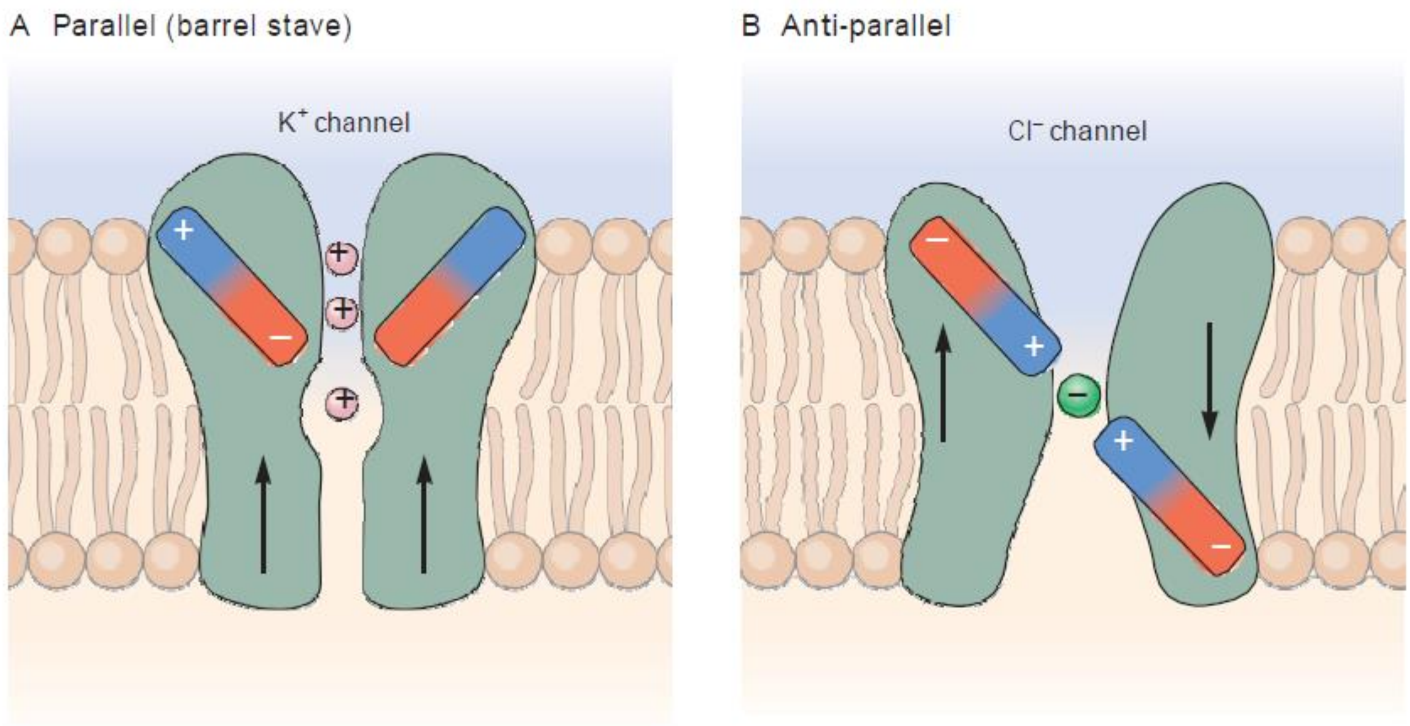


Double-barrel channels: ClC family chloride channels and transporters

Pore open



Comparison of general architectures of potassium and chloride channels



The functional difference between ion channels and pumps