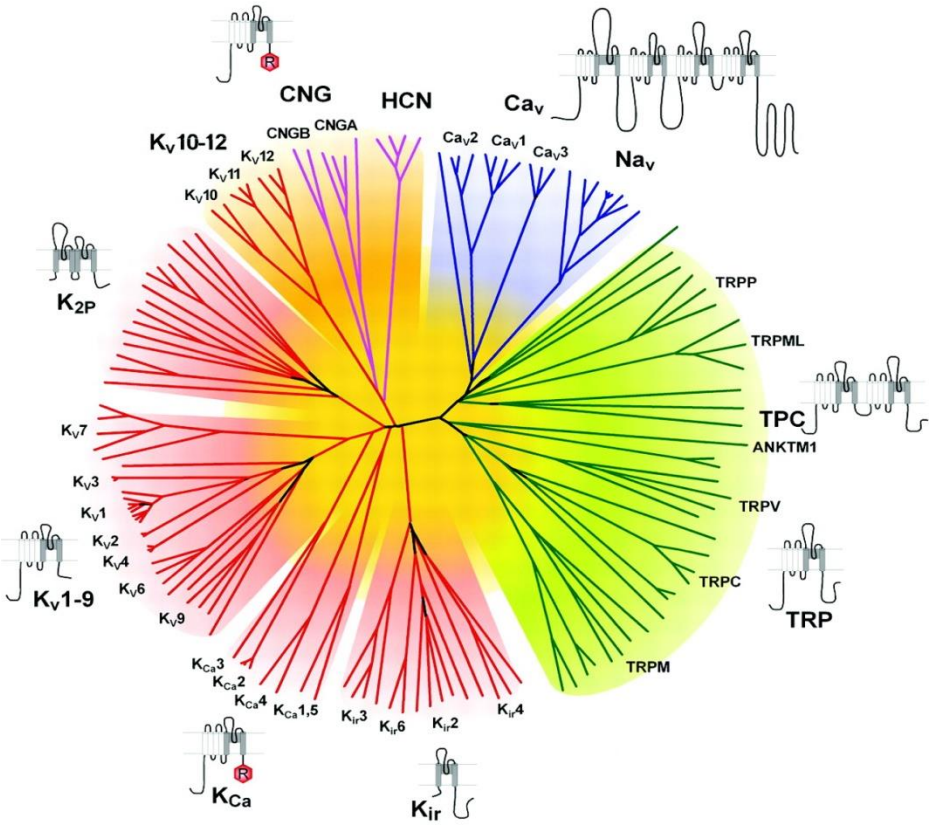
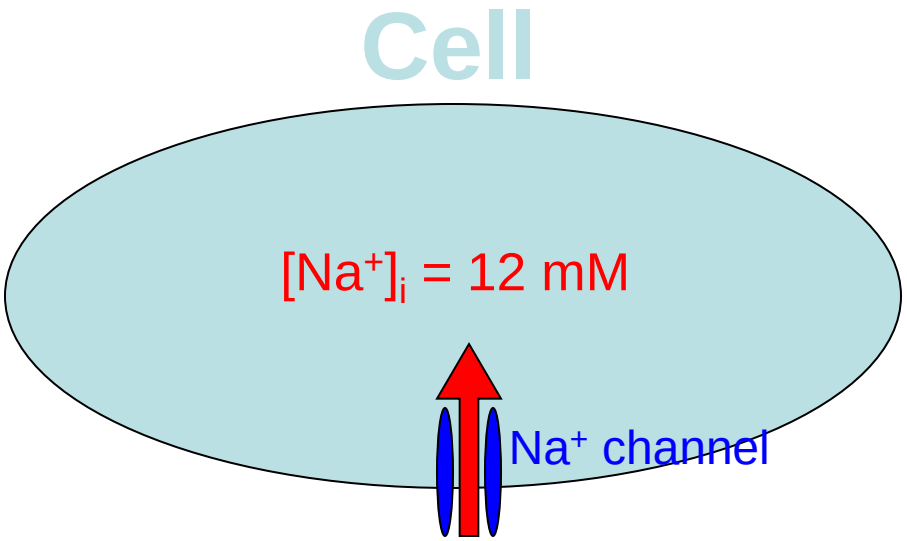


Ion Channel Structure and Function (part 2)

Sodium (Na^+) channels



$V_m \rightarrow$ + 66 mV

$[Na^+]_o$ = 145 mM

Equilibrium (Nernst) potential for Na^+ :

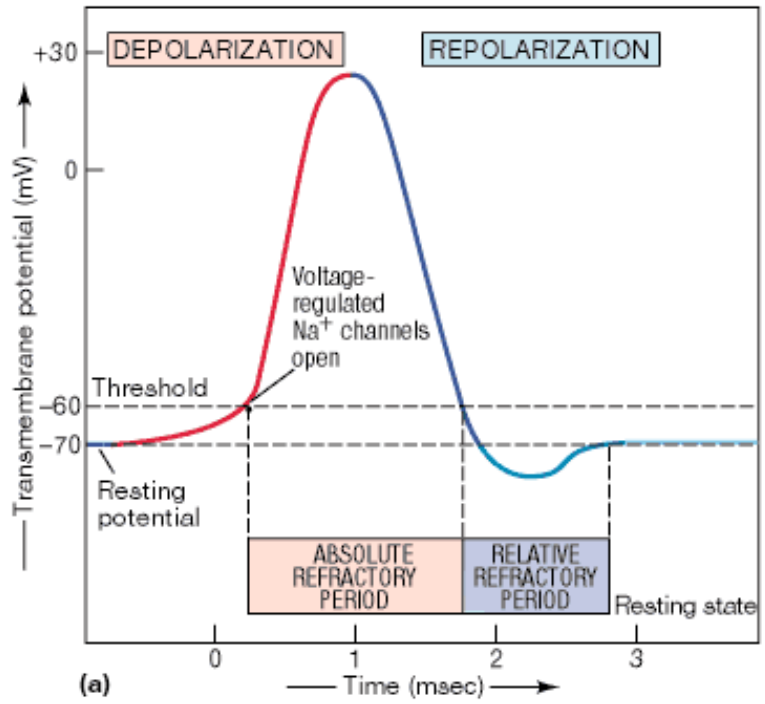
$E_{Na} = RT/zF \{\ln[Na^+]_o/[Na^+]_i\} = 61 \{\log_{10}[Na^+]_o/[Na^+]_i\} = +66$ mV

Na_V, voltage-gated Na^+ channels

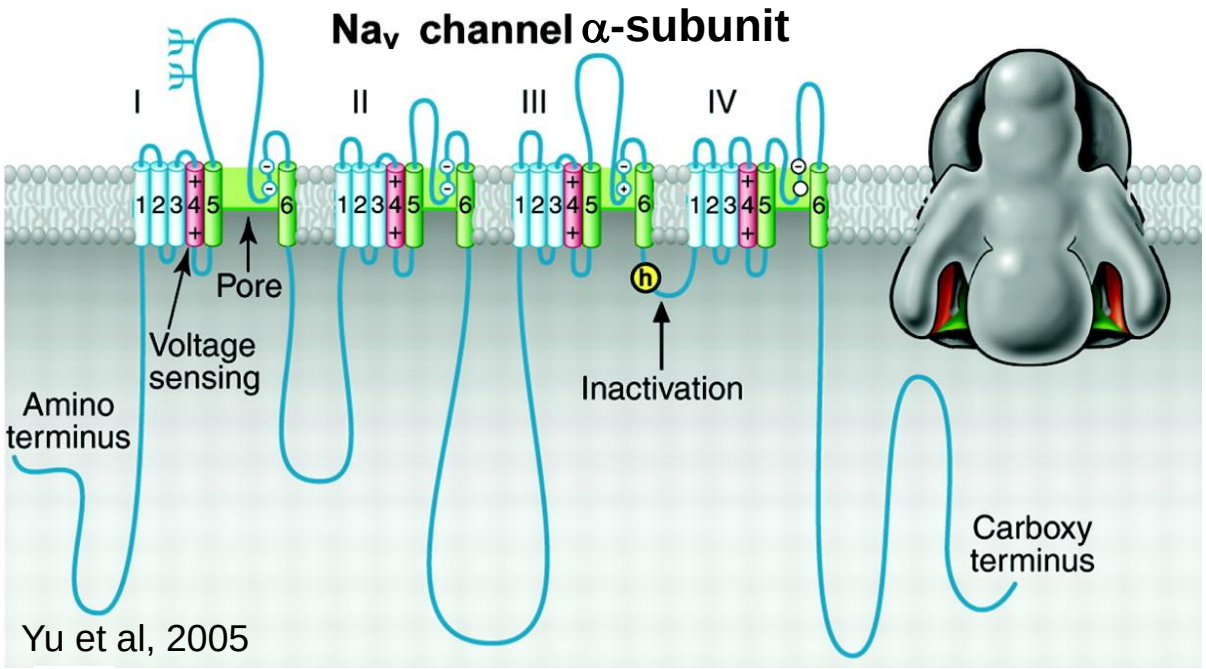
Gating: opened by membrane depolarization, inactivate fast

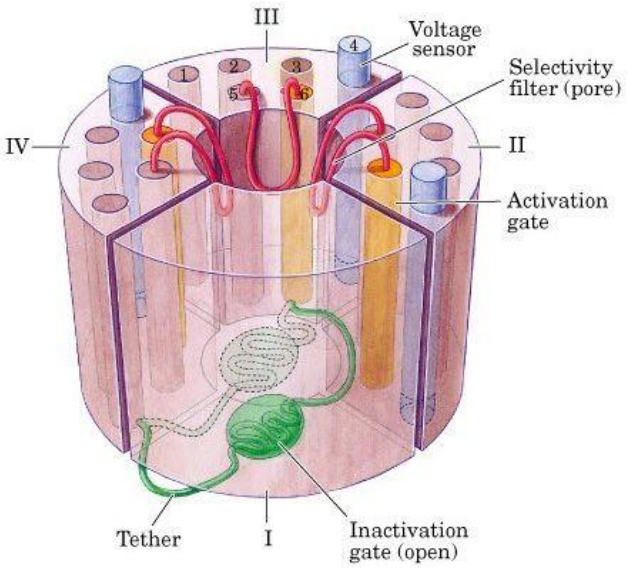
Location: plasma membrane of neurons, skeletal muscle and cardiomyocyte

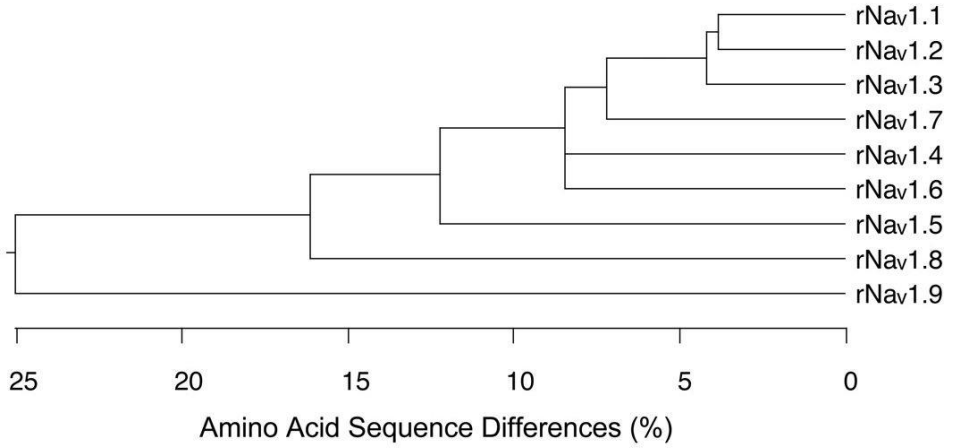
Function: generation of action potential

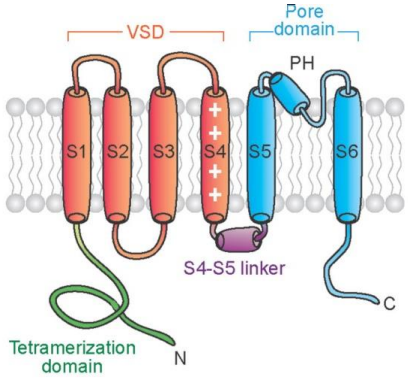


Na_V, voltage-gated Na^+ channels



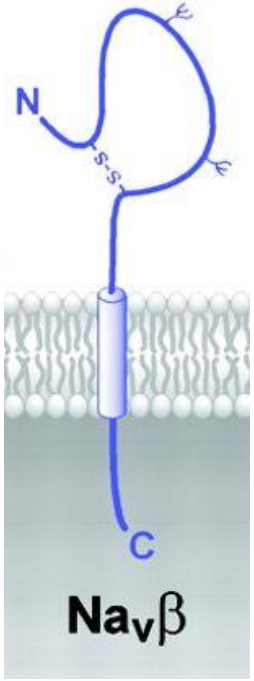


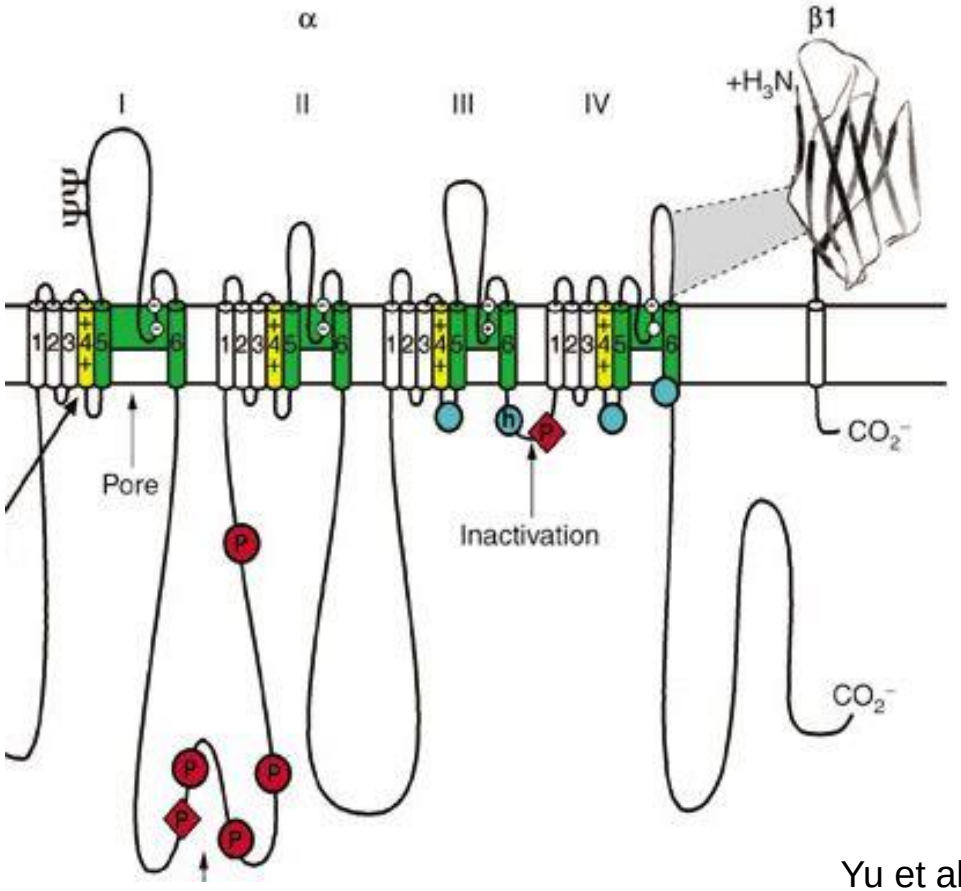




Na_V, voltage-gated Na^+ channels

Auxiliary β-subunit





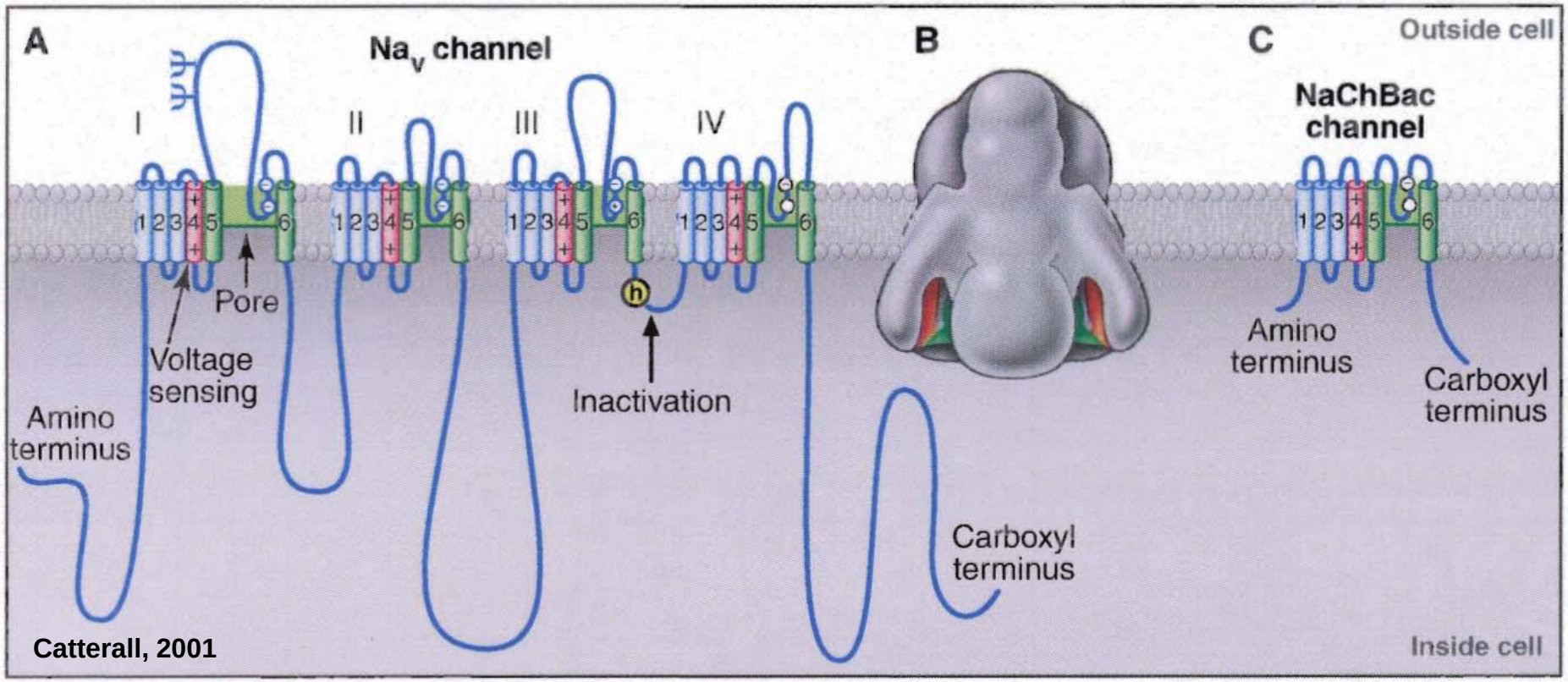
Yu et al, 2003

Navβ1
Navβ2
Navβ3
Navβ4

Na_v channel β-subunits:

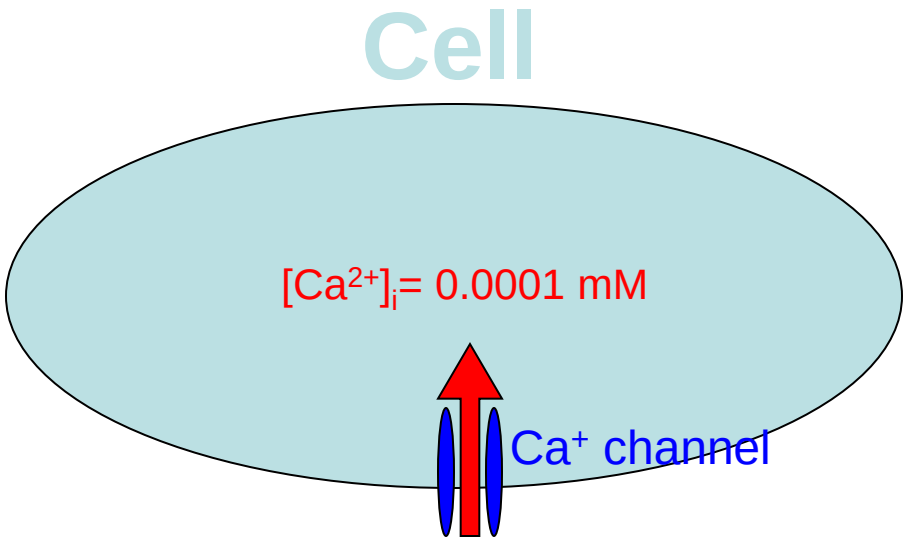
- modulate channel gating
- modulate channel expression
- form links to the intracellular cytoskeleton and extracellular matrix

A 6TM domain voltage-gated Na^+ channel?



NaChBac is a bacterial voltage-gated Na^+ channel that similarly to K_v channels has only 6 transmembrane domains.

Calcium (Ca^{2+}) channels



$V_m \rightarrow$ + 260 mV ???

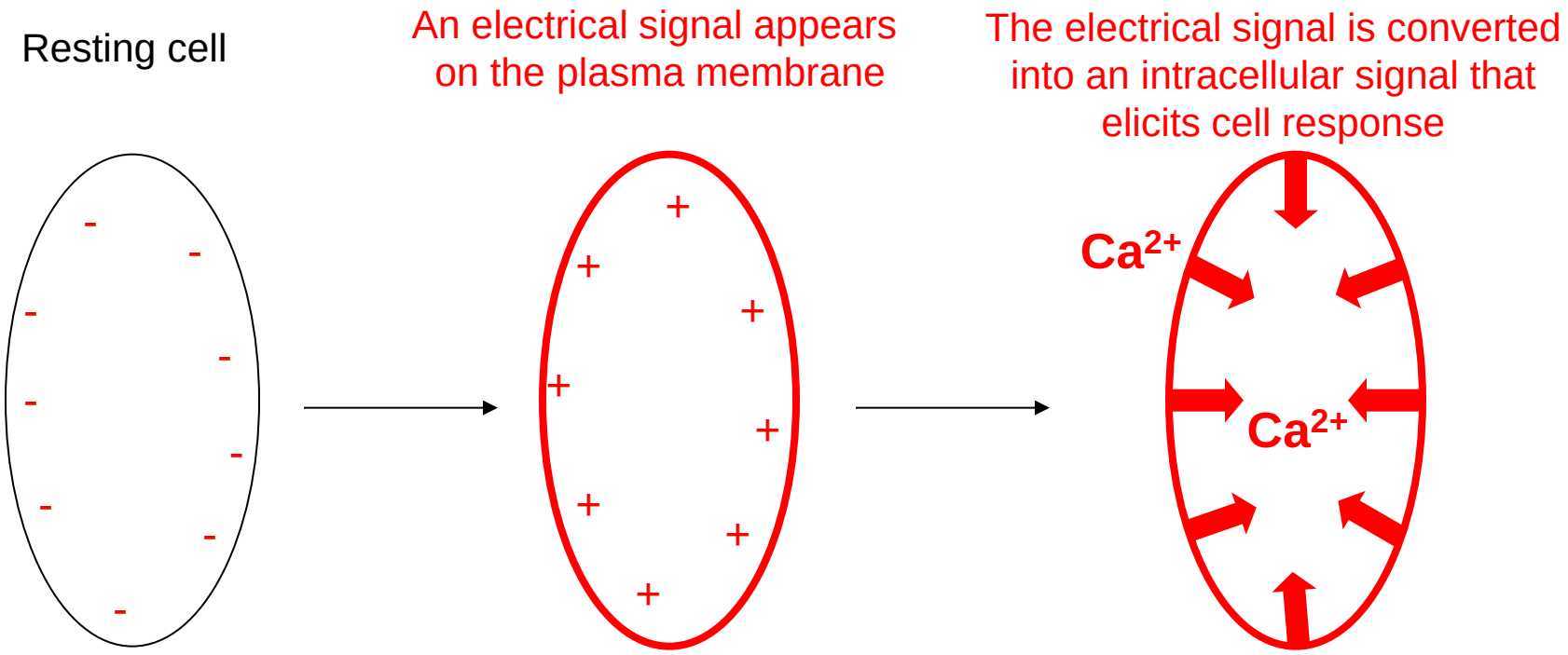
$[Ca^{2+}]_i \rightarrow$ Up

$[Ca^{2+}]_o$ = 1.8 mM

Equilibrium (Nernst) potential for Ca^{+} :

$E_{Na} = RT/zF \{\ln[Ca^{+}]_o/[Ca^{+}]_i\} = 61 \{\log_{10}[Ca^{+}]_o/[Ca^{+}]_i\} = +260$ mV

Voltage-gated Ca^{2+} channels transduce electrical signal into cellular response



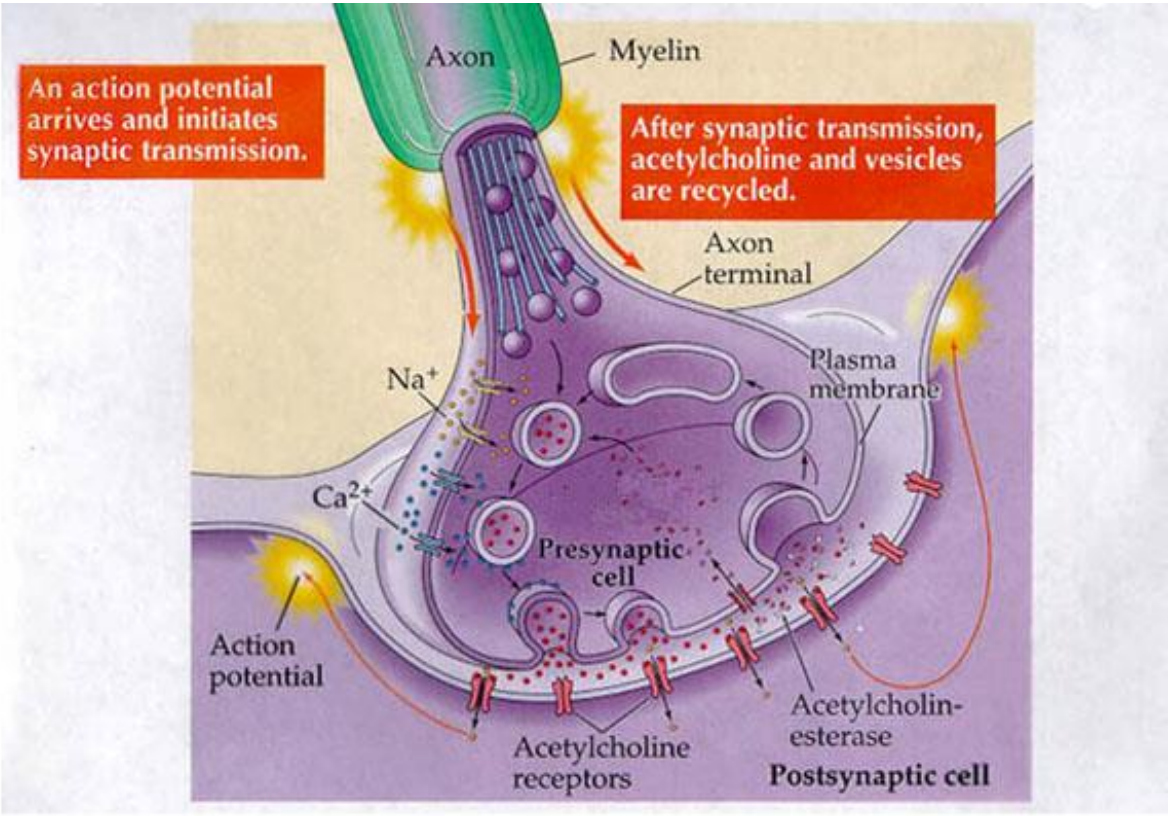
Depolarization opens voltage-gated calcium channels, which leads to elevation of intracellular Ca^{2+} concentration, activation of numerous intracellular signaling pathways and cellular response.

Ca_V, voltage-gated Ca^{2+} channels

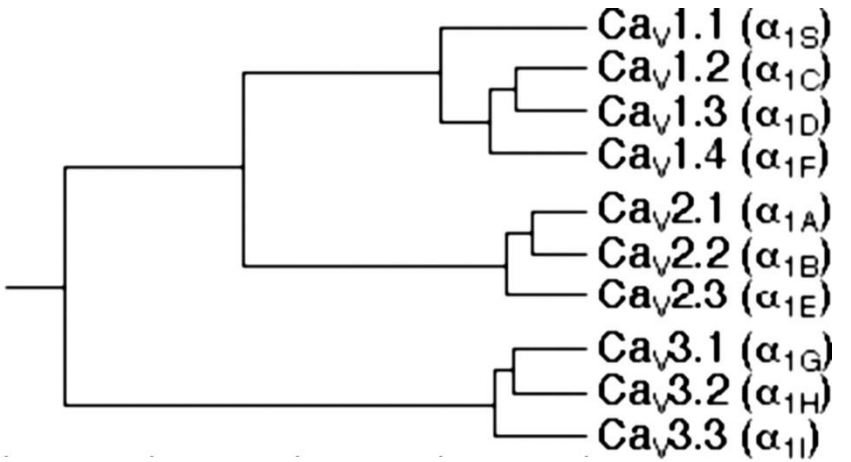
Gating: opened by membrane depolarization, many have robust Ca^{2+}-dependent inactivation

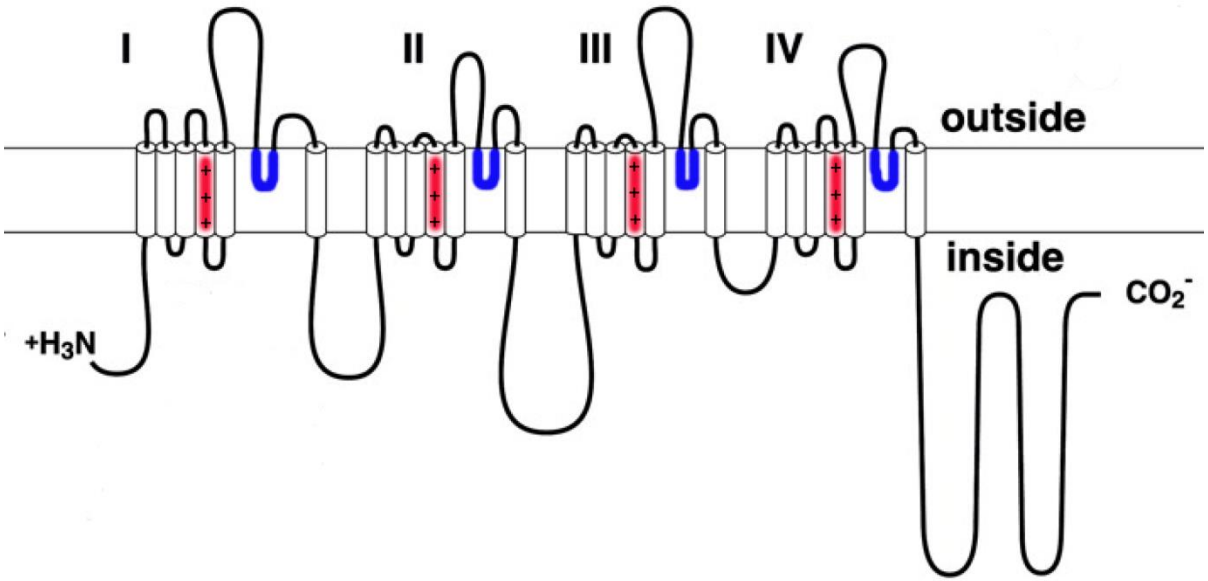
Location: plasma membrane of excitable cells (neurons, muscles) and secretory cells

Function: neurotransmitter release, excitation-contraction coupling, hormone release, regulation of transcription

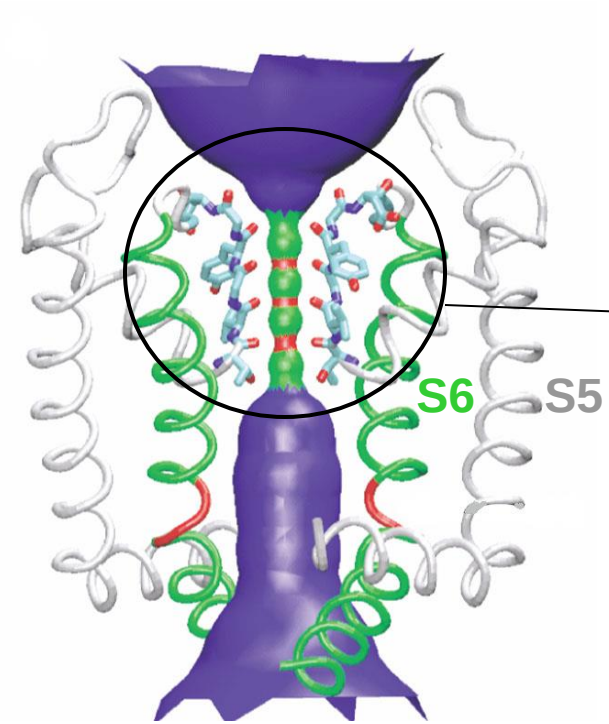


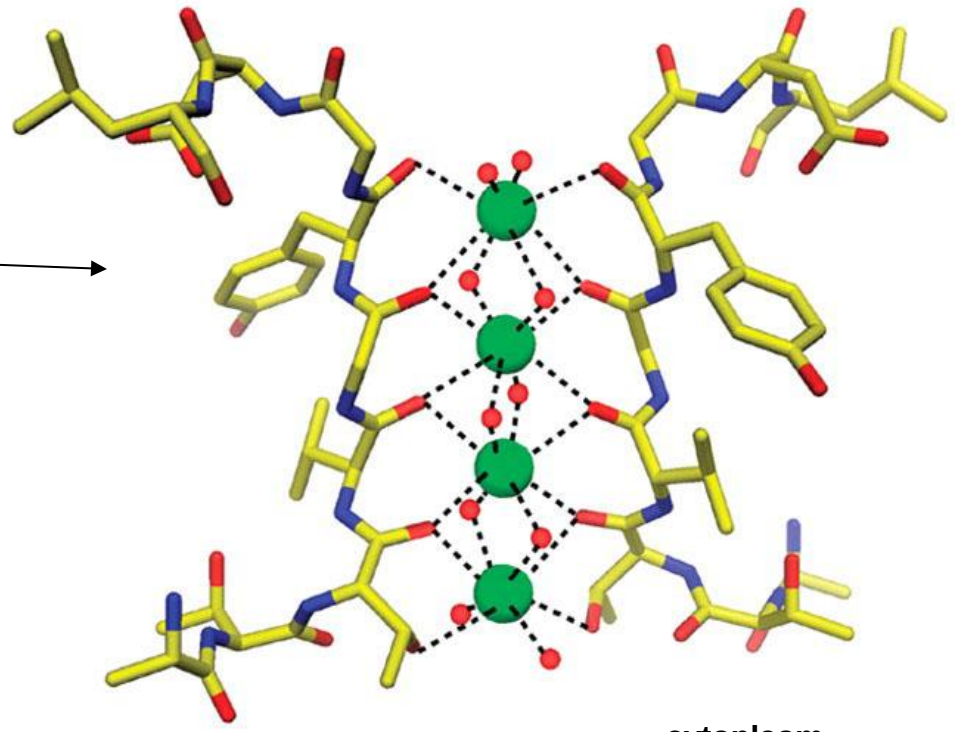
Ca_V, voltage-gated Ca^{2+} channels

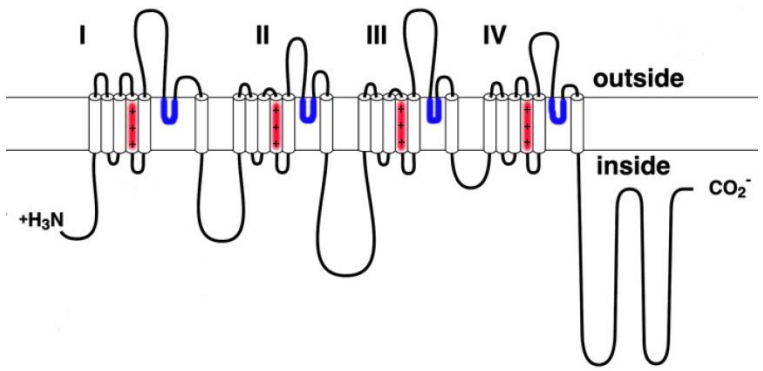




Selectivity of voltage-gated Ca^{2+} channels

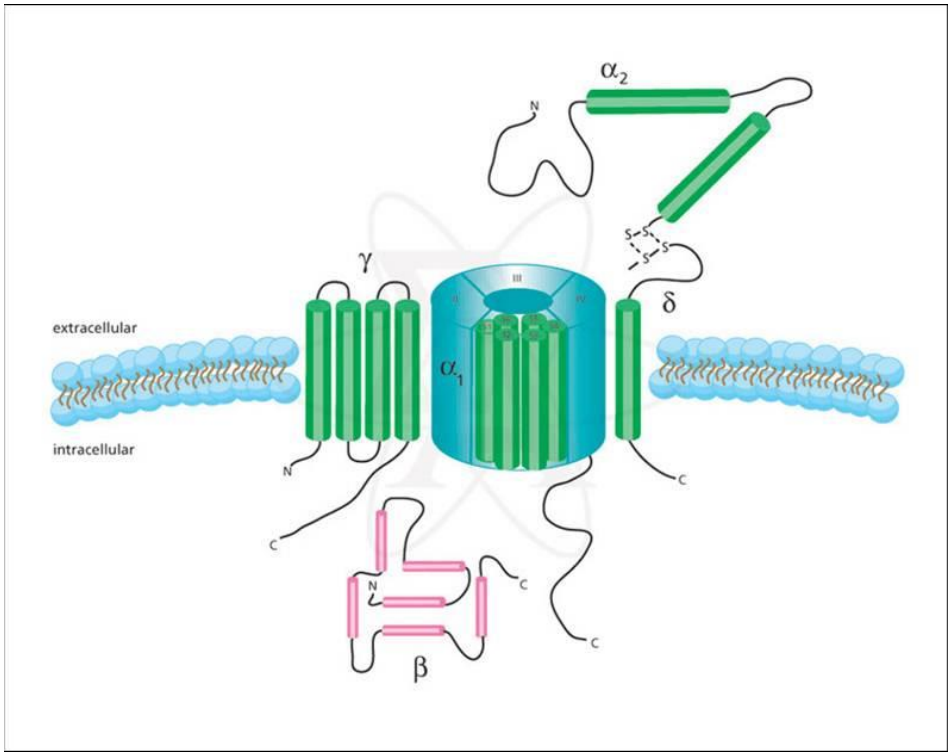






The mechanism of selectivity of Ca_v channels is similar to that of K_v channels: binding of multiple Ca^{2+} ions in the selectivity filter. However, Ca^{2+} ions are hydrated. Na^+ can go through in the absence of Ca^{2+}.

Ca_V, voltage-gated Ca^{2+} channels



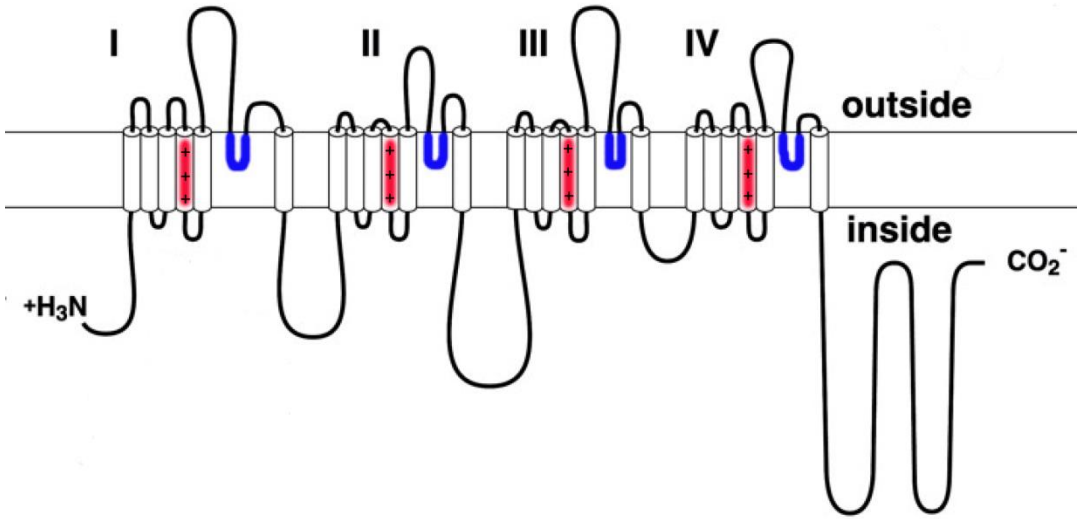
• **α2δ subunits** (α2δ1 - α2δ4) enhances the level of expression of the α1 subunit and causes an increase in current amplitude, faster activation and inactivation kinetics and a hyperpolarizing shift in the voltage dependence of inactivation.

• **β subunits** (β1 - β4) enhance plasma membrane trafficking of the α1 subunit. They also modulates the activation and inactivation kinetics, though different β subunits exhibit different effects on electrophysiological properties of the channel.

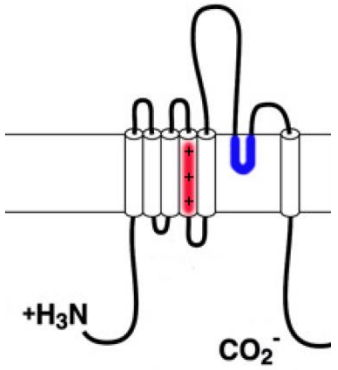
• **γ subunits** (γ1- γ8) inhibit Ca_V channel activity and modulate its activation and inactivation kinetics. Associates with skeletal-muscle Ca_v channels.

Are there 6TM Ca^{2+} channels?

Voltage-gated Ca^{2+} channels (Ca_v)



CatSper1 - 4

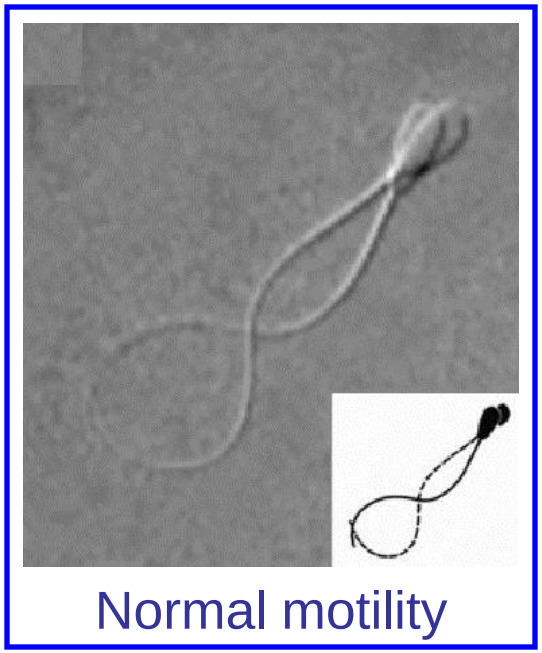


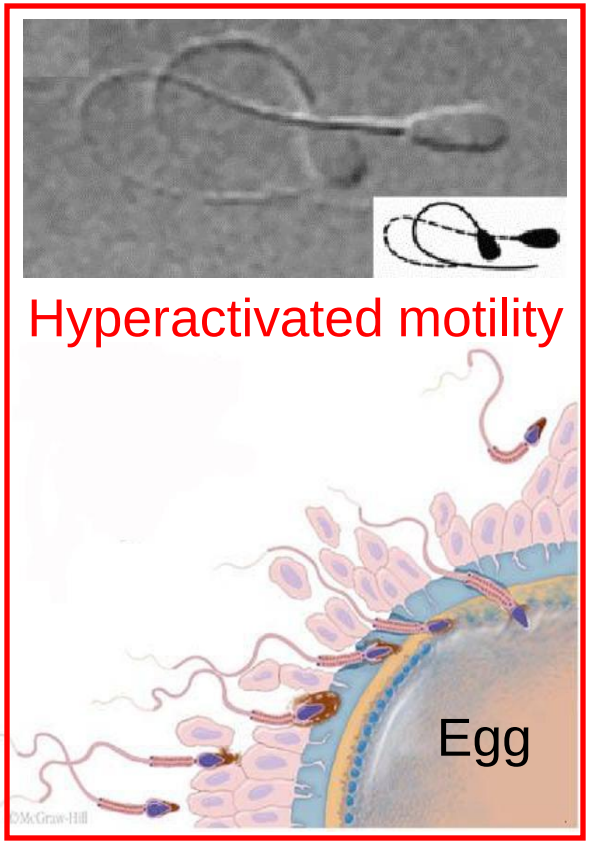
CatSper channel

Gating: activated by intracellular alkalinization, and female steroid hormone progecterone

Location: plasma membrane of sperm flagellum

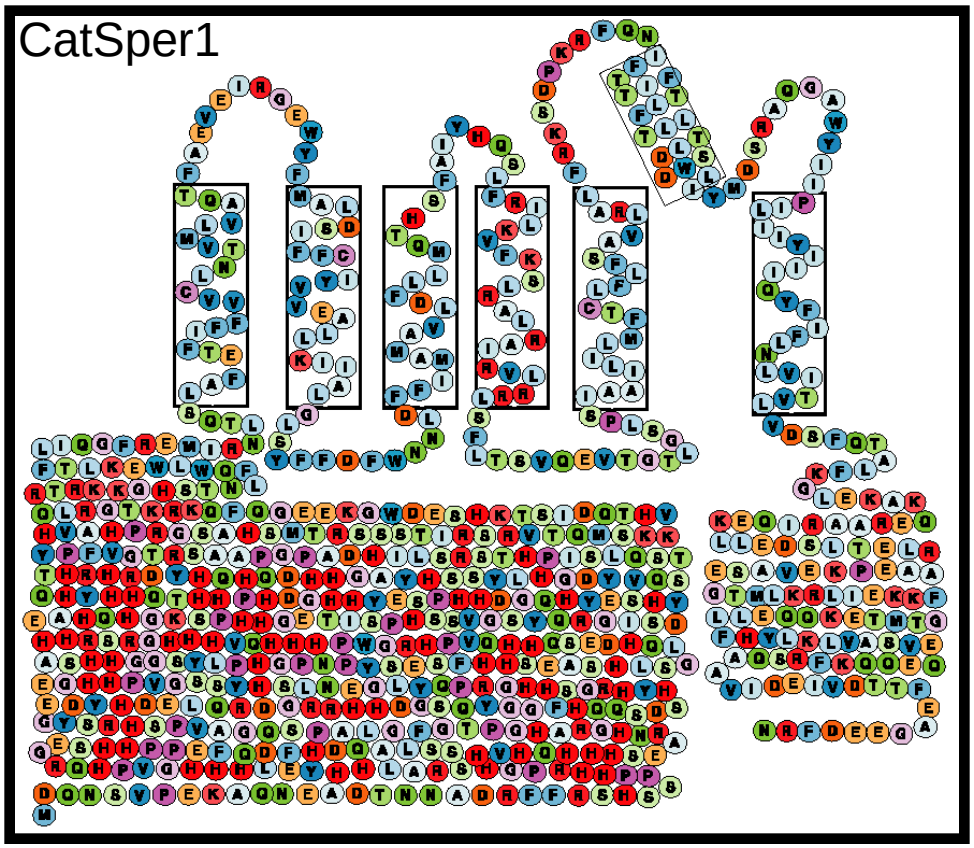
Function: the main pathway for Ca^{2+} entry into sperm cells, required for sperm hyperactivation and male fertility.

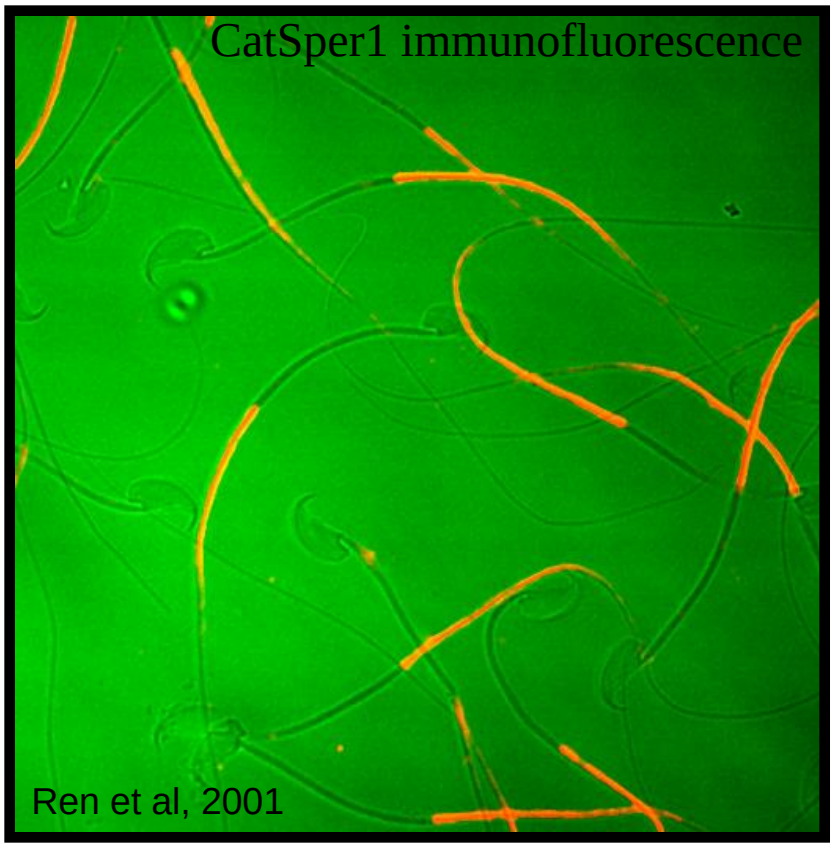




Suarez et al.

CatSper channel





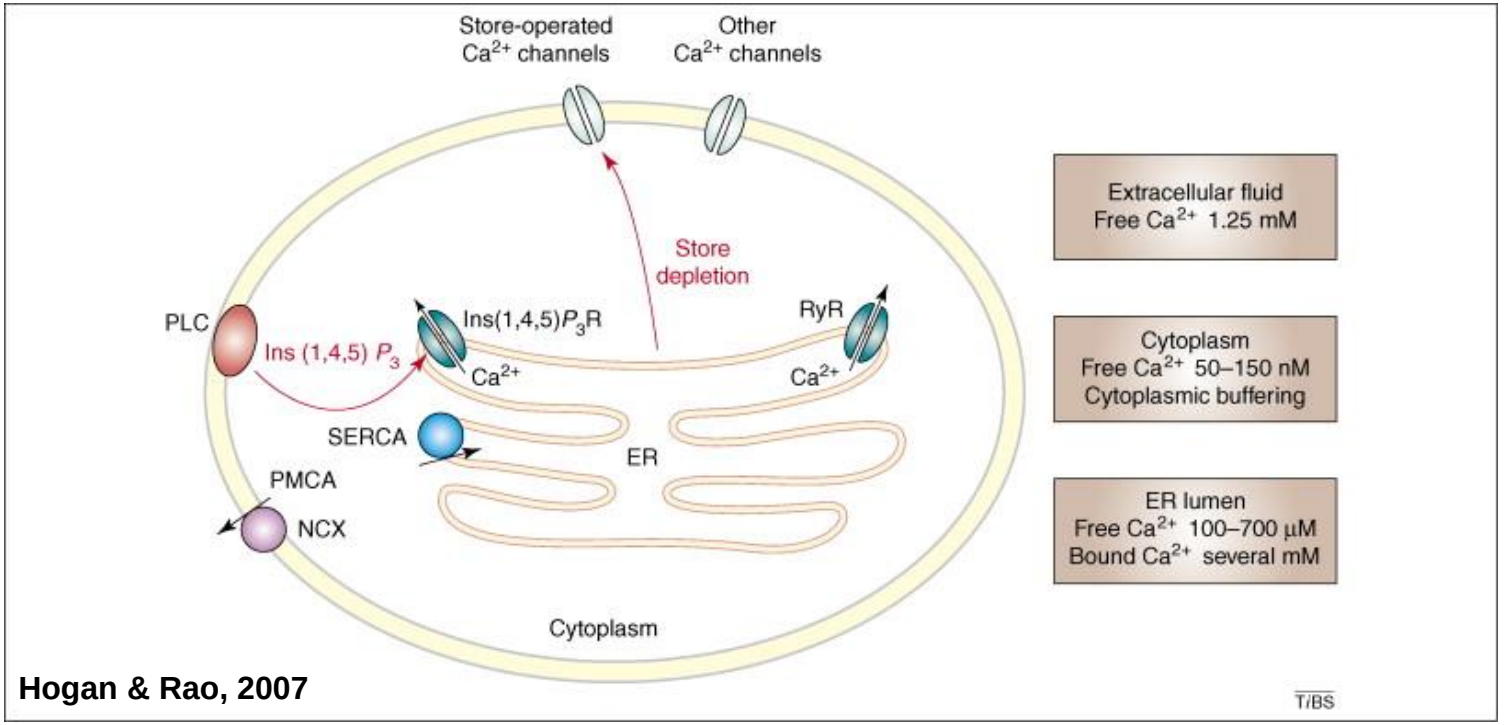
- There are four CatSper subunits: CatSper1 – 4.
- All four subunits are required for formation of the functional CatSper channel in the membrane of the sperm flagellum. Thus the CatSper channel is a hetero-tetrameric channel.

Calcium Release-Activated Calcium (CRAC) channel

Gating: opened by depletion of intracellular Ca^{2+} stores (endoplasmic reticulum)

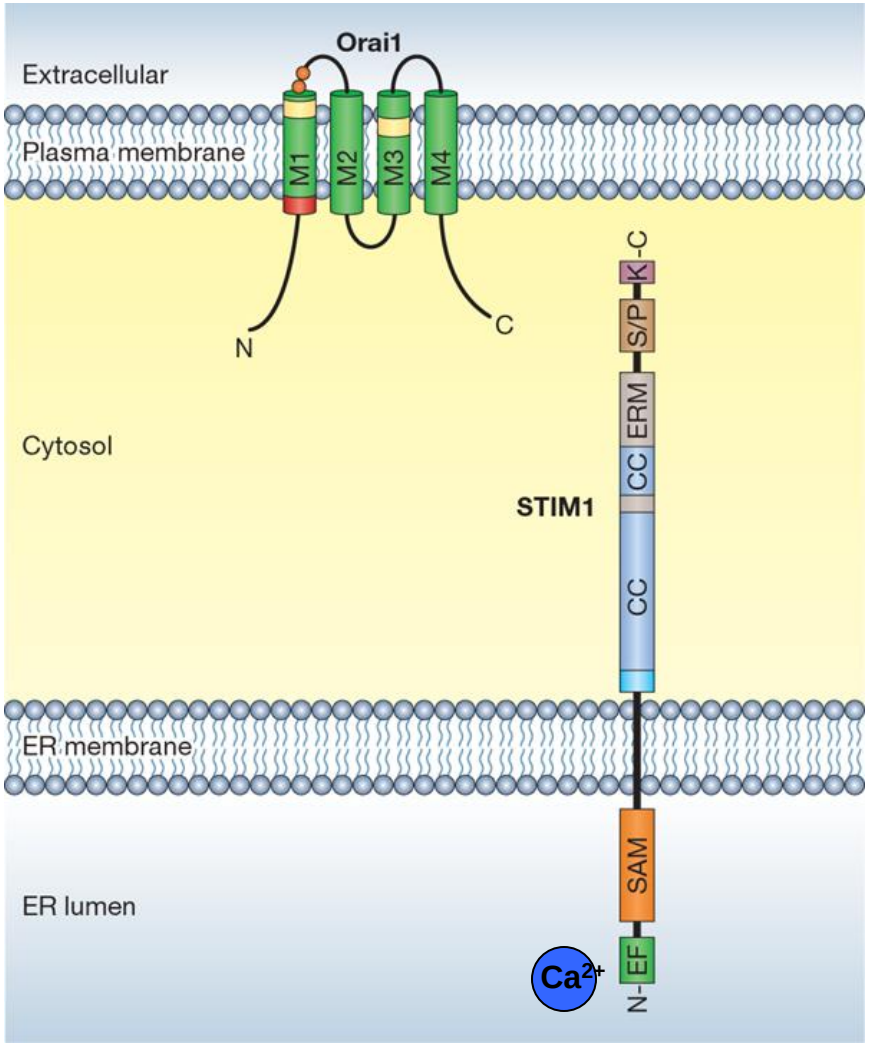
Location: plasma membrane of non-excitable cells (though CRAC presence in excitable cells cannot be excluded)

Function: **the main pathway for Ca^{2+} entry into non-excitable cells,** replenishment of intracellular Ca^{2+} stores, triggering exocytosis and regulation of transcription

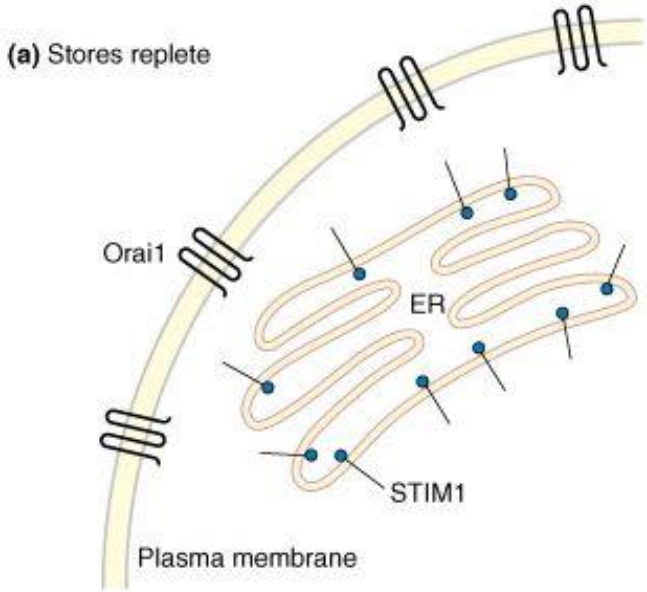


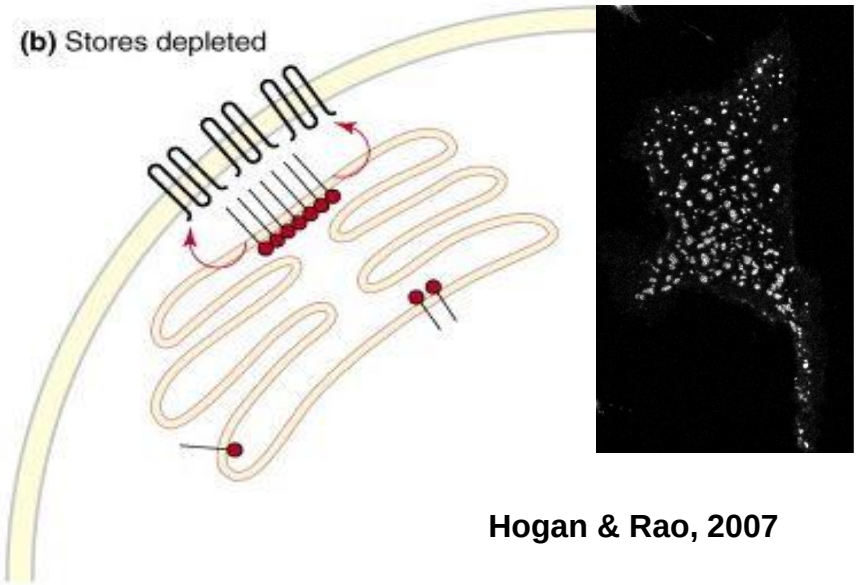
Hogan & Rao, 2007

Calcium Release-Activated Calcium (CRAC) channel



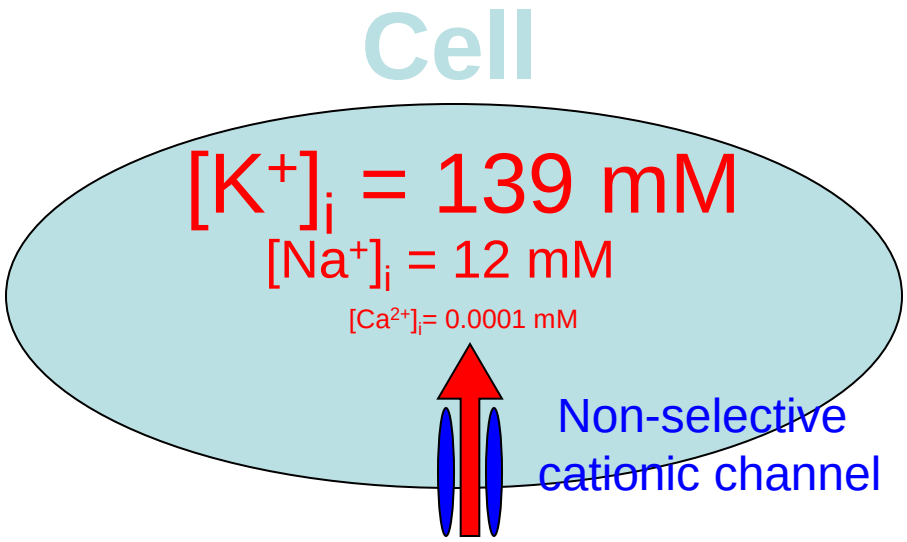
Lewis, 2007





Hogan & Rao, 2007

Non-selective cationic channels



$V_m \rightarrow$ depolarization

$[Ca^{2+}]_i \rightarrow$ up

Cyclic nucleotide-gated channels

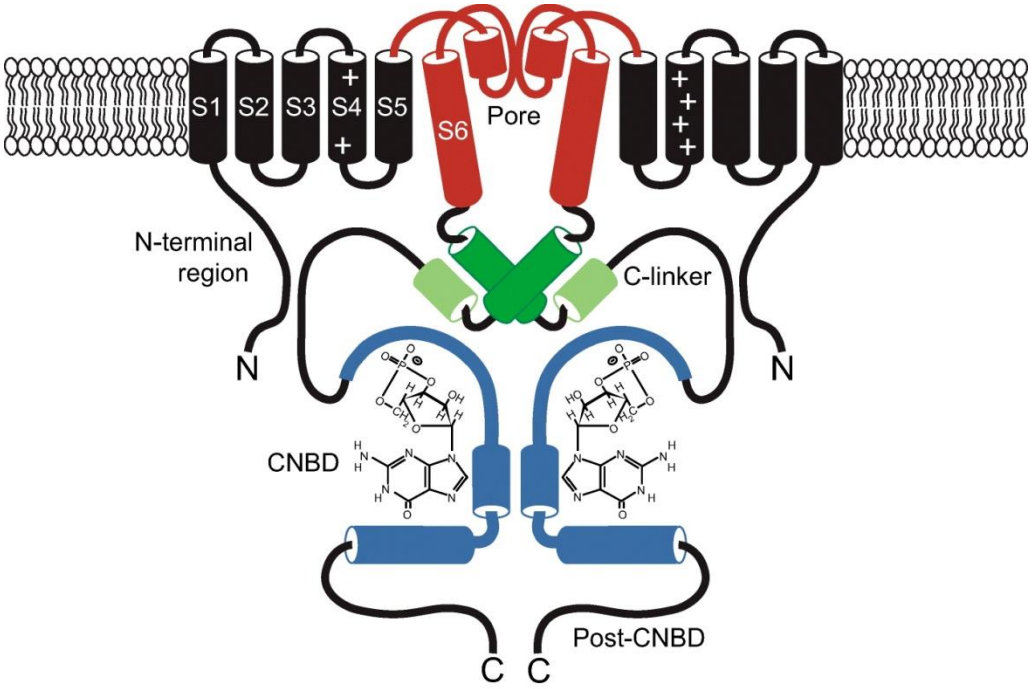
- There are two groups of channels in this family: cyclic nucleotide-gated (CNG) channels and hyperpolarization-activated cyclic nucleotide-modulated (HCN) channels

Gating: HCN channels are activated by membrane hyperpolarization, and intracellular cAMP can further enhance the activation. CNG channels are activated by intracellular cyclic nucleotides (cAMP and cGMP) and very weakly by membrane depolarization.

Location: plasma membrane of photoreceptor and olfactory receptor (CNG); plasma membrane of heart pacemaker cells and neurons (HCN).

Function: CNG channels play key role in sensory transduction of the photoreceptor and olfactory receptor; HCN channels control heart rate, mediate pacemaker activity in nervous system, and contribute to determination of neuronal resting potential.

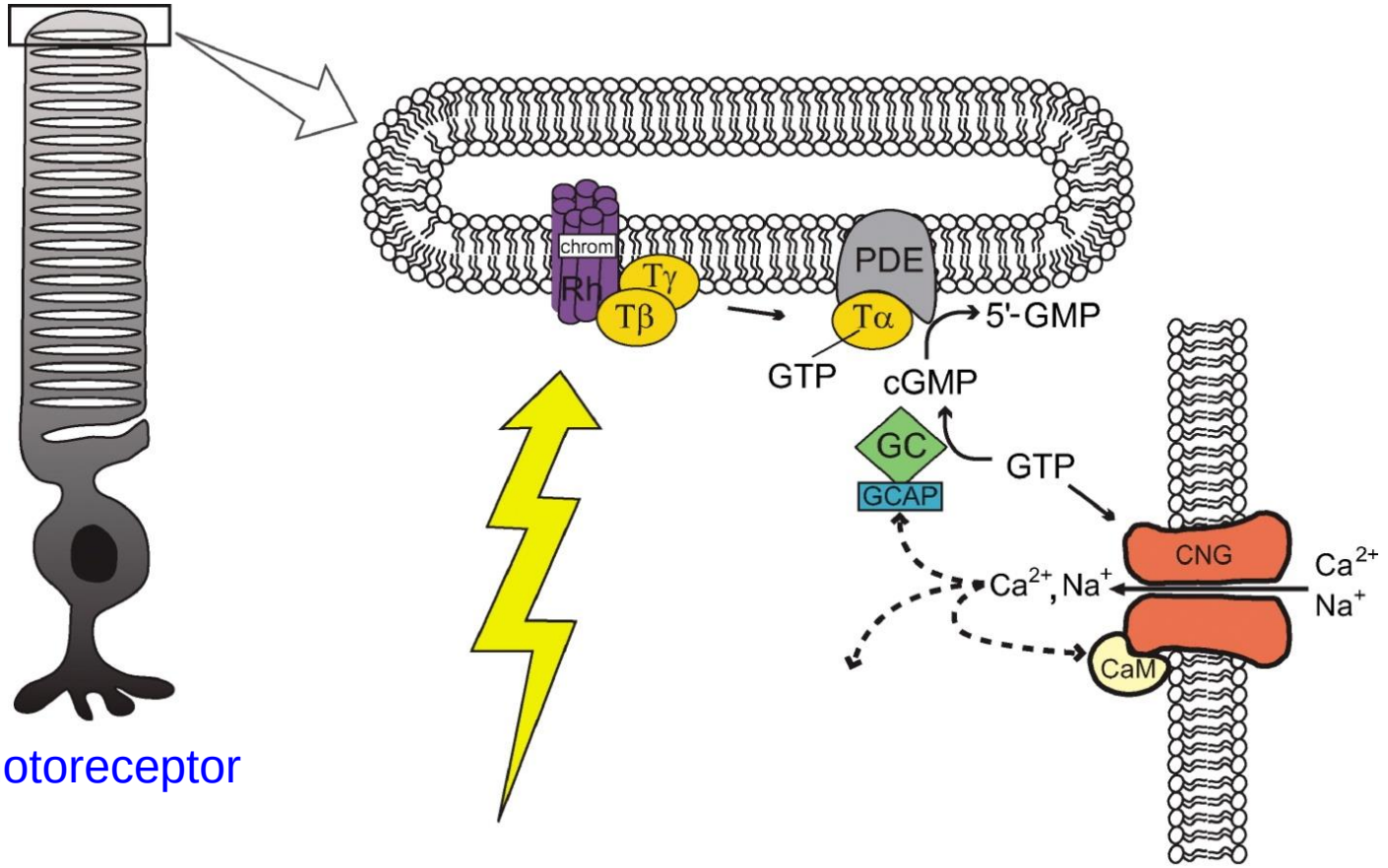
Cyclic nucleotide-gated channels



Craven KB, Zagotta WN. 2006.
Annu. Rev. Physiol. 68:375–401

- There are six CNG subunits: CNGA1- 4, CNGB1 and CNGB3
- There are four HCN subunits: HCN1 - 4
- The functional channel is homo- or hetero-tetramer of either CNG or HCN subunits.

Cyclic nucleotide-gated channels



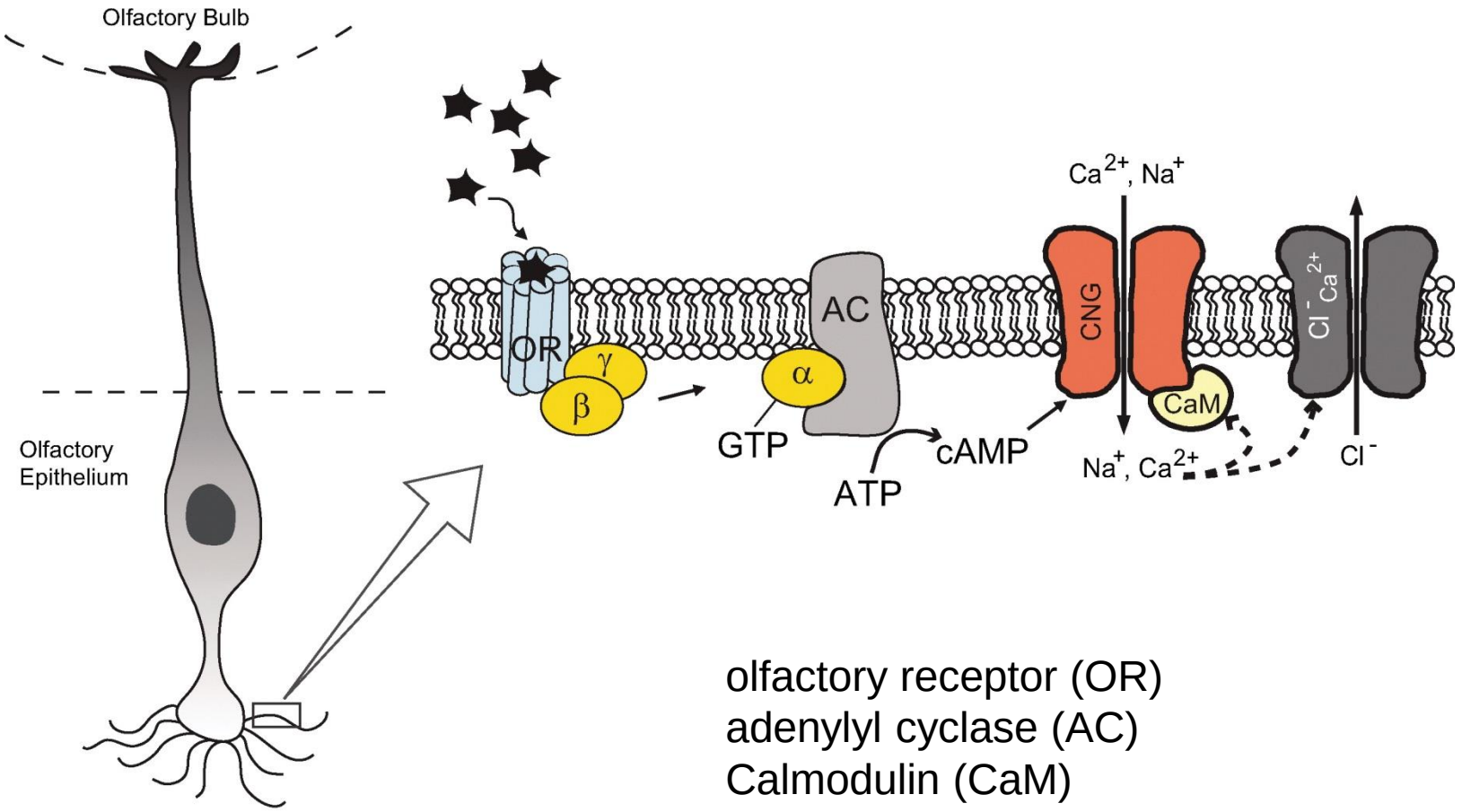
Photoreceptor

Craven KB, Zagotta WN. 2006.
Annu. Rev. Physiol. 68:375–401

rhodopsin (Rh)
G-protein transducin (T)
phosphodiesterase (PDE)

guanylyl cyclase (GC)
guanylyl cyclase–activating protein (GCAP)
CaM calmodulin

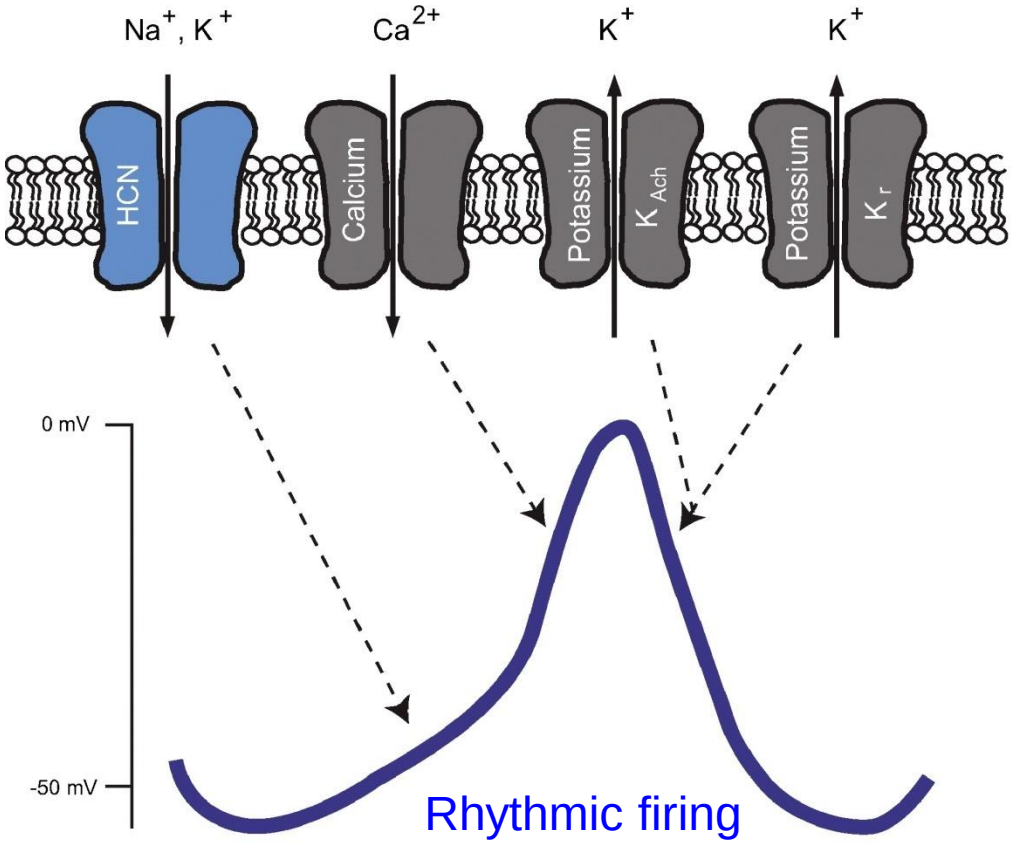
Cyclic nucleotide-gated channels

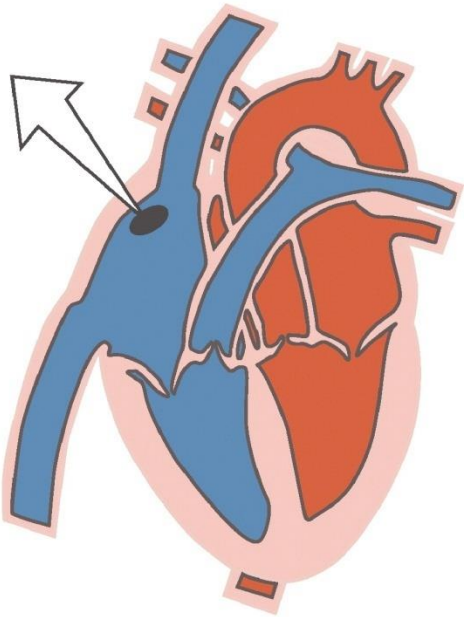


olfactory receptor (OR)
adenylyl cyclase (AC)
Calmodulin (CaM)

Craven KB, Zagotta WN. 2006.
Annu. Rev. Physiol. 68:375–401

Cyclic nucleotide-gated channels





Craven KB, Zagotta WN. 2006.
Annu. Rev. Physiol. 68:375–401

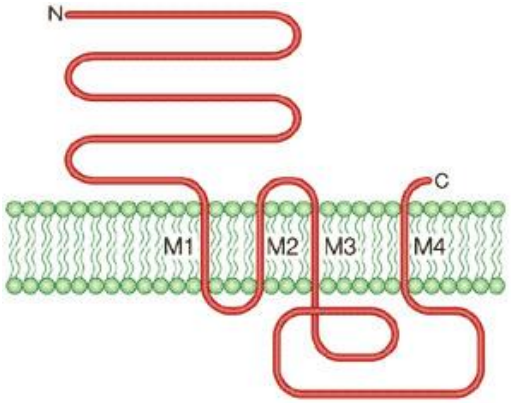
Nicotinic acetylcholine receptor

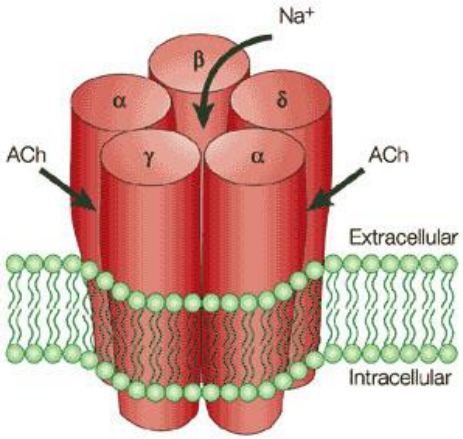
Gating: opened by neurotransmitter acetylcholine

Location: postsynaptic plasma membrane of skeletal muscle and neurons

Function: mediates synaptic transmission at the nerve-muscle junction and in the CNS

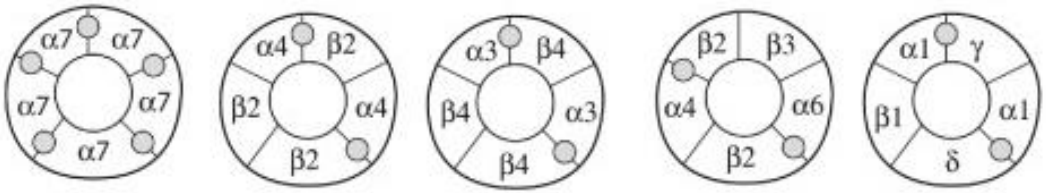
Acetylcholine receptor is a pentamer and is related to serotonin receptor, glycine receptor, and GABA receptor. Seventeen nAChR subunits have been identified in vertebrate species (α1–α10, β1–β4, γ, δ and ε).





Karlin, 2002

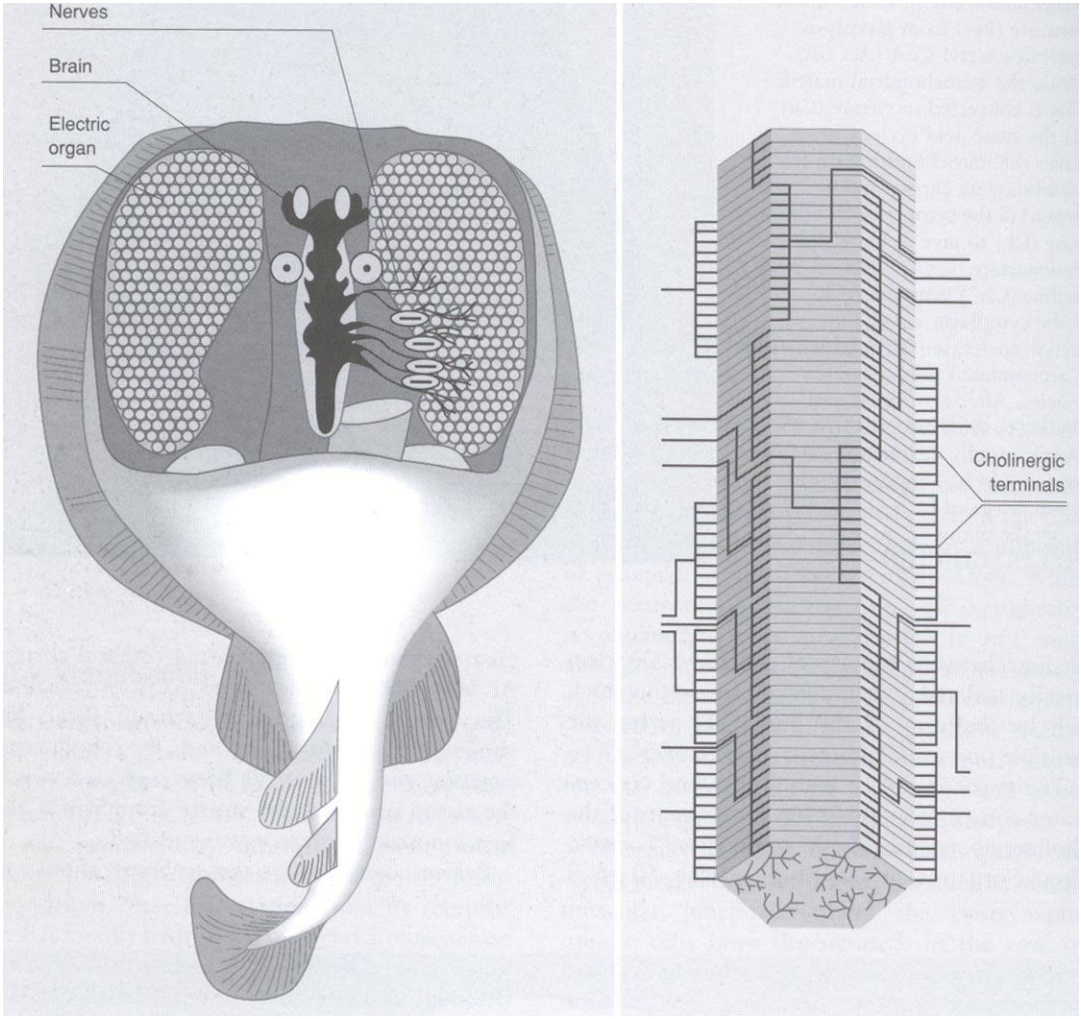
Examples of existing subunit compositions



Nicotinic receptors from Torpedo ray

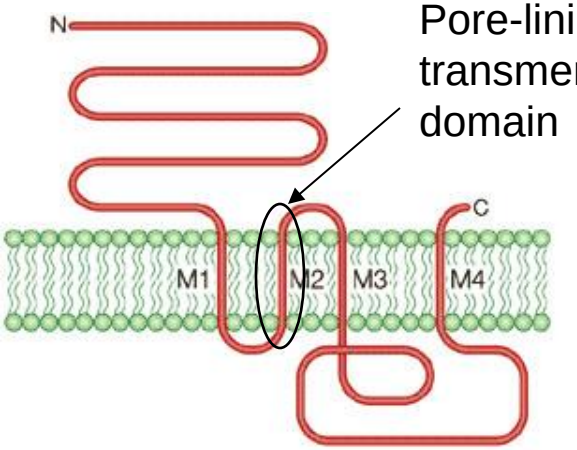
Torpedo marmorata

Cross-section of a tubular crystal

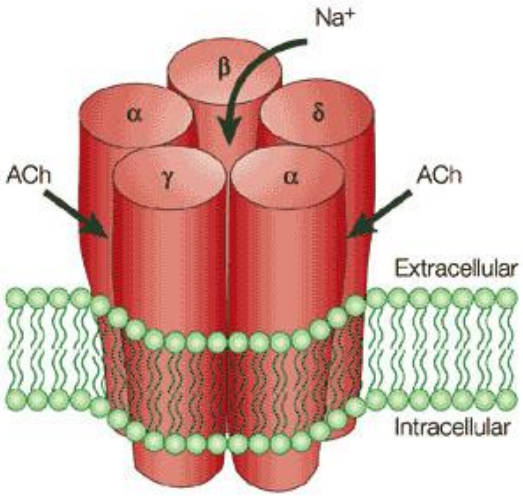


Electric organ from *Torpedo* - rich source of nAChRs

Overall architecture of the nicotinic receptor

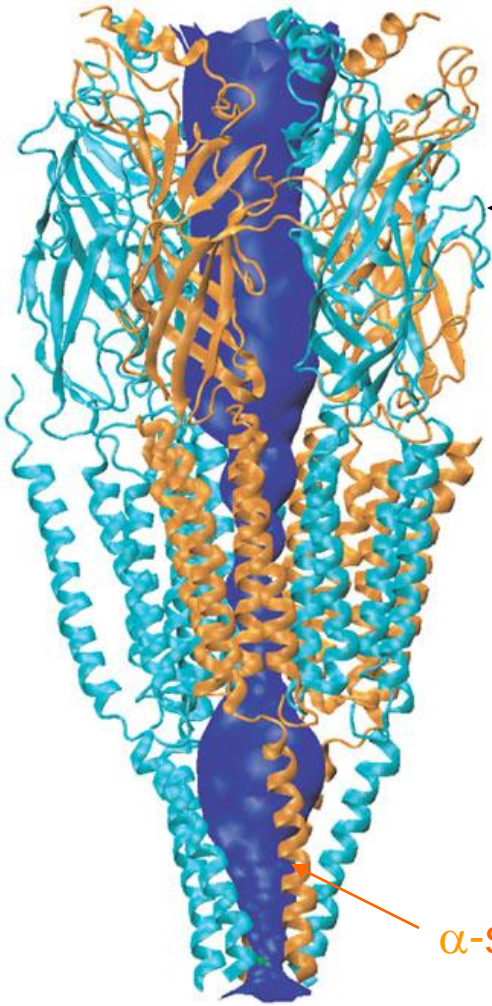


Pore-lining transmembrane domain

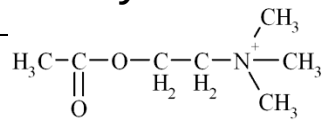


Karlin, 2002

Membrane



acetylcholine

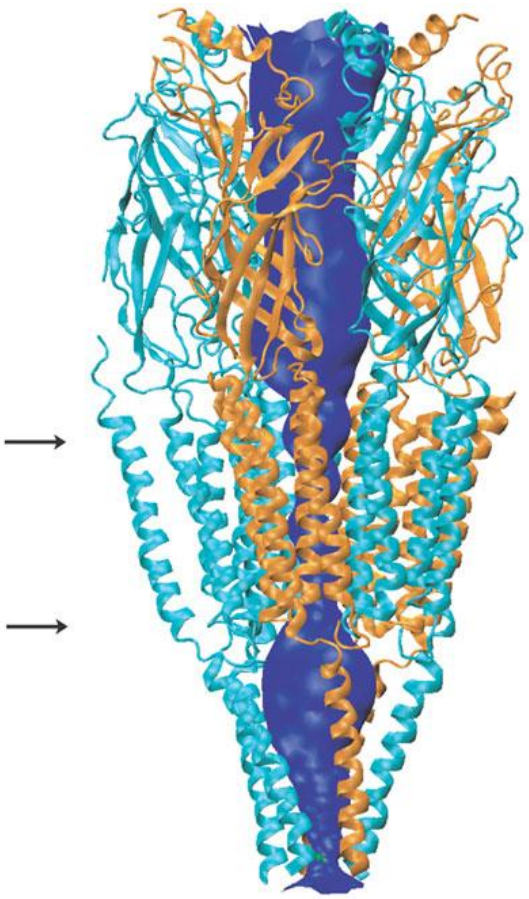


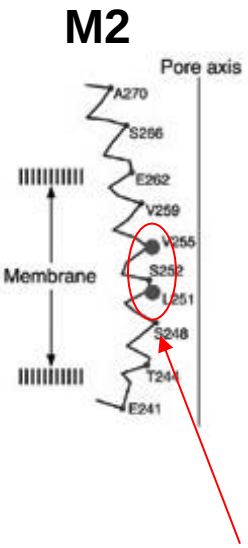
α-subunit

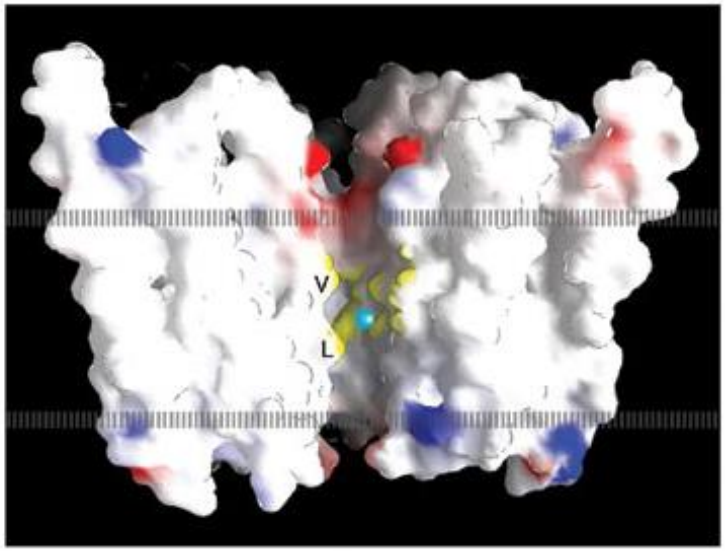
Miyazawa, A. *et al*., 2003

Sine and Engel, 2006

Nicotinic receptor – the pore







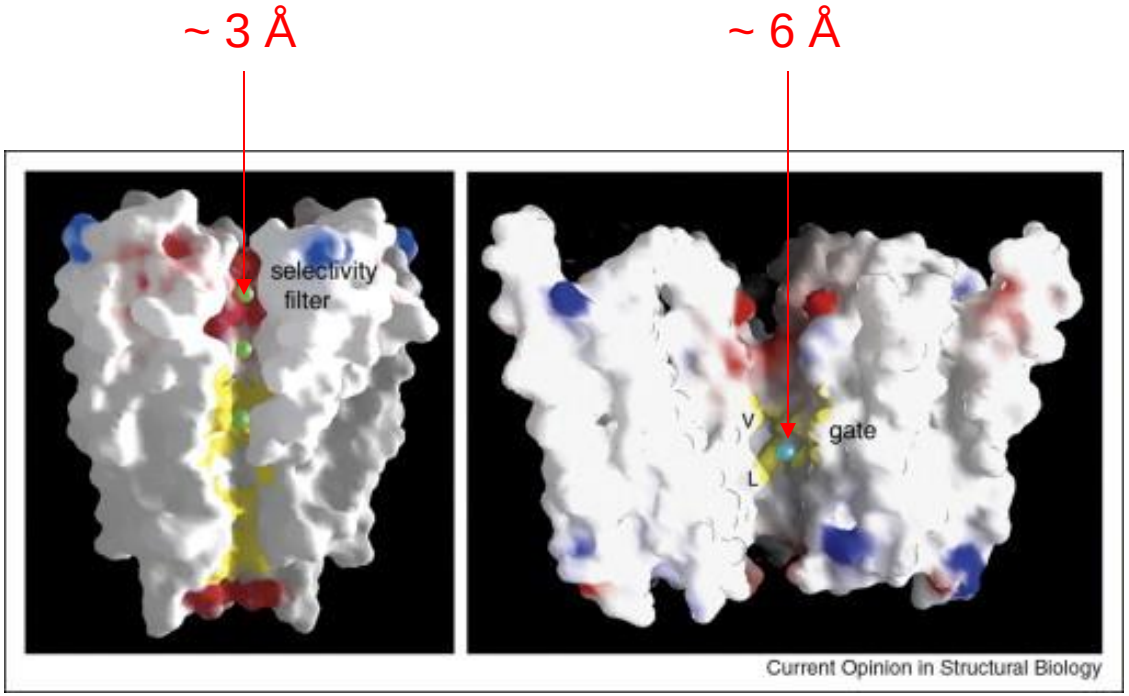
The narrowest part of the pore contains hydrophobic amino acids Valine and Leucine.

- Positive charge
- Negative charge
- Neutral
- Hydrophobic

Miyazawa *et al*., 2003

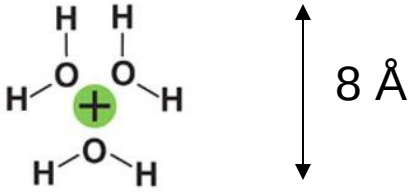
Sine and Engel, 2006

Nicotinic receptor – mechanism of permeation



K^+ channel Nicotinic Receptor

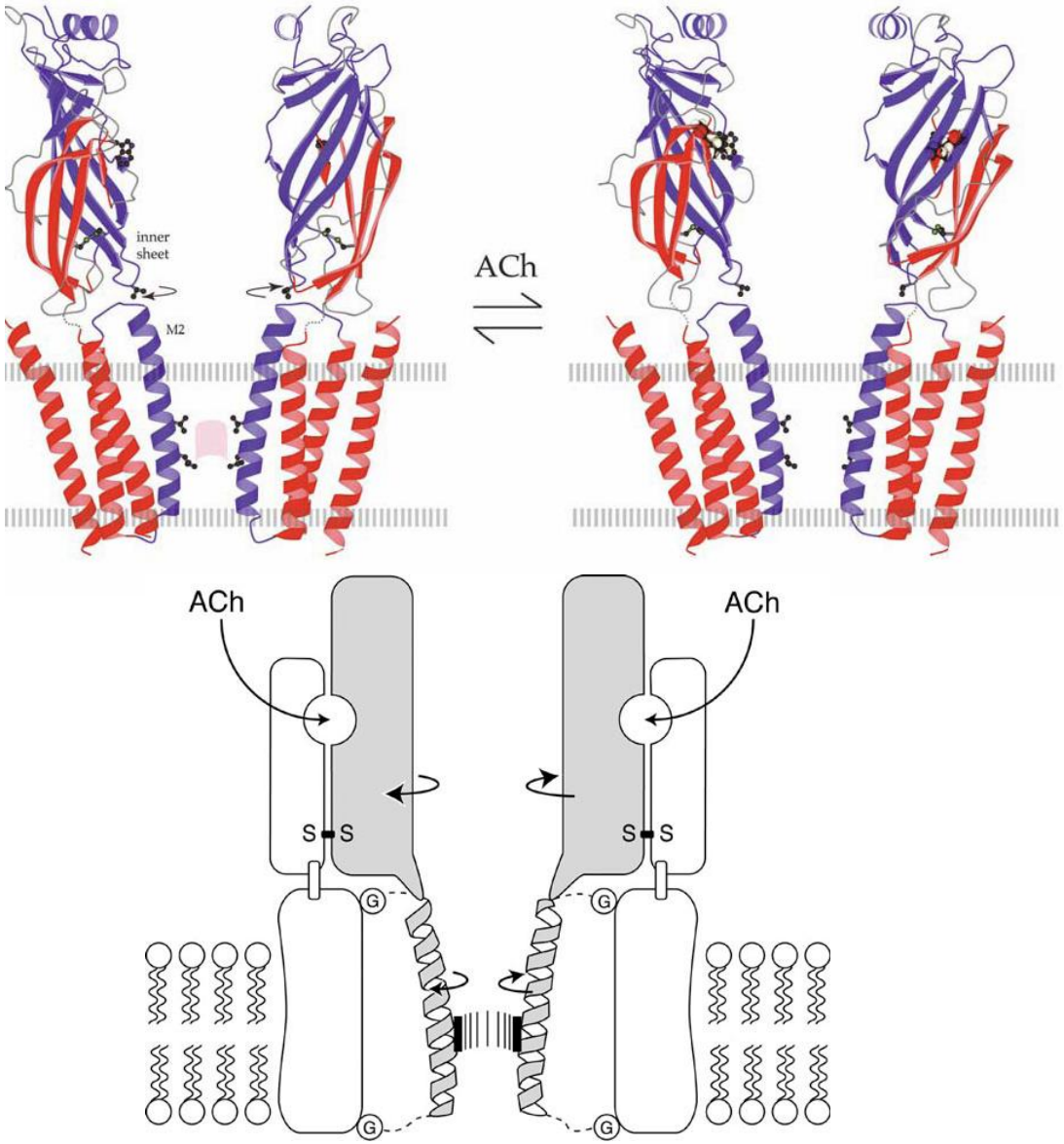
Na^+ or K^+ with hydration shell

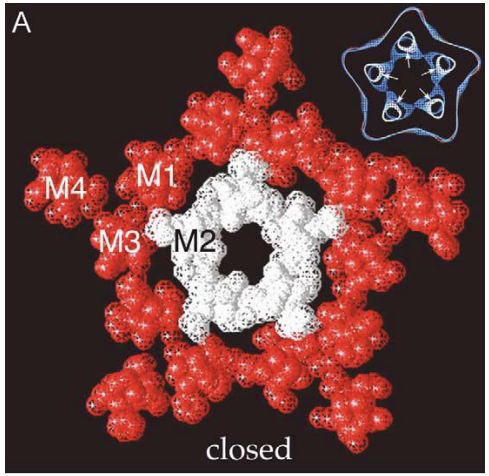


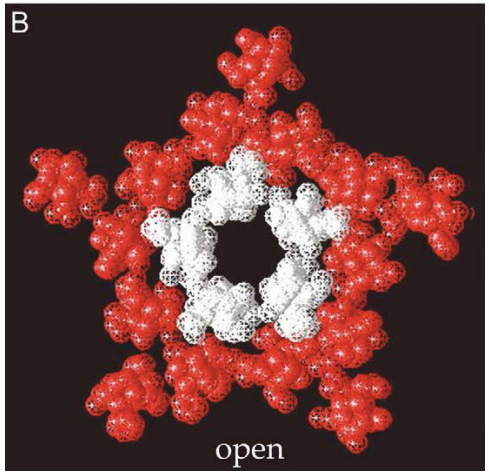
- Positive charge
- Negative charge
- Neutral
- Hydrophobic

Fujiyoshi and Unwin, 2008

Nicotinic receptor – gating mechanism







Miyazawa, A. *et al*., 2003