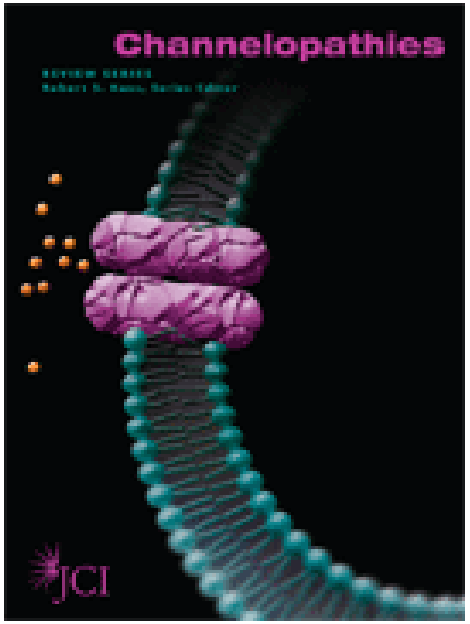
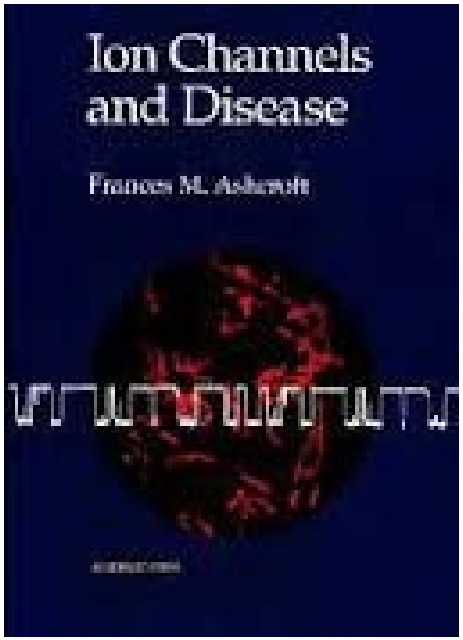
Ion Channels and Channelopathies



J Clin Invest. 2005;115(8)
review series



Frances M. Ashcroft
2005

Lai-Hua Xie, PhD (xiela@njms.rutger.edu)
MSB C-506; 973-972-2411
May 11, 2015

Outline

Part I: Ion Channels

- Introduction
- Classification
- Structure
- Function

Part II: Channelopathies

- Long QT syndromes Type 1 and 2 : LQT1 and LQT2: delayed K^+ channel
- Long QT syndrome type 3: LQT3: Na^+ channel
- Epilepsy: Voltage-gated Ca^{2+} channel
- Diabetes Mellitus: ATP-sensitive K^+ channel
- Cystic fibrosis: CFTR, Cl^- channel

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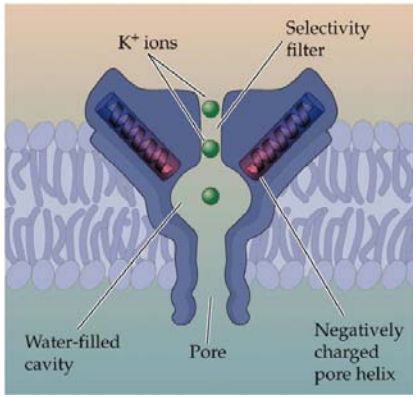
What are Ion Channels ?



- **Ion channels - structure**
  - are proteins that span (or traverse) the membrane
  - have water-filled ‘channel’ that runs through the protein
  - ions move through channel, and so through membrane

- **Ion channel - properties**
  - Selectivity: Each specific ion crosses through specific channels
  - Gating: transition between states (closed ↔ open ↔Inactivation)
    Voltage-gated ; Ligand-gated
  - Channels mediate ion movement down electrochemical gradients.
  - Activation of channel permeable to ion X shifts membrane potential towards to its Equilibrium Potential, E_X

Equilibrium Potential or Nernst Potential

The voltage at which there is zero net flux of a given ion
(Electrical gradient = a chemical concentration gradient)

For K^+ : ~ -90 mV

$$E_K = \frac{RT}{ZF} \ln \frac{[K^+]_o}{[K^+]_i}$$

Hermann (Walther) Nernst
1864-1941
1920 Nobel Prize for chemistry

- R = gas constant
- F = Faraday constant
- T = temperature (K)
- Z = valence (charge) of ion ~

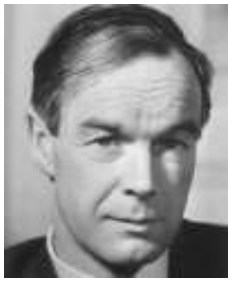
K current (I_{K1}) is the major contributor for RMP

Four Milestones in Ion Channel Research

1. Ionic conductance

Noble 1963 (Physiol/Medicine)

Alan L. Hodgkin



Andrew F. Huxley

2. Patch clamp methodology

Noble 1991 (Physiol/Medicine)

Erwin Neher

Bert Sakmann

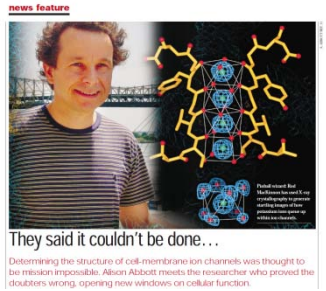
3. Channel cloning sequencing (Ach receptor, Na, Ca channels)

Japan Academy Prize 1985

Shosaku Numa (沼 正作)

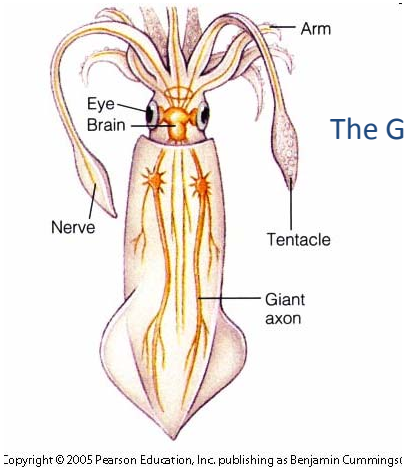
4. K channel structure

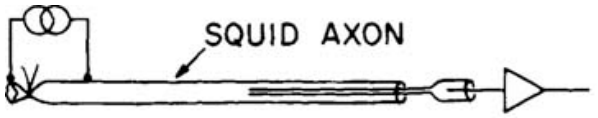
Noble 2003 (Chemistry)



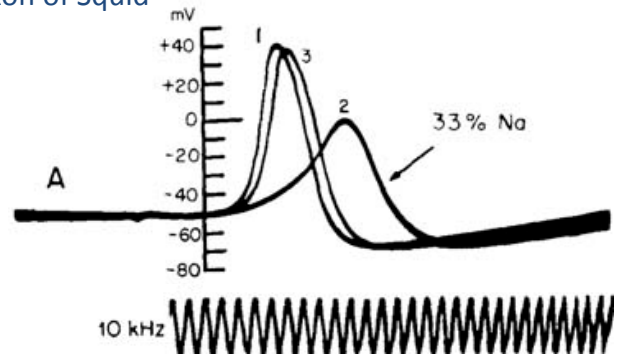
Rod MacKinnon

Hodgkin-Huxley Model Predicted the Existence of Ion Channels





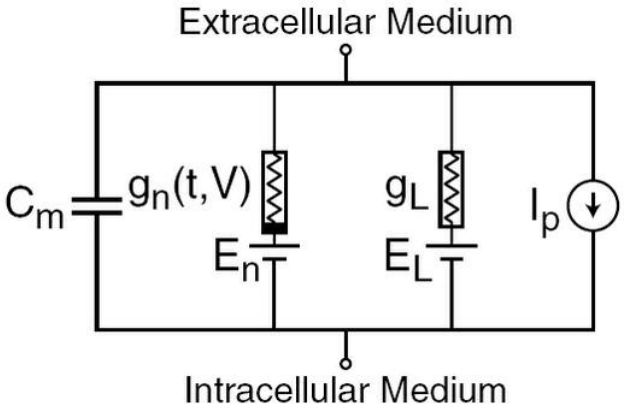
The Giant Axon of Squid

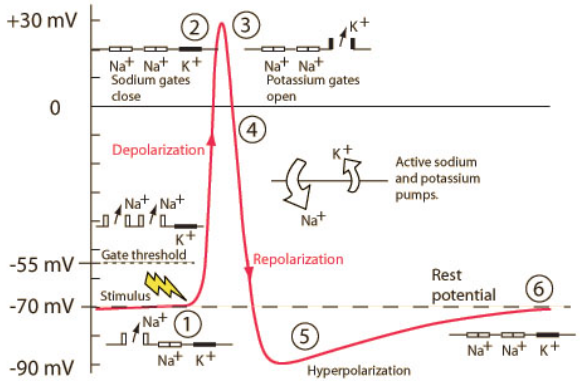


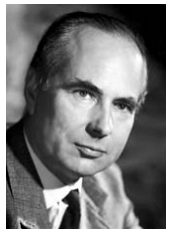
$$C\frac{dV}{dt} = \bar{g}_{Na} m^3 h (V_{Na} - V) + \bar{g}_K n^4 (V_K - V) + g_L (V_L - V) + I_{ext}$$

Na channel gating

K channel gating



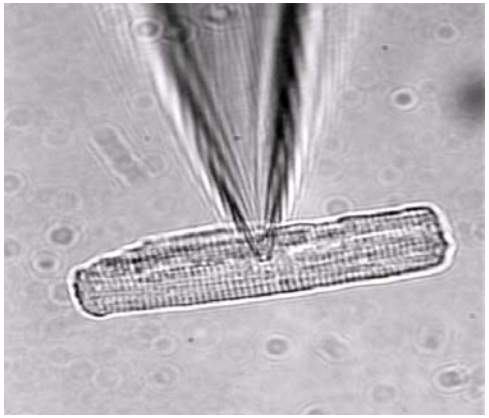


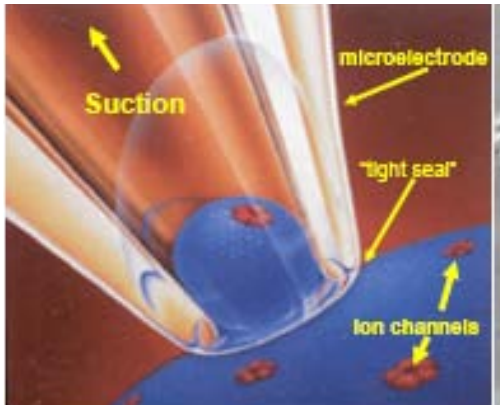


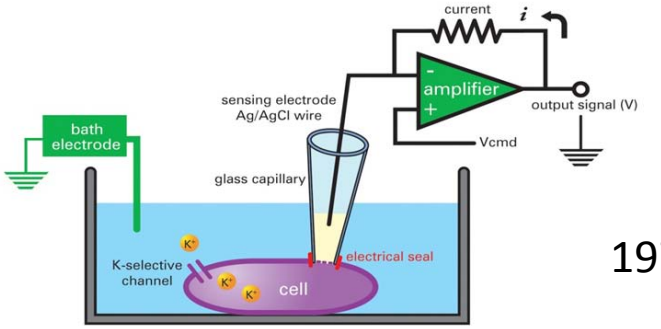
1963 noble Prize

Patch-Clamp Techniques

1991 Nobel Prize

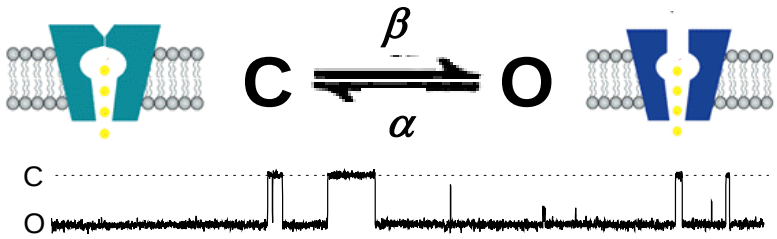






1976

Erwin Neher & Bert Sakmann
Nobel prize for medicine in 1991
for the development of the patch-clamp technique making possible the characterization of single ion channels



Channel cloning sequencing

NATURE VOL. 305 27 OCTOBER 1983

Cloning and sequence analysis of calf cDNA and human genomic DNA encoding α-subunit precursor of muscle acetylcholine receptor

Masaharu Noda, Yasuji Furutani, Hideo Takahashi, Mitsuyoshi Toyosato, Tsutomu Tanabe, Shin Shimizu, Sho Kikyotani, Toshiaki Kayano, Tadaaki Hirose*, Seiichi Inayama* & Shosaku Numa

Department of Medical Chemistry, Kyoto University Faculty of Medicine, Kyoto 606, Japan
* Pharmaceutical Institute, Keio University School of Medicine, Tokyo 160, Japan

Numa

Sakmann

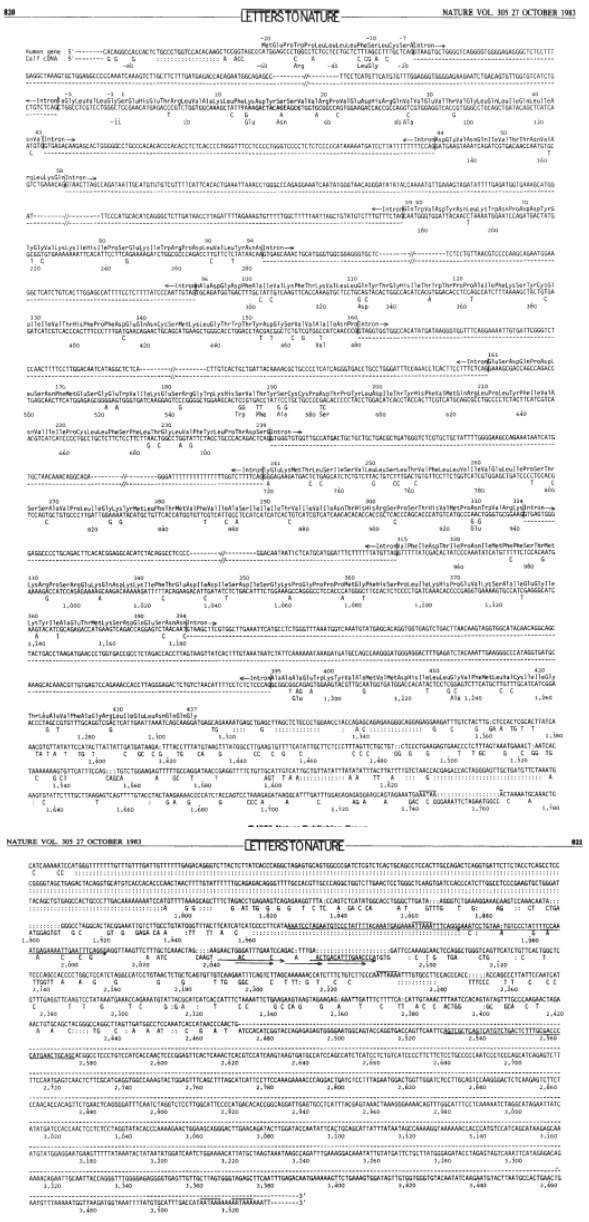
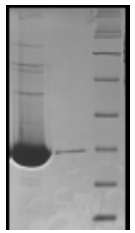


Fig. 2 Nucleotide sequences of the human genomic DNA (upper line) and the calf cDNA (lower line) encoding the AChR α-subunit precursor. The nucleotide sequence of the human message strand, together with the deduced amino acid sequence, is shown, and the nucleotide and amino acid differences found in the calf sequences aligned are displayed beneath the human sequences; the absence of a nucleotide or an amino acid in the calf sequence indicates that the human and calf sequences are the same; the presence of a colon in either nucleotide sequence indicates a gap; the hyphens indicate sequences that have not been determined or cloned or that exhibit no evident homology with their counterpart. Amino acid residues are numbered beginning with the amino-terminal residue of the mature α-subunit, and the preceding residues are indicated by negative numbers. Nucleotide residues in the calf cDNA are numbered in the 5′ to 3′ direction, beginning with the first residue of the codon specifying the amino-terminal residue of the mature α-subunit, and the nucleotides on the 5′ side of residue 1 are indicated by negative numbers. The exon–intron junctions, which are positioned according to the G-T/A-G rule[36], are indicated by vertical lines. The 5′-terminal sequences shown do not extend to the 5′ end of the mRNA or the gene. The 3′-terminal cDNA sequence presented is followed by a poly(A) tract of 66 nucleotides connected with the vector DNA sequence[37,57], thus apparently representing the complete sequence of this region, whereas the 3′-terminal gene sequence shown is probably incomplete (see text). The polyadenylation signals AATAAA and ATTAAA (refs 18, 39) present downstream of the translational termination site are overlined. The sequence homologous with the bovine repetitive DNA sequences (complementary to a portion of the consensus sequence given in ref. 26) and the direct repeats present in the 3′-untranslated region are shown by an underline and by horizontal arrows beneath the sequences, respectively.

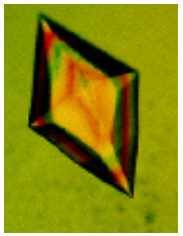
Nobel Prize for Chemistry 2003

Protein x-ray crystallography

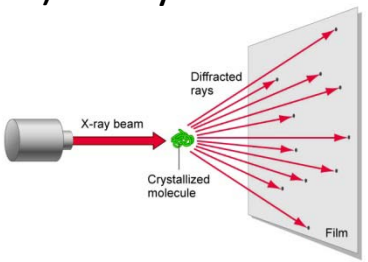
1) Purification

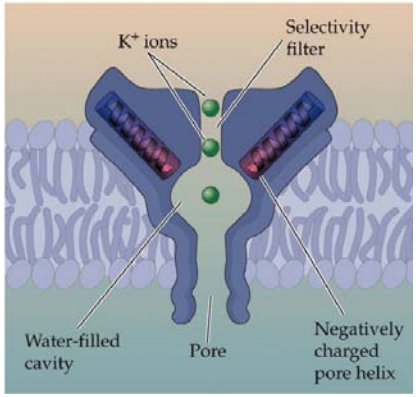


2) Crystallization



3) X-Ray Diffraction





Crystal structure of ion channel

The Nobel Prize in Chemistry 2003
Peter Agre, Roderick MacKinnon

Classification of Ion Channels

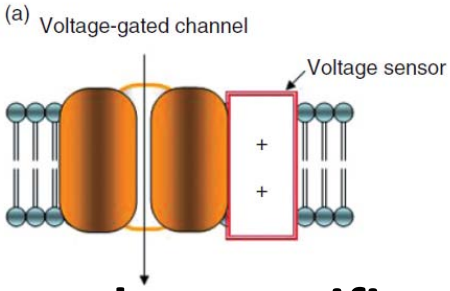
1) Based on ion selectivity:

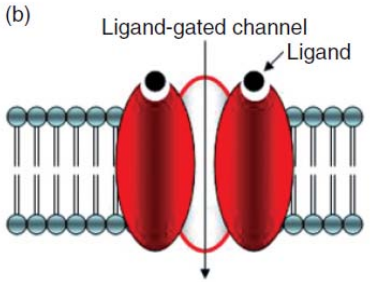
K^+, Na^+, Ca^{2+}, Cl^- channels

2) Based on gating:

Voltage-gated : ions

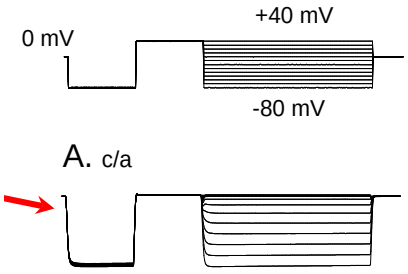
Ligand-gated: Glutamate, GABA, ACh, ATP, cAMP

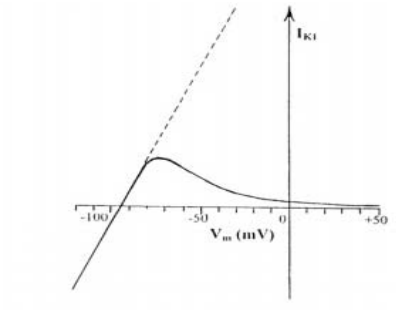


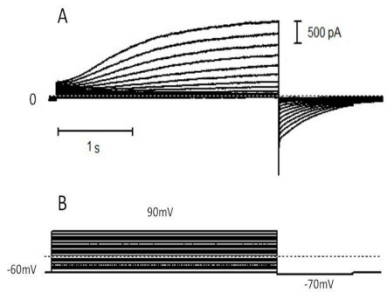


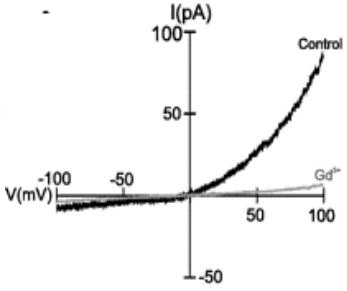
3) Based on rectification:

Inwardly or outwardly rectifying

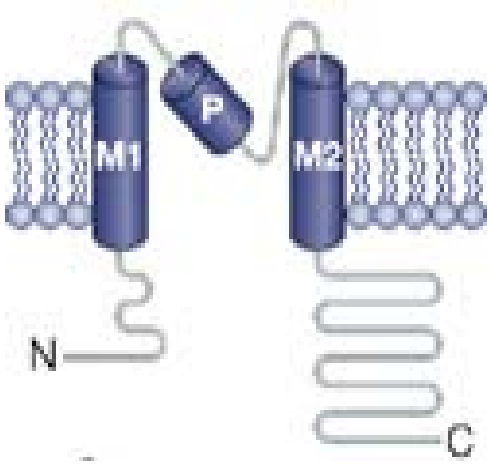


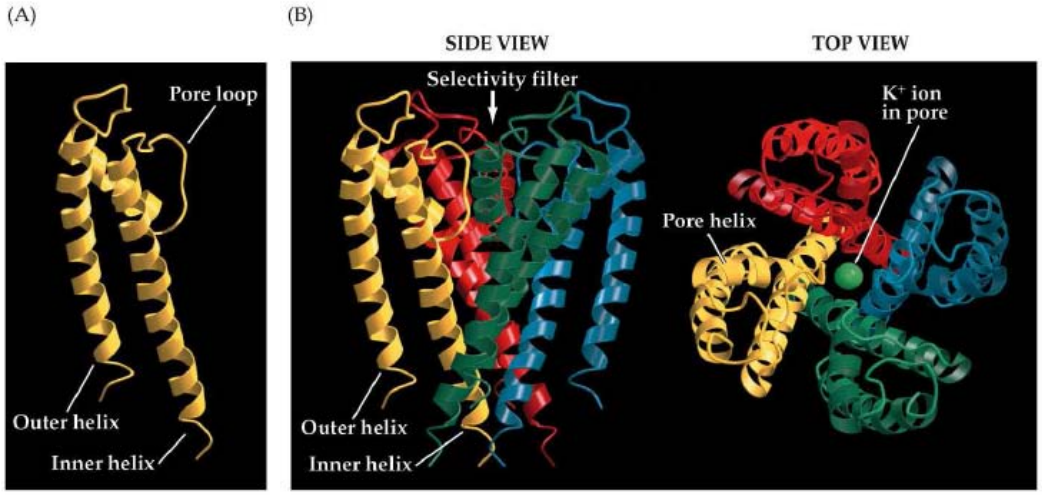


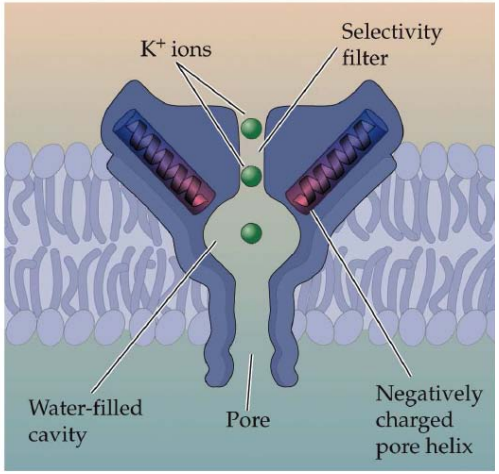




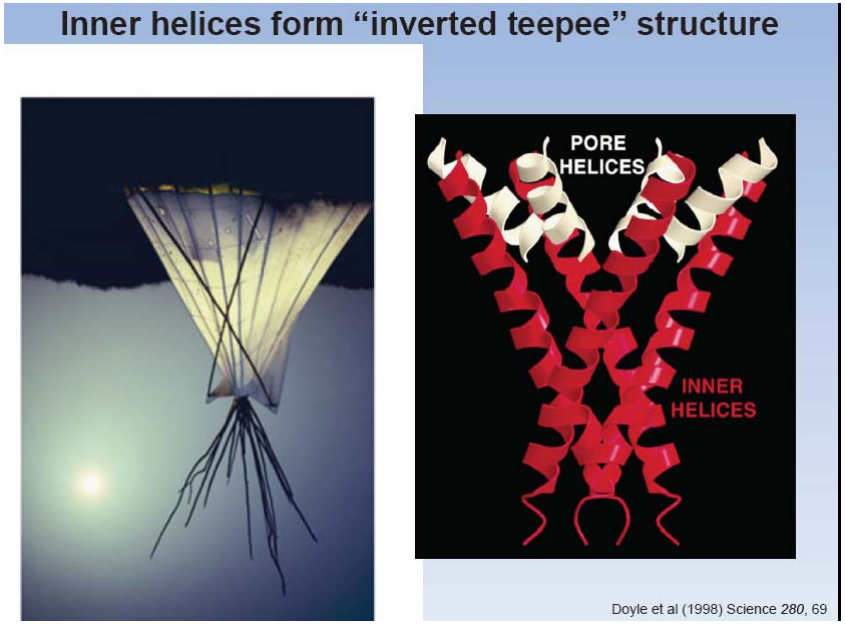
Structure of K_{CSA} Channels: Selectivity Filter and Gating





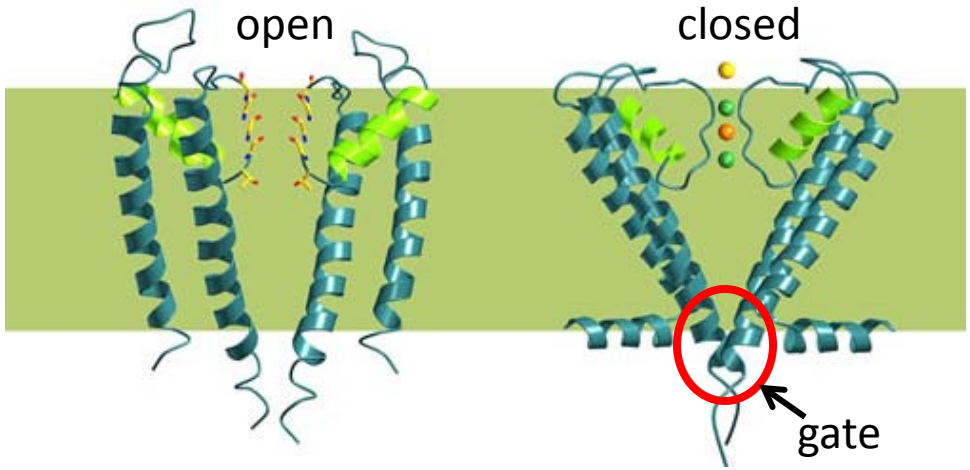


profile



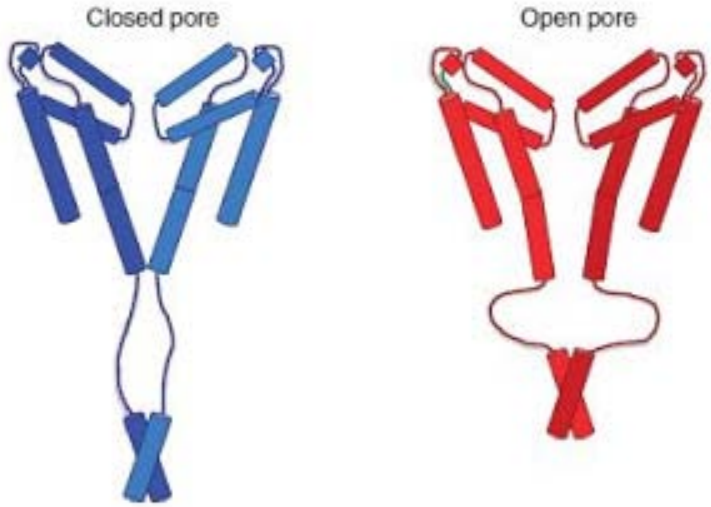
Doyle *et al*. Science 1998;

Open-Close Gating



Doyle *et al*. Science 1998;

Bacterial K channel
selective filter: P-loop; **Gating: intracellular side of the pore bundle crossing**

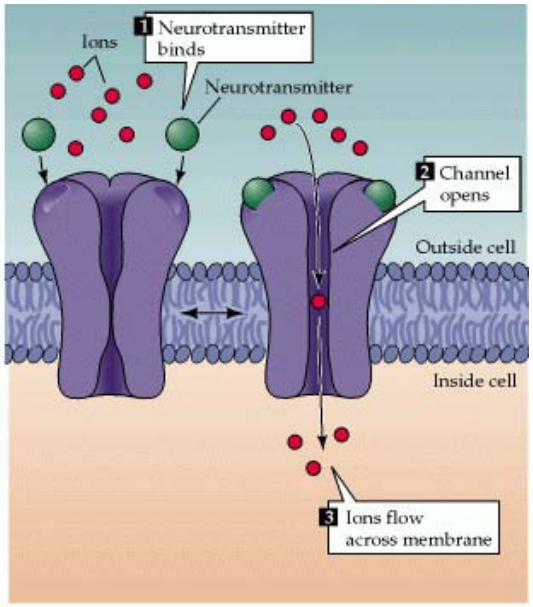


Bacterial Na channel pore in the closed and “open” conformation

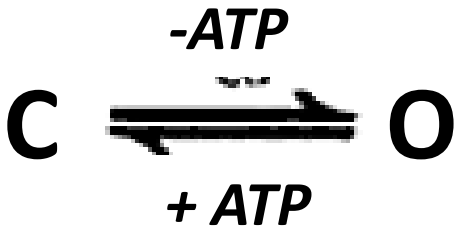
Ligand-Gated Channels

ACh receptor channel

ACh



ATP-sensitive K channel

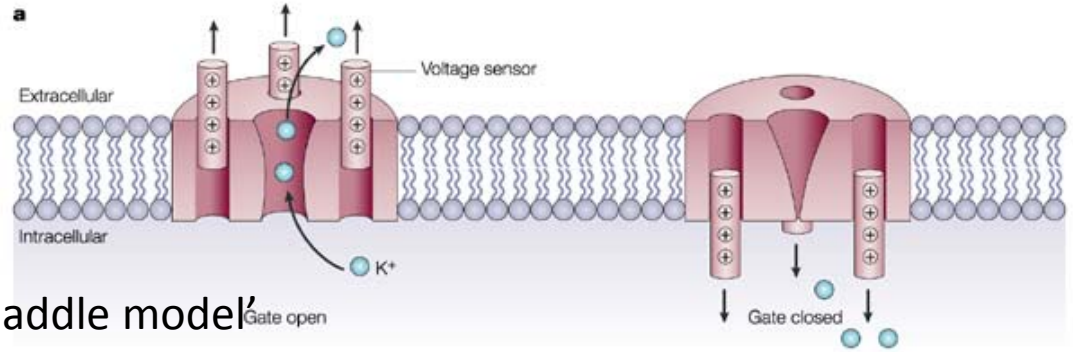


Also a weak inward rectifier

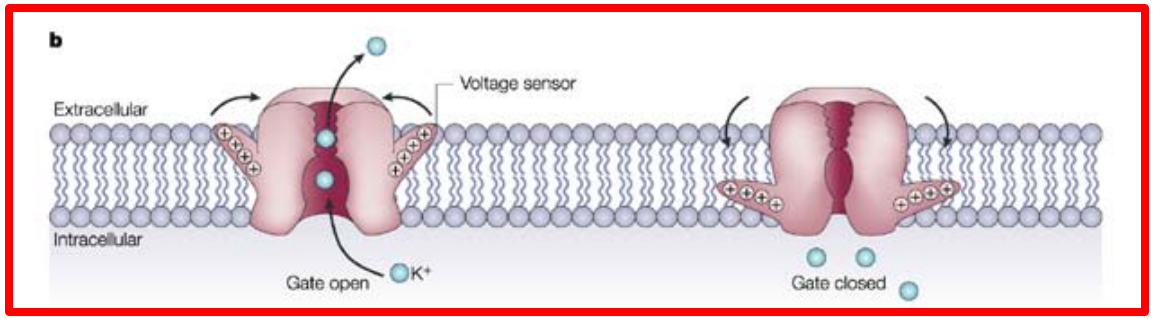
- Open when a signal molecule (ligand) binds to an extracellular receptor region of the channel protein.
- This binding changes the structural arrangements of the channel protein, which then causes the channels to open or close in response to the binding of a ligand such as a neurotransmitter.
- This ligand-gated ion channel, allows specific ions (Na+, K+, Ca2+, or Cl-) to flow in and out of the membrane.

Models for Voltage Gate

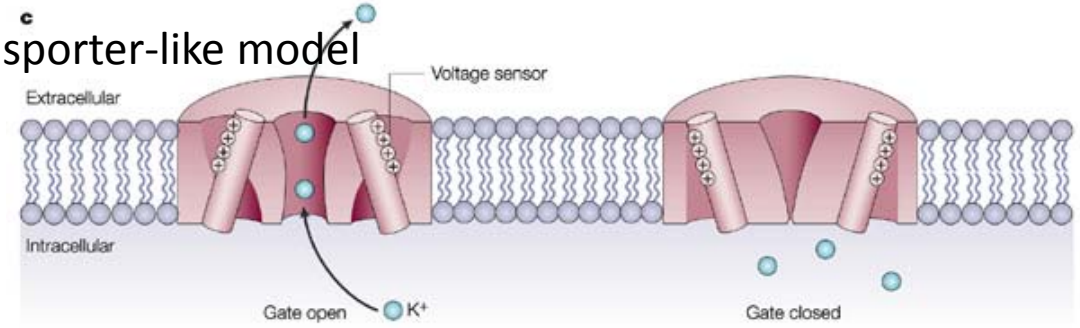
The conventional model



A new 'paddle model'



The transporter-like model



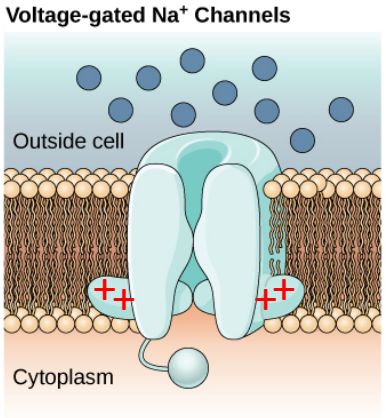
Nature Reviews | Drug Discovery

the S4 segment is responsible for detecting voltage changes.

The movement of positively-charged S4 segments within the membrane electric field

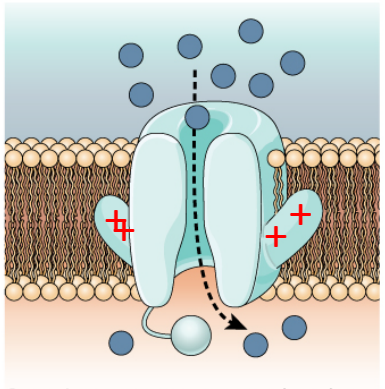
Transition between Close, Open, and Inactivation States

C



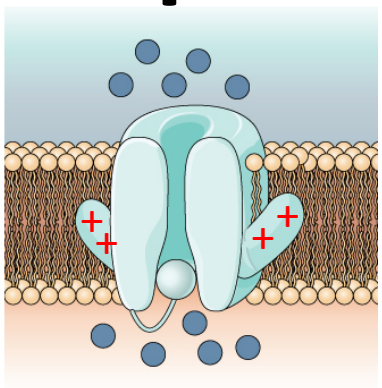
Closed At the resting potential, the channel is closed.

O



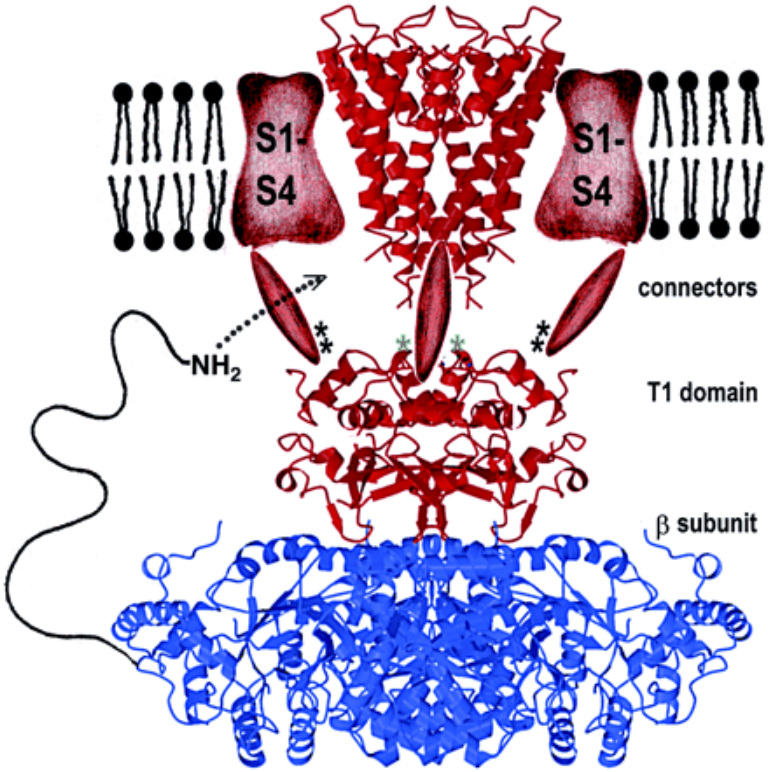
Open In response to a nerve impulse, the gate opens and Na^+ enters the cell.

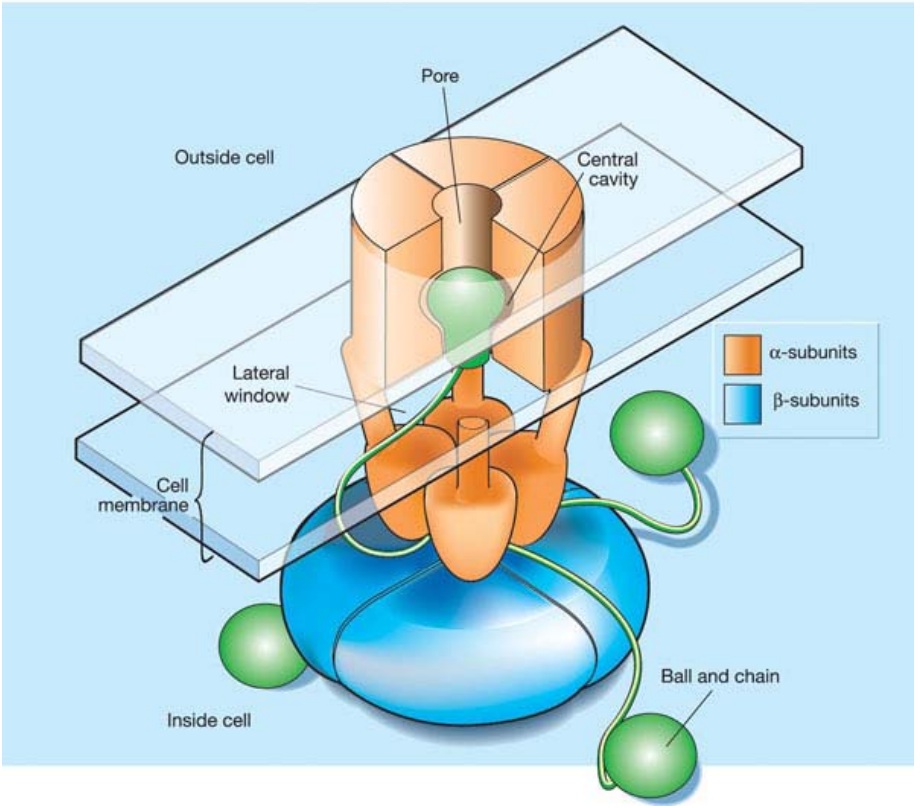
I



Inactivated For a brief period following activation, the channel does not open in response to a new signal.

Inactivation Gating of Voltage-Gated Channels -Ball and Chain



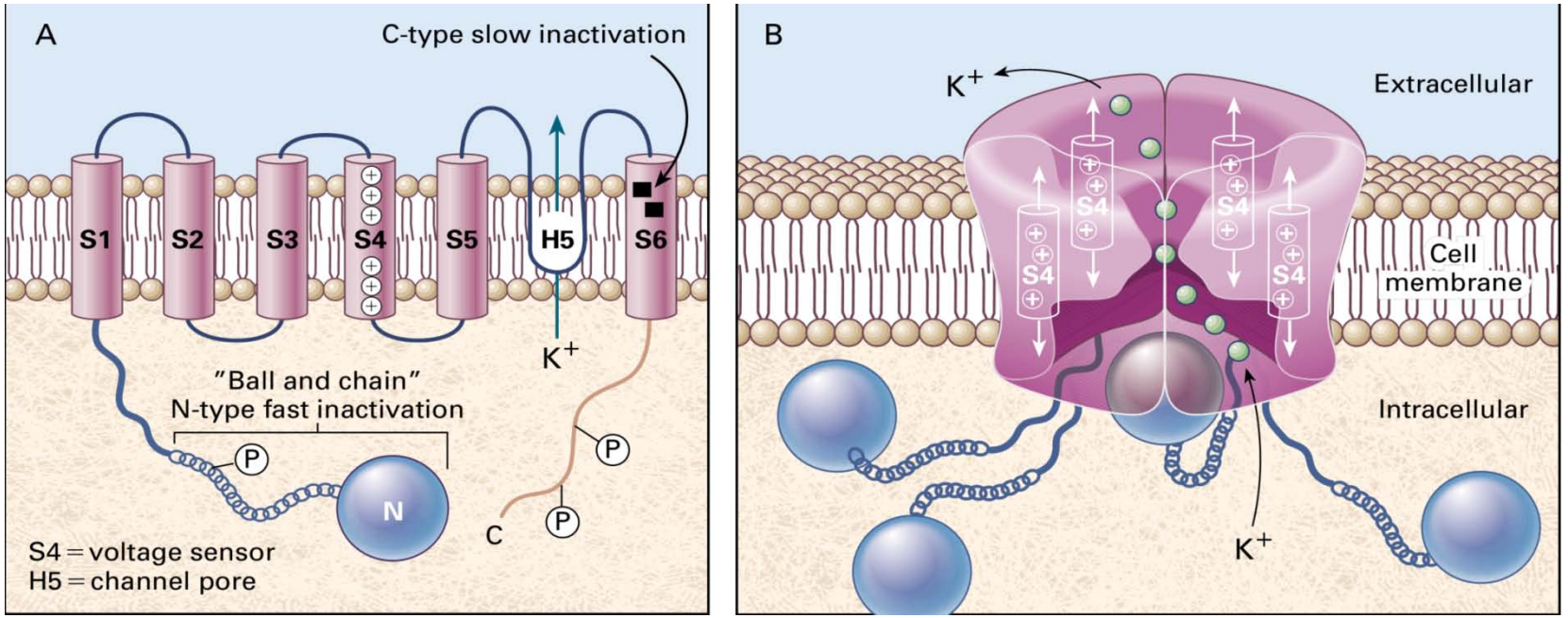


(Gulbis et al, Science 2000)

N-terminal inactivation gate

A positively charged inactivation particle (ball) has to pass through one of the lateral windows and bind in the hydrophobic binding pocket of the pore's central cavity. This blocks the flow of potassium ions through the pore. There are four balls and chains to each channel, but only one is needed for inactivation.

Structural Basis of Gating in a Voltage-gated Channel



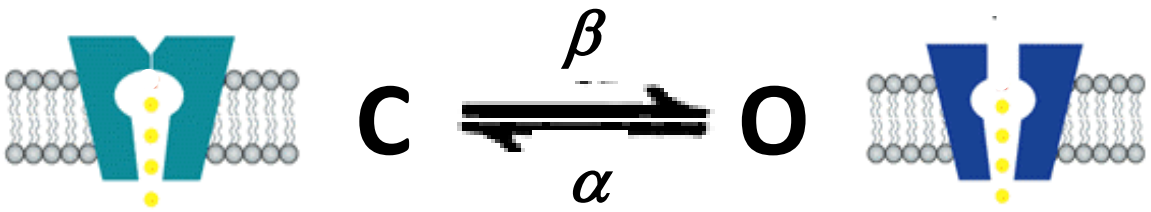
A: a subunit containing six transmembrane-spanning motifs. S5 and S6 and the pore loop are responsible for ion conduction (channel pore). S4 is the the *voltage sensor, which* bears positively charged amino acids (Arg) that relocate upon changes in the membrane electric field. N-terminal ball-and-chain is responsible for inactivation

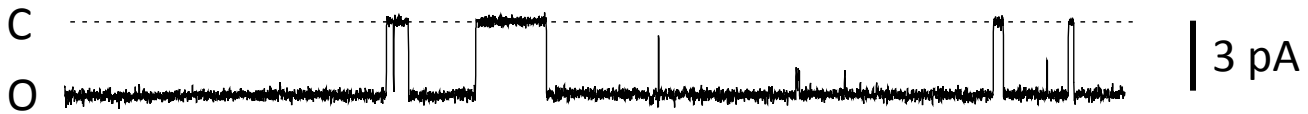
B: four such subunits assembled to form a potassium channel.

Channel Function:
Single Channel and Whole-cell Current

- Ion channels are not open continuously but open and close in a stochastic or random fashion.

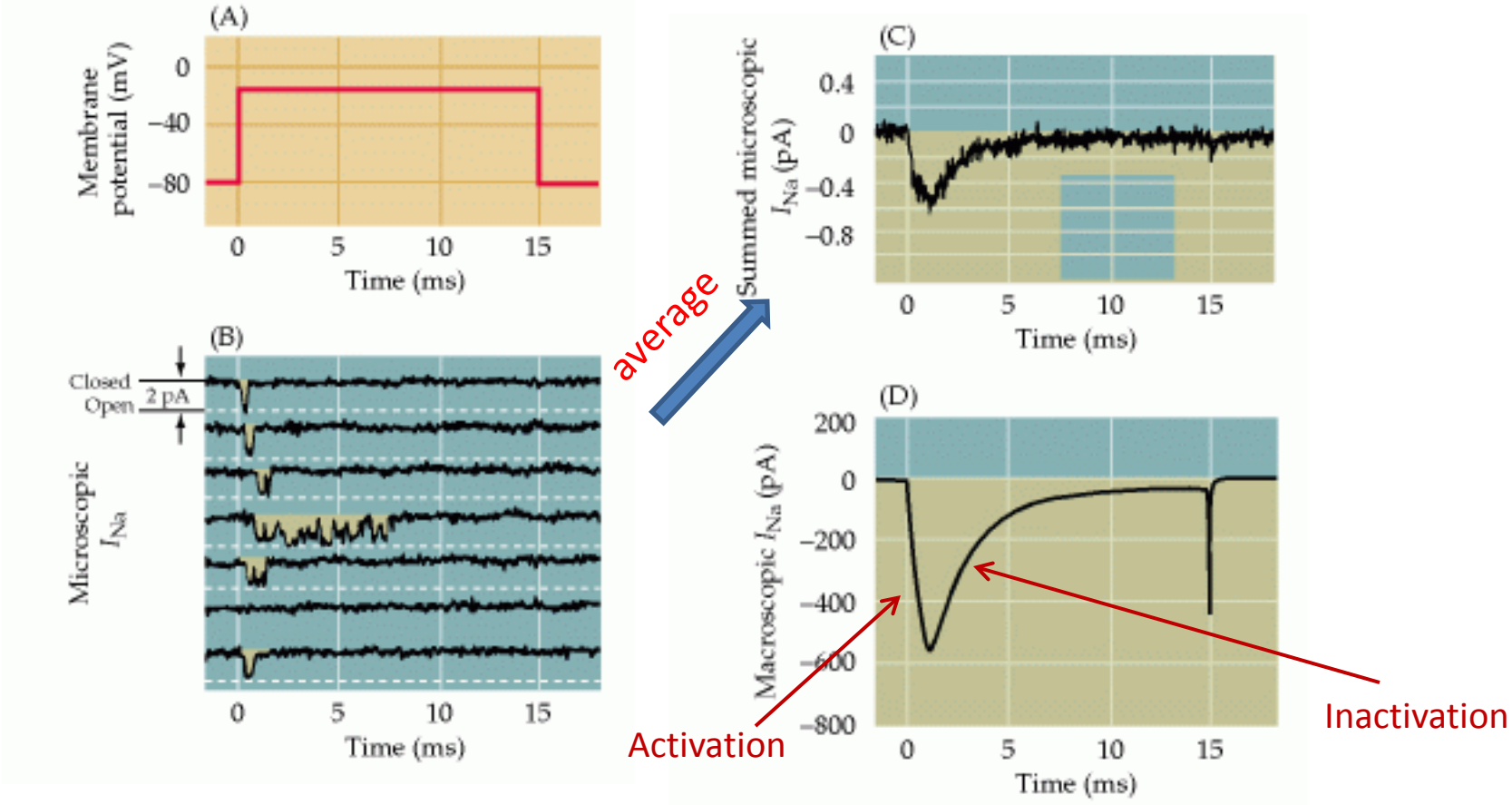
- Ion channel function may be decreased by
  - decreasing the open time (O),
  - increasing the closed time (C),
  - decreasing the single channel current amplitude (i)
  - or decreasing the number of channels (n).





$$I = n * P_o * i \qquad P_O = \frac{\tau_o}{\tau_o + \tau_c}$$

Channel Function:
Single Channel and Whole-cell Current



Depolarizing voltage pulses result in brief openings in the seven successive recordings of membrane current

Close correlation between the time courses of microscopic and macroscopic Na+ currents

Physiological Function of Ion Channels

- **Maintain cell resting membrane potential:** inward rectifier K and Cl channels.
- **Action potential and Conduction of electrical signal:** Na, K, and Ca channels of nerve axons and muscles
- **Excitation-contraction (E-C) coupling:** Ca channels of skeletal and heart muscles
- **Synaptic transmission at nerve terminals:** glutamate, Ach receptor channels
- **Intracellular transfer of ion, metabolite,** propagation: gap junctions
- **Cell volume regulation:** Cl channel, aquaporins
- **Sensory perception:** cyclic necleotide gated channels of rods, cones
- **Oscillators:** pacemaker channels of the heart and central neurons
- **Stimulation-secretion coupling:** release of insulin form pancreas (ATP sensitive K channel)

Outline

Part I: Ion Channels

- Instruction
- Classification
- Structure
- Function

Part II: Channelopathies

- Long QT syndrome Type 1 and 2 : LQT1 and LQT2: delayed K^+ channel
- Long QT syndrome type 3: LQT3: Na^+ channel
- Epilepsy: Voltage-gated Ca^{2+} channel
- Diabetes Mellitus: ATP-sensitive K^+ channel
- Cystic fibrosis: CFTR, Cl^- channel

Channelopathies?

1. Definition: Disorders of ion channels or ion channel disease

Diseases that result from defects in ion channel function. Mostly caused by mutations of ion channels.

2. Channelopathies can be inherited or acquired:

a. Inherited channelopathies result from mutations in genes encoding channel proteins (major)

b. Acquired channelopathies result from *de novo mutations,* actions of drugs/toxins, or autoimmune attack of ion channels

- Drug/Toxin - *e.g. Drugs that cause long QT syndrome*

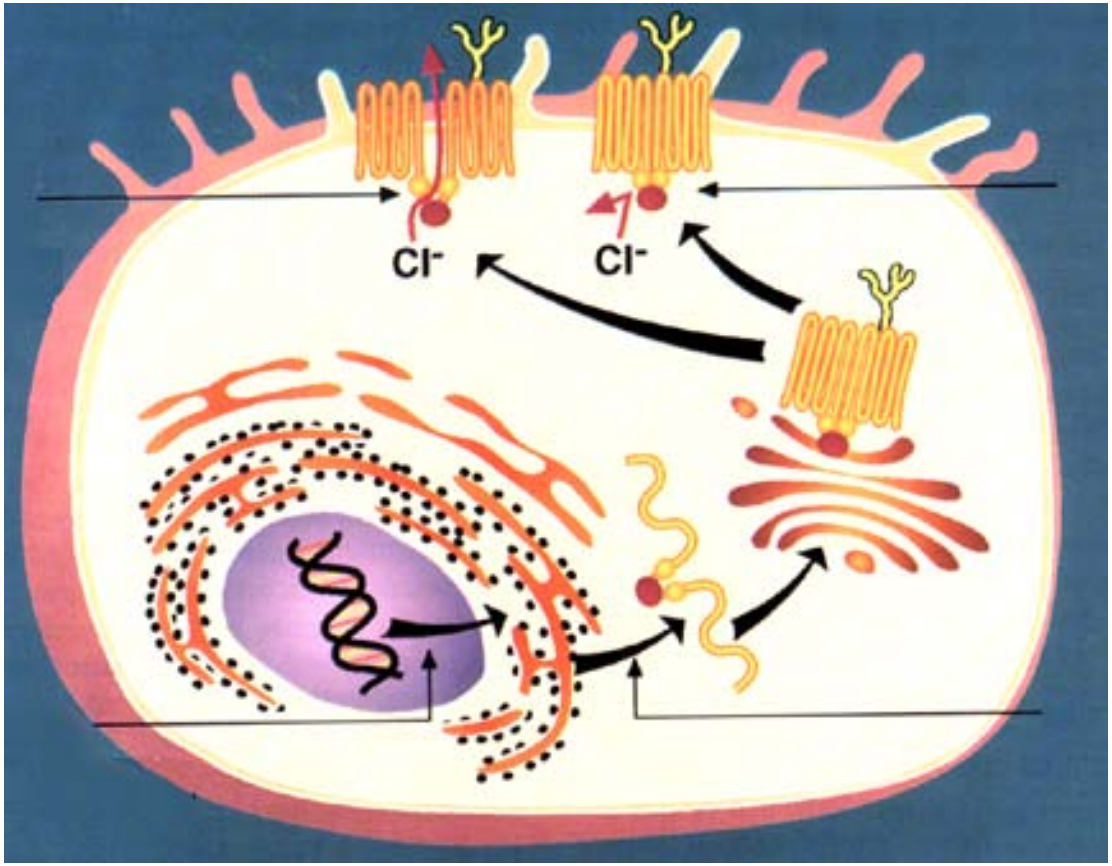
3. Increasingly recognized as important cause of disease (>30 diseases).

4. Numerous mutation sites may cause similar channelopathy

e.g. cystic fibrosis where >1000 different mutations of CFTR described

Molecular Mechanisms of Channel Disruption

IV. Gating



III. Conduction

I. Production

II. Processing

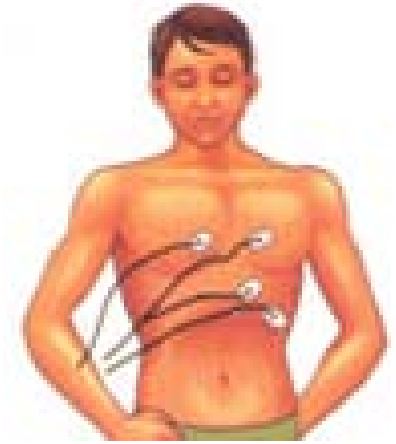
Consequences of Ion Channel Mutations

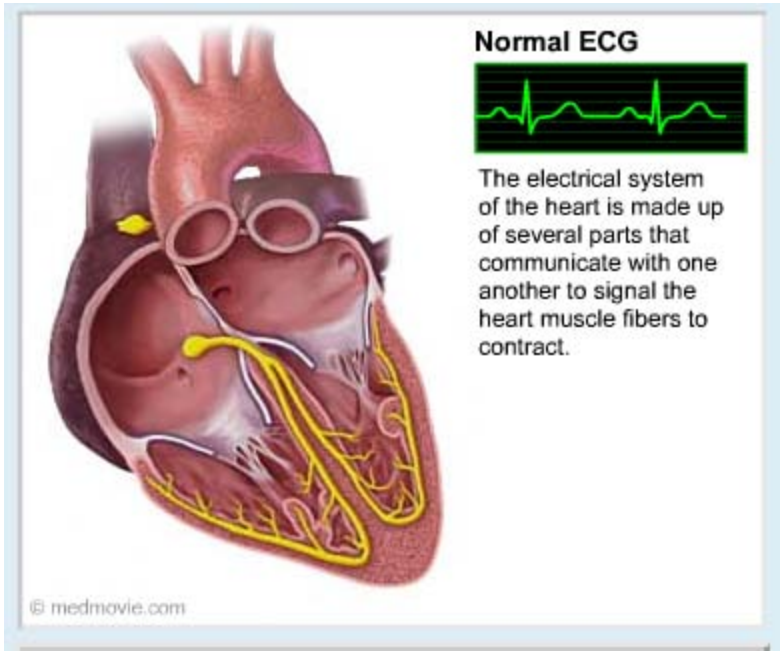
- Mutation of ion channel can alter
  - Activation
  - Inactivation
  - Ion selectivity/Conduction
- Abnormal gain of function
- Loss of function

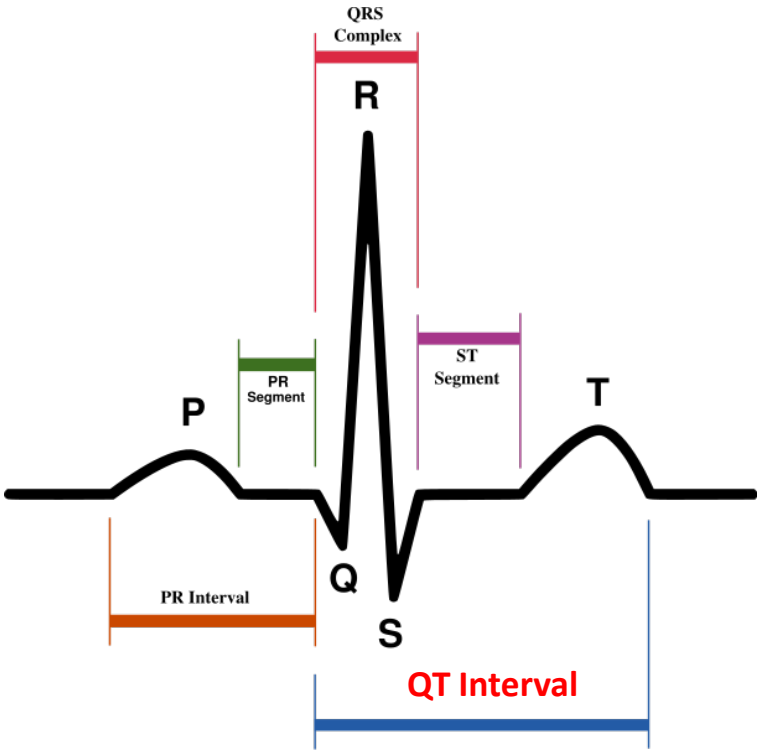
Cardiac Channelopathies

- Long QT Syndrome (types 1-12, various genes)
- Short QT Syndrome (Kir2.1, L-type Ca^{2+} channel)
- Burgada Syndrome (I_{to}, Na^{+}, Ca^{2+} channels)
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (RyR2, SR Ca release)

ECG and QT interval



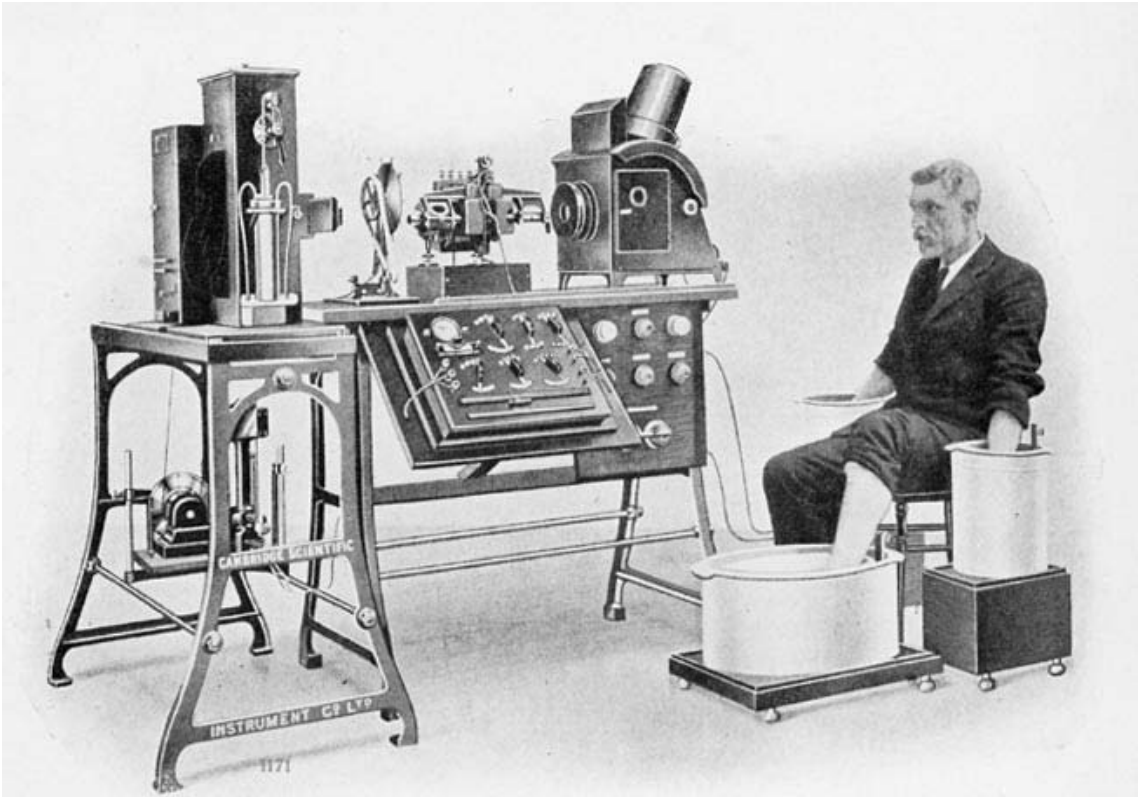




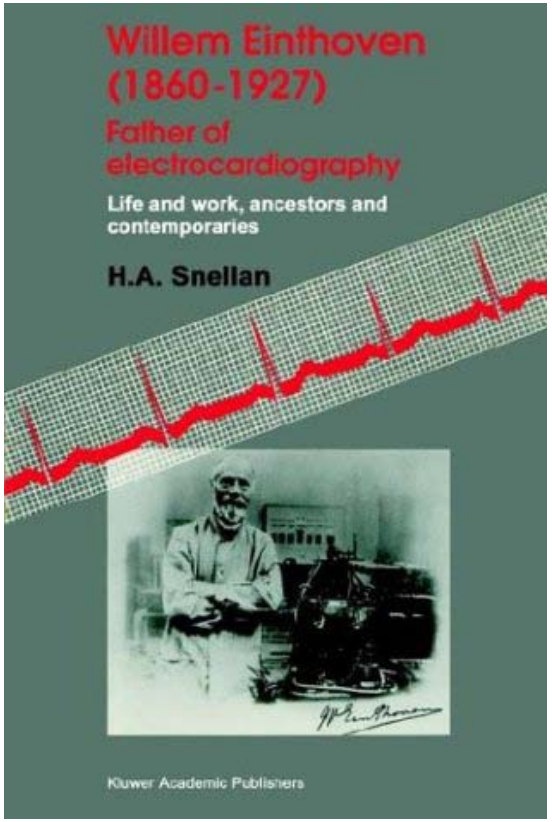
$$QT_C = \frac{QT\ interval}{\sqrt{R\text{-}R\ interval}}$$

Bazett's Formula:

FYI: ECG Recording 120 Years Ago



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION



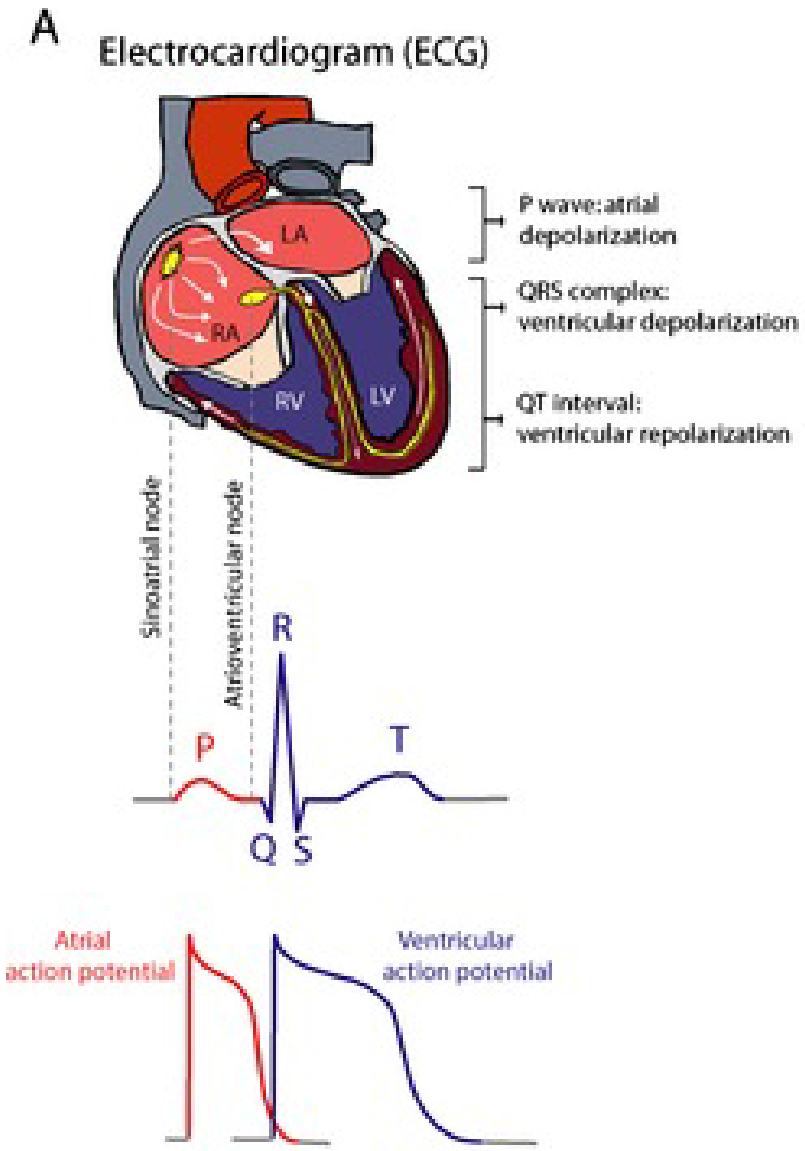
First recorded in 1887

In order to conduct the weak current of the heart's electrical activity, Einthoven used electrolyte (saline-filled) tubs ["E" in photo] as *electrode* contacts to each of three limbs, the right arm, the left arm, and the left foot, respectively.[10] He chose two of these limb electrodes to monitor each *lead*, making one electrode positive and the other electrode negative to record each of his three classic *bipolar limb leads*. He named these bipolar limb leads *Lead I* (left arm positive, right arm negative), *Lead II* (left foot positive, right arm negative), and *Lead III* (left foot positive, left arm negative). Note that the original string galvanometer consisted of massive equipment that filled a room.

FYI: ECG Recording 120 Years Ago

AP Correlation to ECG Waveform

- P wave: Electrical activation (depolarization) of the atrial myocardium.
- PR segment: This is a time of electrical quiescence during which the wave of electrical excitation (depolarization) passes through mainly the AV node.
- QRS wave: Depolarization of the ventricular myocardium.
- T wave: Ending of ventricular myocardium repolarization
- ST segment: Ventricular repolarization



LQTS-facts

- Normal QT interval: 360-440 ms
- Delayed repolarization of the myocardium, QT prolongation (>450 in man; > 470 in women).
- Increased risk for syncope, seizures, and SCD in the setting of a structurally normal heart
- 1/2500 persons.
- Usually asymptomatic, certain triggers leads to potentially life-threatening arrhythmias, such as Torsades de Pointes (TdP)

FYI: QT Interval Ranges

QT interval ranges

	Age 1 to 15	Adult man	Adult woman
Normal	Less than 0.44 second	Less than 0.43 second	Less than 0.45 second
Borderline	0.44 to 0.46 second	0.43 to 0.45 second	0.45 to 0.47 second
Prolonged	Greater than 0.46 second	Greater than 0.45 second	Greater than 0.47 second

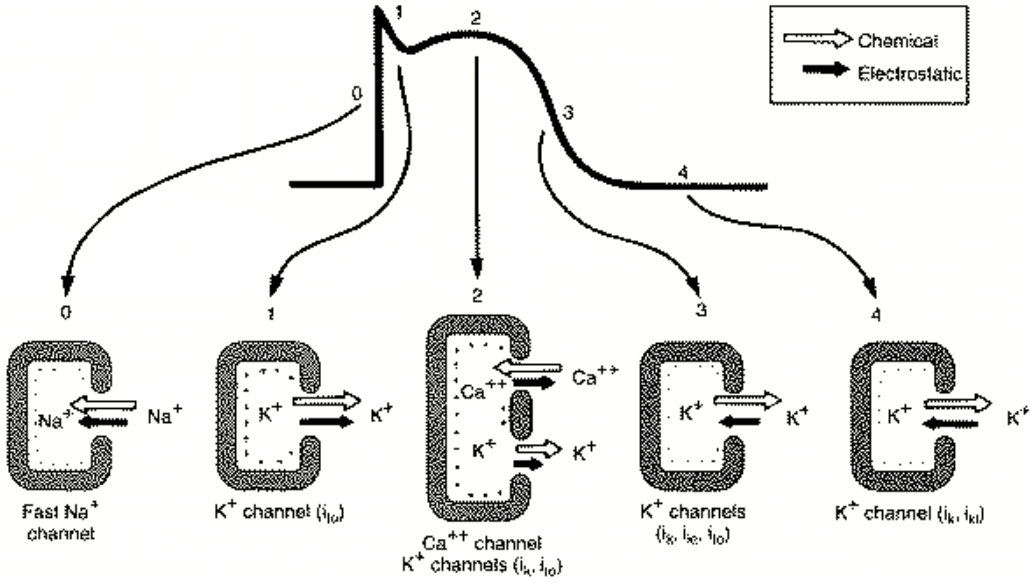
Source: Jacobson C. Long and short of it: What's up with the QT interval? http://hosted.mediasite.com/mediasite/Viewer/?peid=9ed8856fcdab4bc0bb066c25a148435b1d.

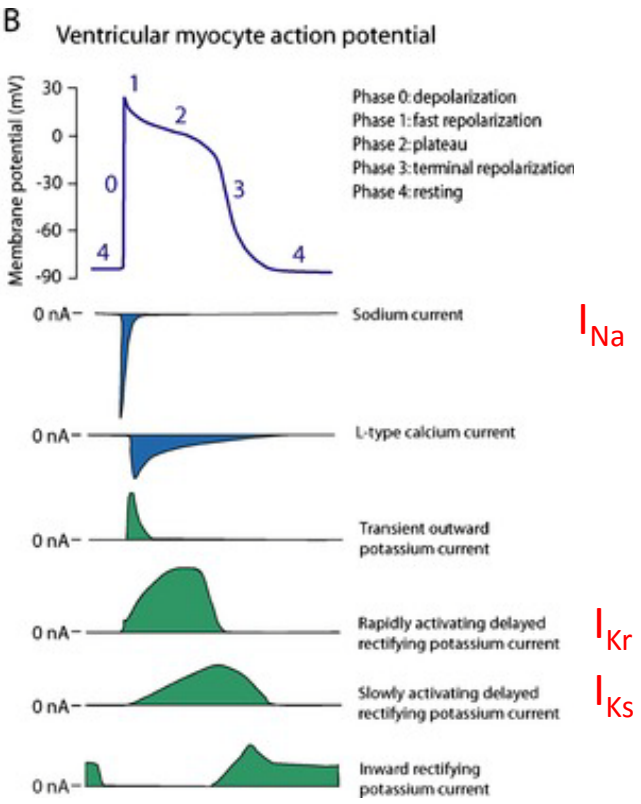
FYI: Genetic Basis for LQT syndromes

Type	Locus	Gene	Protein	Function	Frequency
LQT1	11p15.5	KCNQ1	KV7.1 α	$I_{Ks}\downarrow$	30%–35%
LQT2	7q35	KCNH2	KV11.1 α	$I_{Kr}\downarrow$	25%–30%
LQT3	3p21	SCN5A	NaV1.5 α	$I_{Na}\uparrow$	5%–10%
LQT4	4q25	ANK2	Ankyrin-B	$I_{Na,K}\downarrow$ $I_{NCX}\downarrow$	1%–2%
LQT5	21q22.1	KCNE1	minK β	$I_{Ks}\downarrow$	1%
LQT6	21q22.1	KCNE2	MiRP1 β	$I_{Kr}\downarrow$	Rare
LQT7*	17q23	KCNJ2	Kir2.1 α	$I_{K1}\downarrow$	Rare
LQT8†	12p13.3	CACNA1C	CaV 1.2 α1c	$I_{Ca,L}\uparrow$	Rare
LQT9	3p25	CAV3	Caveolin-3	$I_{Na}\uparrow$	Rare
LQT10	11q23	SCN4B	NaV1.5 β4	$I_{Na}\uparrow$	Rare
LQT11	7q21	AKAP9	Yotiao	$I_{Ks}\downarrow$	Rare
LQT12	20q11.2	SNTA1	A1-syntrophin	$I_{Na}\uparrow$	Rare

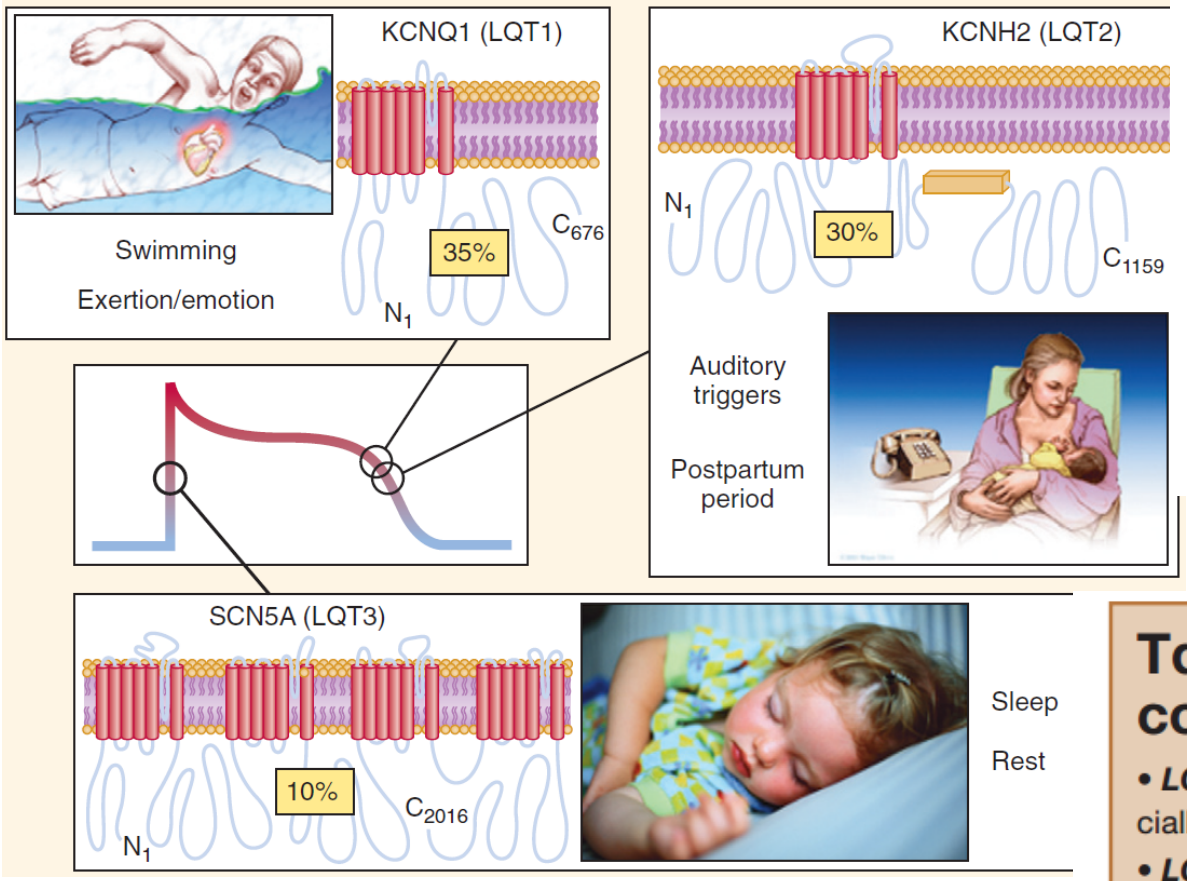
Cardiac action potential

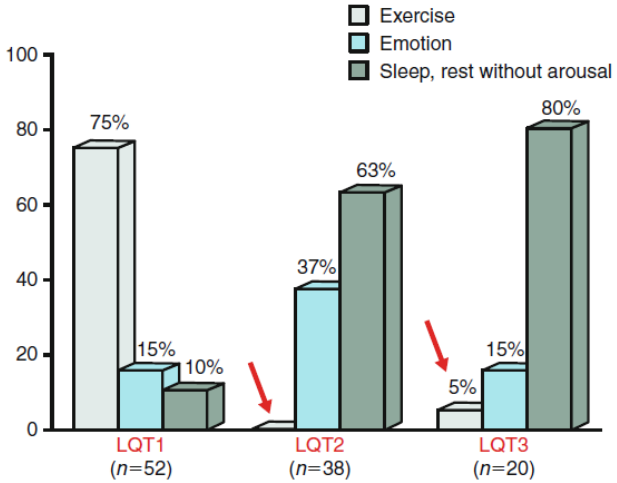
- **Phase 0. Influx of Na^+ (I_{Na}). Induces membrane depolarization**
- **Phase 1. Efflux of K^+ (I_{to}). Limits the Na^+ spike**
- **Phase 2. Influx of Ca^{2+} (I_{Ca}). Activation of I_K. Balance between Ca^{2+} influx and K^+ efflux. Ca^{2+} enters the cell to trigger the Ca^{2+}-induced Ca^{2+} release.**
- **Phase 3. Efflux of K^+ (I_K) increases. Repolarization starts**
- **Phase 4. Restoration of the resting potential: equilibrium potential of K via I_{K1}. and Na^+ / K^+ pump, Na^+ / Ca^{2+} pump.**





Pathophysiology of LQT (1, 2, 3)





TdP triggers in congenital LQTS

- ***LQTS1:*** Emotional stress or exercise, especially swimming or diving
- ***LQTS2:*** Extreme emotions or surprises, such as harsh, sudden noises
- ***LQTS3:*** Slow heart rate while sleeping

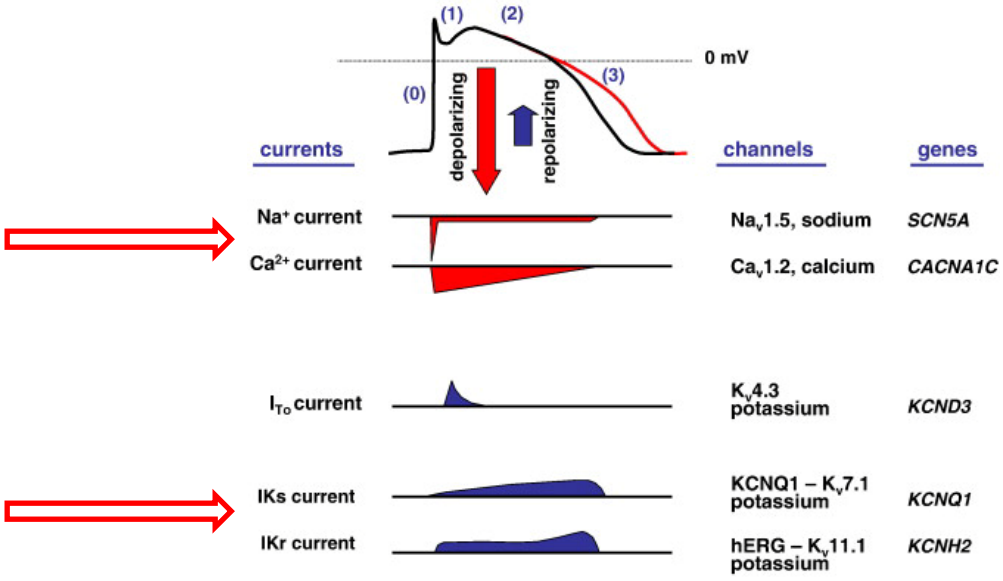
Source: National Heart, Lung, and Blood Institute. What is long QT syndrome? http://www.nhlbi.nih.gov/health/dci/Diseases/qt/qt_all.html.

LQT syndromes: proarrhythmic mechanisms

- Upregulation of inward currents

  Or

- Downregulation of outward currents

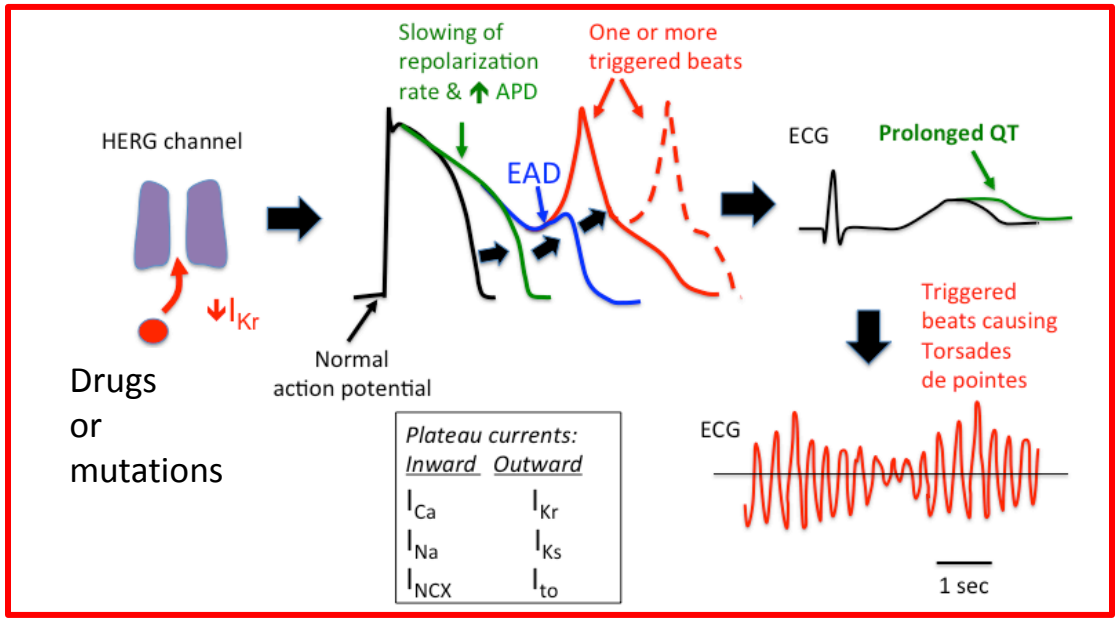


- EADs→ triggers

- Dispersion of APDs

  → substrates

  → reentry

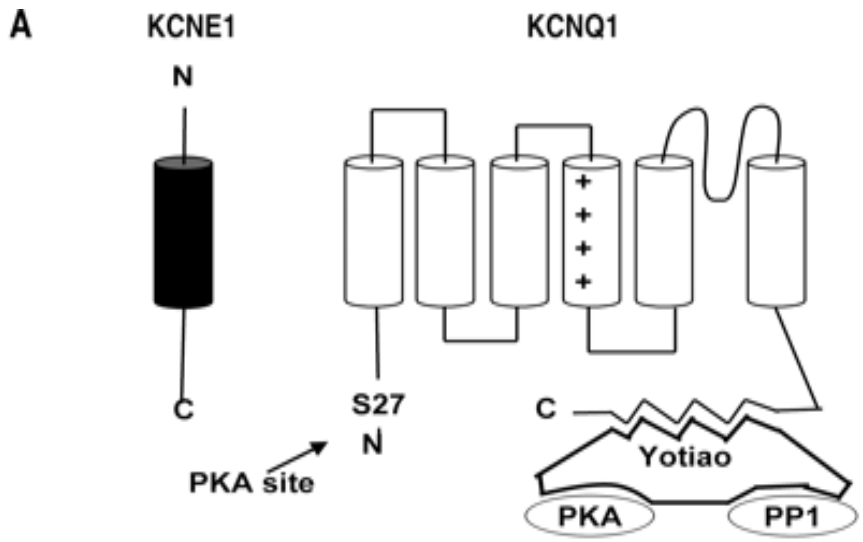


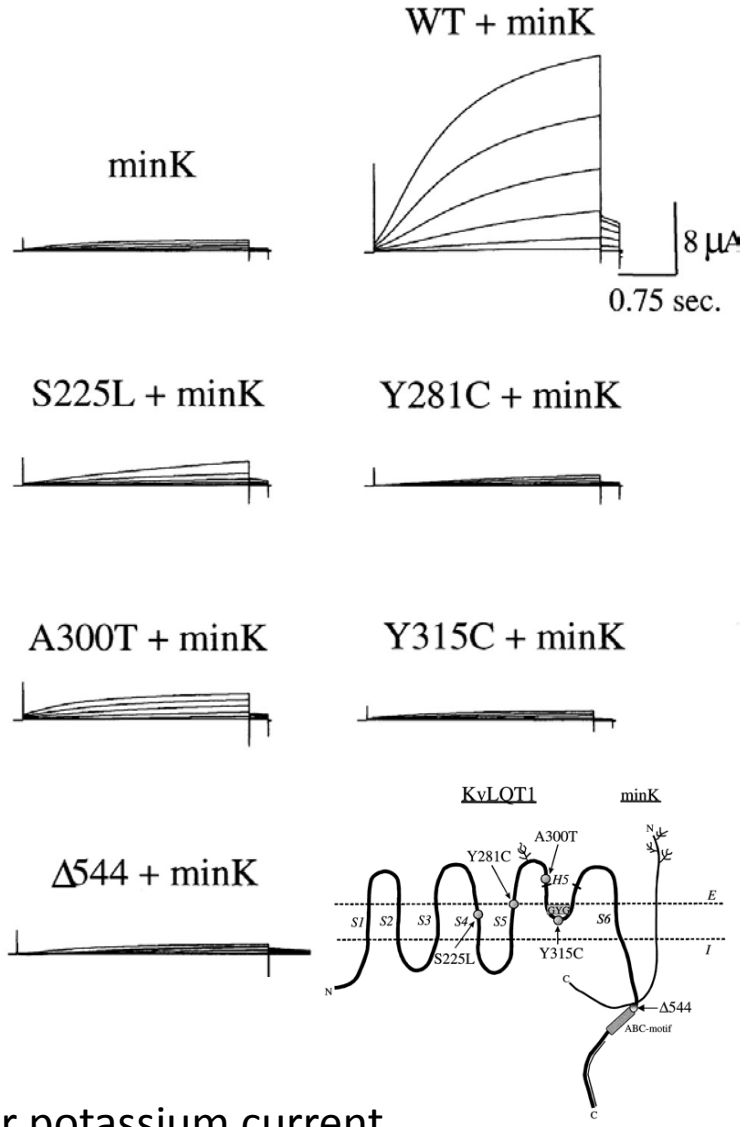
Example 1:

LQT1 and LQT2

Downregualtion of delayed K^+ channel, I_{Ks} and I_{Kr}

LQT1: KCNQ1 (KvLQT1) mutations

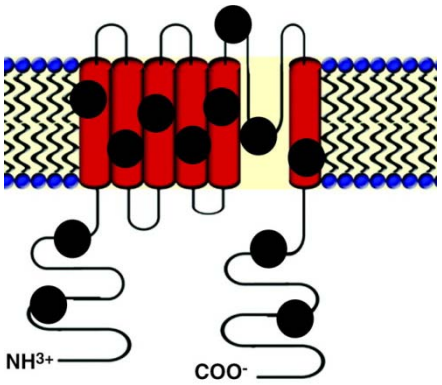


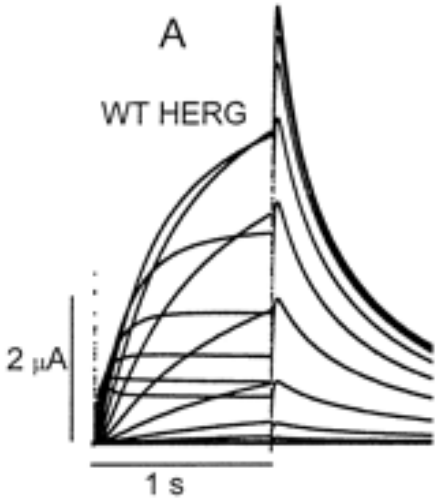


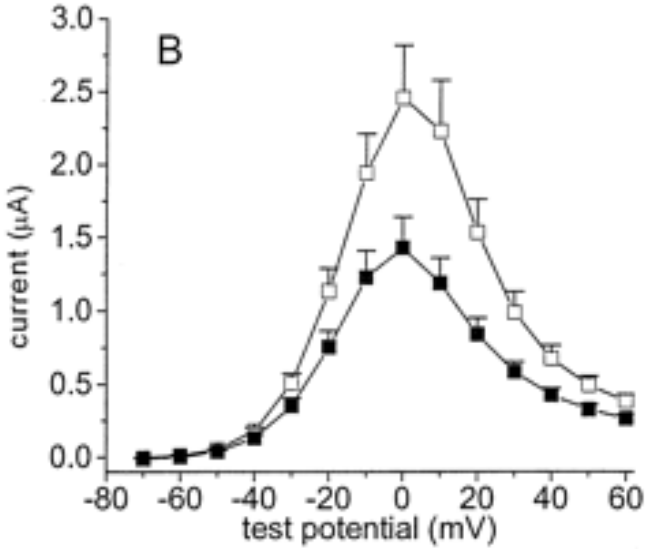
IKs: Slow component of the delayed rectifier potassium current

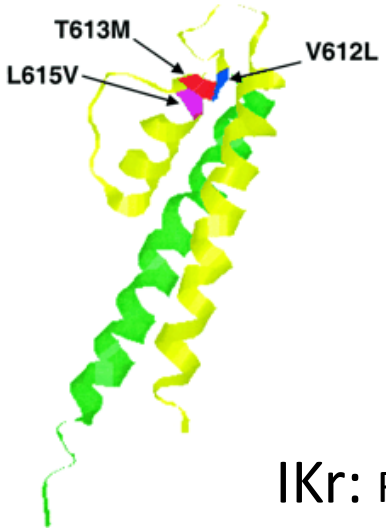
LQT2: KCNH2(HERG) MUTATIONS

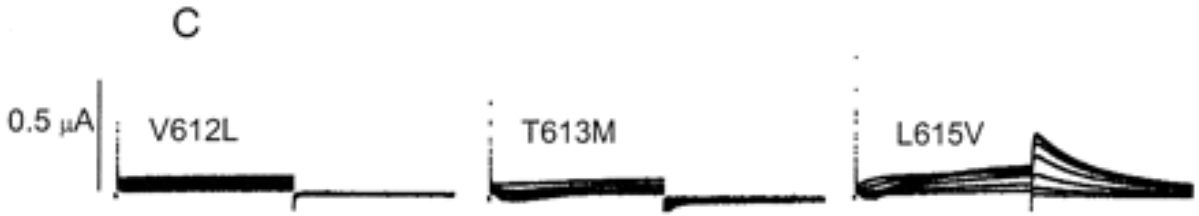
KCNH2 (HERG)





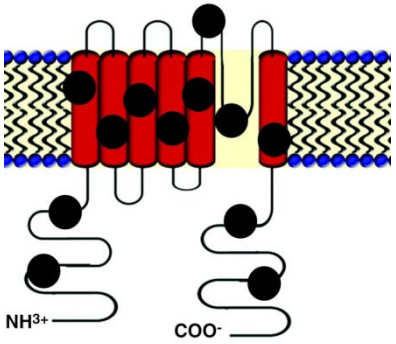




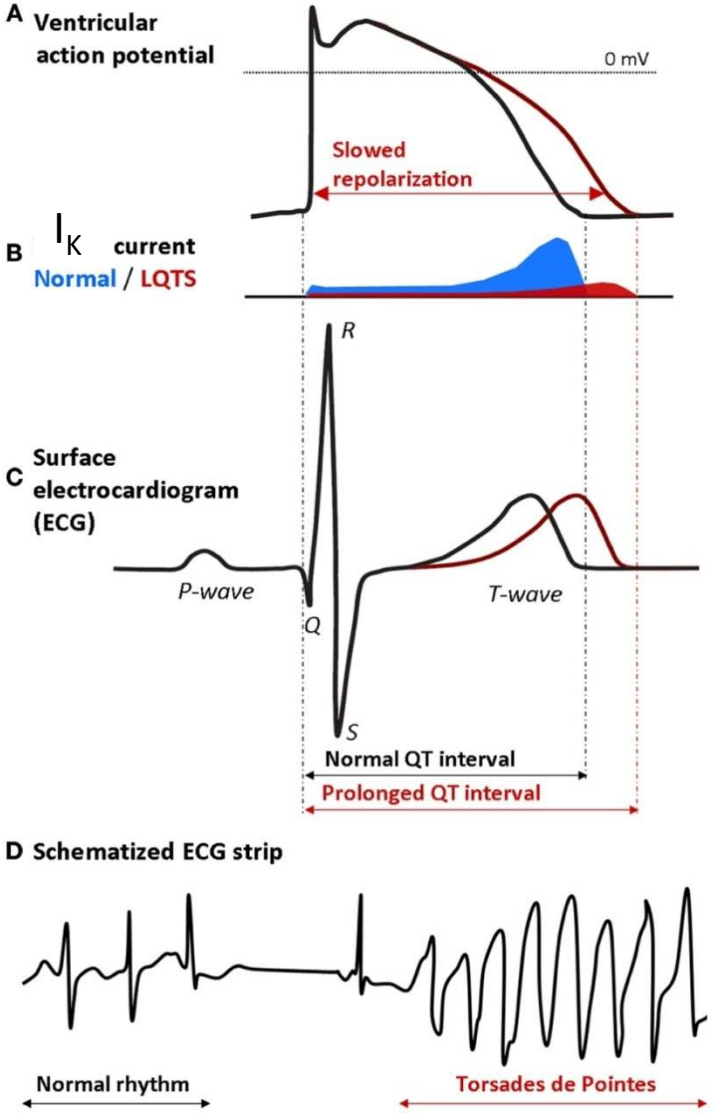


IKr: Rapid component of the delayed rectifier potassium current

LQT 1 and 2: I_{Ks} and I_{Kr} downregulation



KCNQ1 or KCNE2 gene mutations
(I_{Ks}) (I_{Kr})

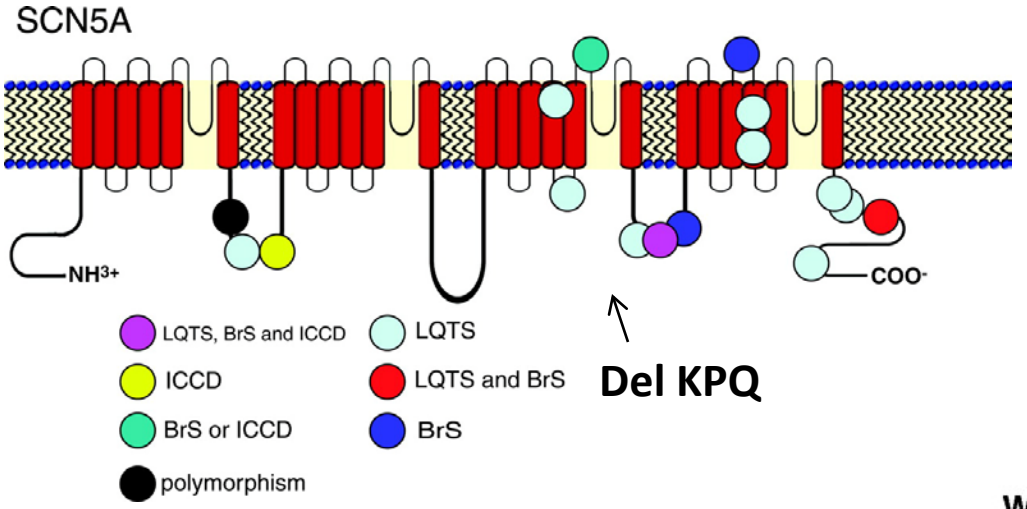


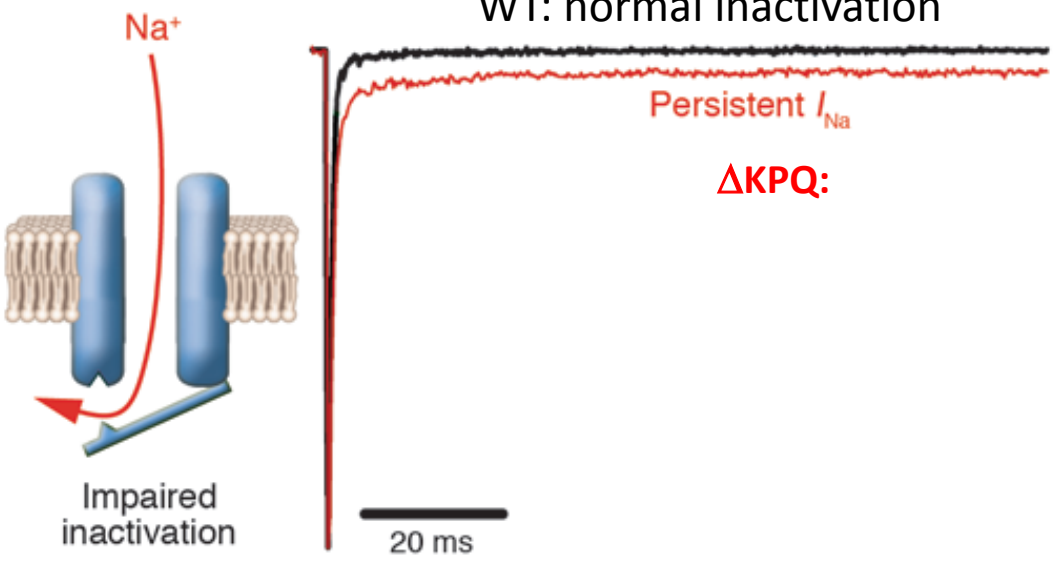
Example 2:

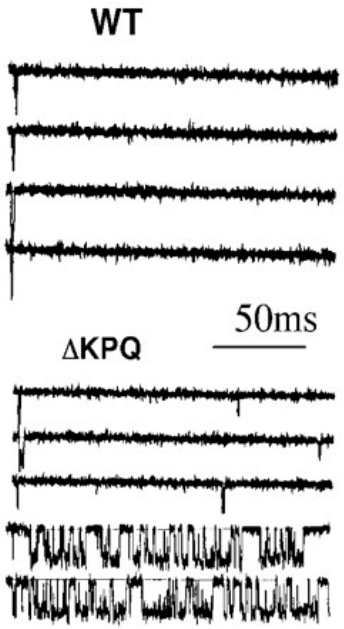
LQT3

Inactivation of Na^+ channel

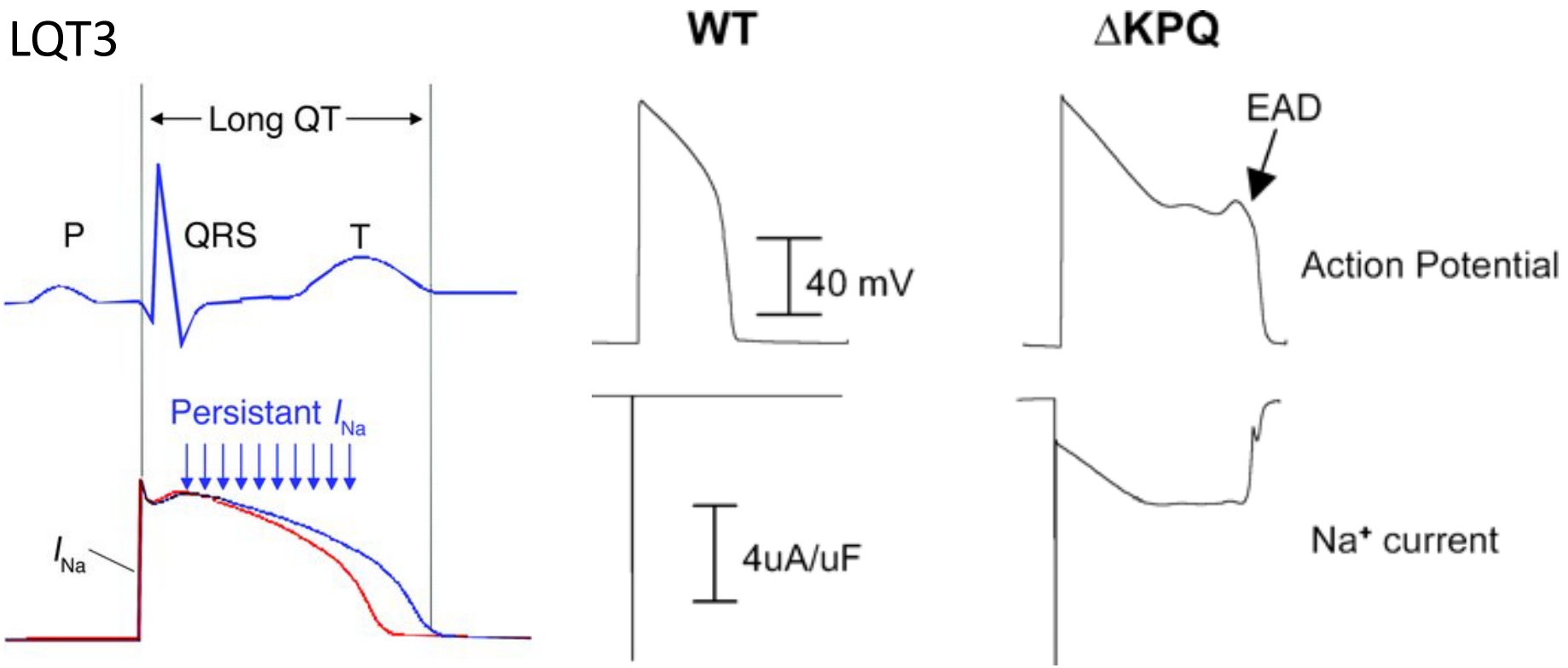
LQT3: Increased persistent Na Current





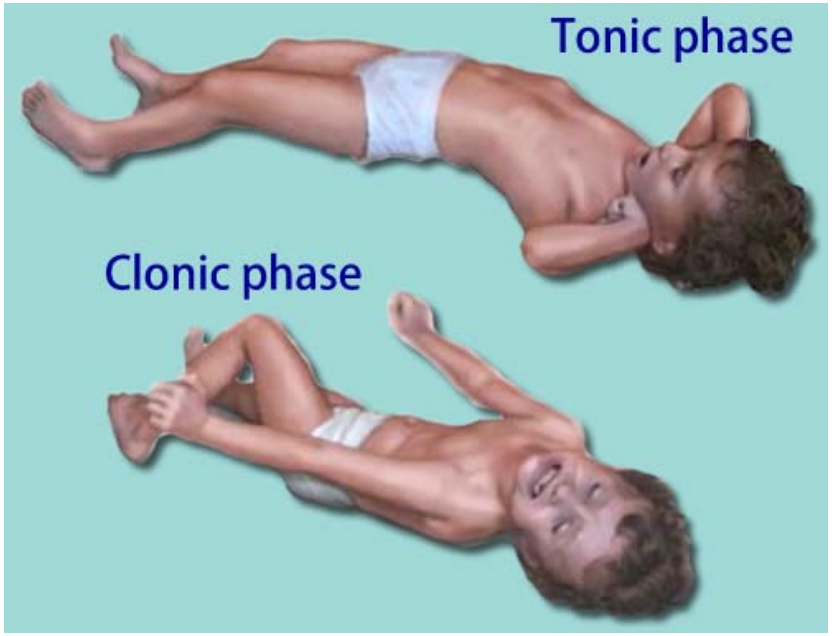


Functional mechanisms in LQT3



Example 3:
Epilepsy - a CNS Channelopathies

Epileptic seizure



Epilepsy is a disorder marked by disturbed electrical rhythms in the central nervous system

FYI: Ion Channels Implicated in Epilepsy

Channel	Protein	Gene	Syndrome
Voltage-gated			
Sodium channel	Type I α_1 subunit	*SCN1A*	Generalized epilepsy with febrile seizures plus syndrome (GEFS+)
	Type I β_1 subunit	*SCN1B*	Generalized epilepsy with febrile seizures plus syndrome (GEFS+)
	Type I α_1 subunit	*SCN1A*	Severe myoclonic epilepsy of infancy (SMEI)
	Type I α_1 subunit	*SCN1A*	Intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTCS)
	Type I α_1 subunit	*SCN1A*	Infantile spasms (IS)
	Type II α_1 subunit	*SCN2A*	Benign familial neonatal-infantile seizures (BFNIS)
Calcium channel	P/Q-type α_1 subunit	*CACNA1A*	Episodic ataxia type 2 (EA2) Familial hemiplegic migraine (FHM) Spinocerebellar ataxia type 6 (SCA 6)
		CACNB4	Episodic ataxia type 2 (EA2)
	T-type α_1 subunit	*CACNA1H*	Childhood absence epilepsy (CAE)[a]
Potassium channel	$K_V1.1$	*KCNA1*	Episodic ataxia type 1 (EA1)
	M-channel	*KCNQ2* *KCNQ3*	Benign familial neonatal convulsions (BFNC)
	BK channel	*KCNMA1*	Generalized epilepsy with paroxysmal dyskinesia (GEPD)
Chloride channel	CLC-2	*CLCN2*	Juvenile myoclonic epilepsy (JME) Juvenile absence epilepsy (JAE) Epilepsy with grand mal seizures on awakening (EGMA) CAE
Ligand-gated			
Acetylcholine receptor	β_2 subunit	*CHRNB2*	Autosomal dominant frontal lobe epilepsy (ADNFLE)
	α_4 subunit	*CHRNA4*	
GABA receptor	γ_2 subunit	*GABRG2*	GEFS+, CAE, SMEI
	α_1 subunit	*GABRA1*	JME
	β subunit	*GABRD*	JME[a]

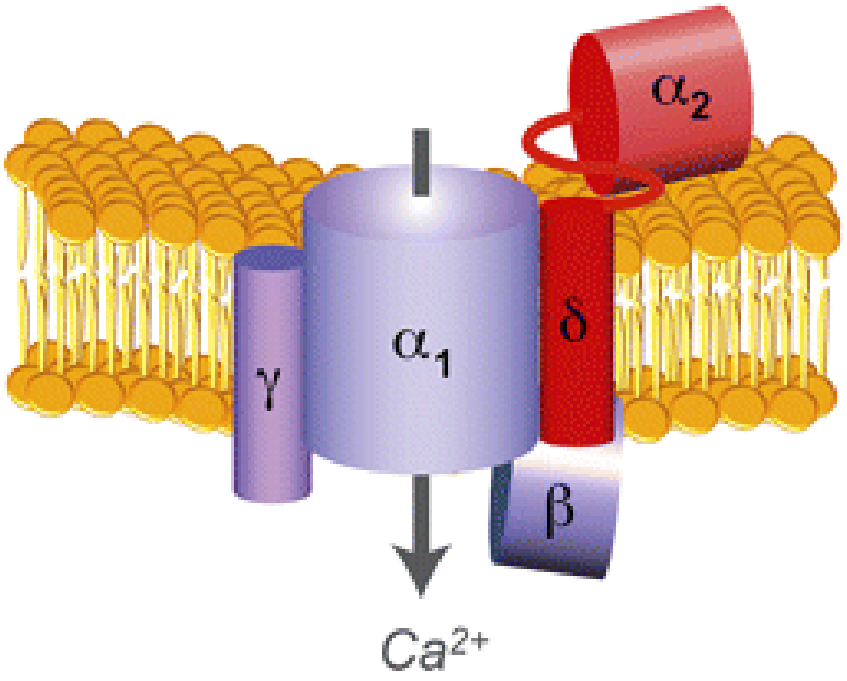
Voltage-gated Ca Channels: Subunit Assembly and Subtypes

Ancillary subunits

$\beta_1, \beta_2, \beta_3, \beta_4$

γ_1 through γ_8

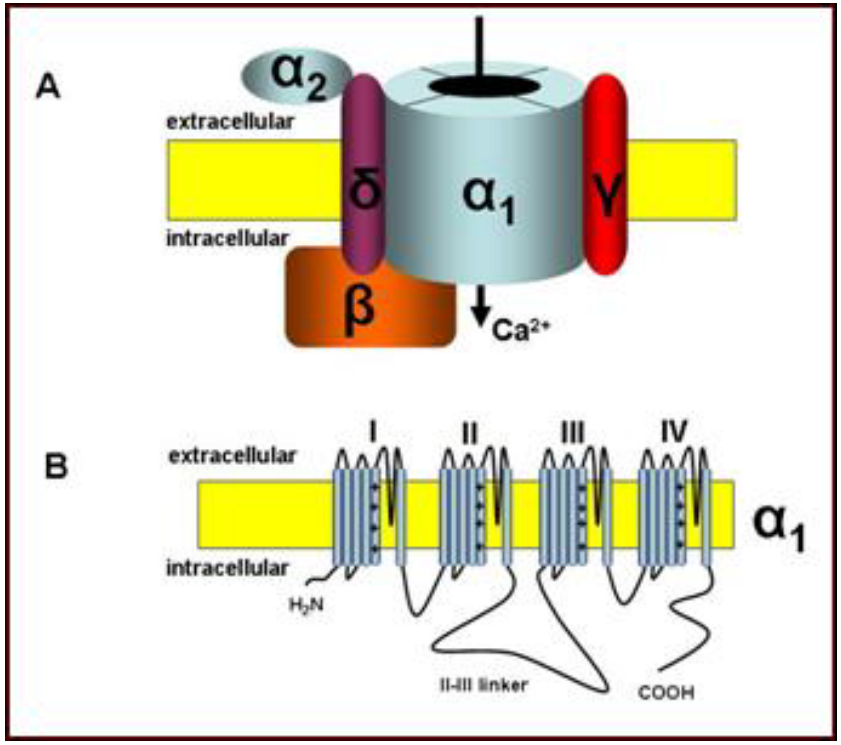
α_2-δ_1 through α_2-δ_4

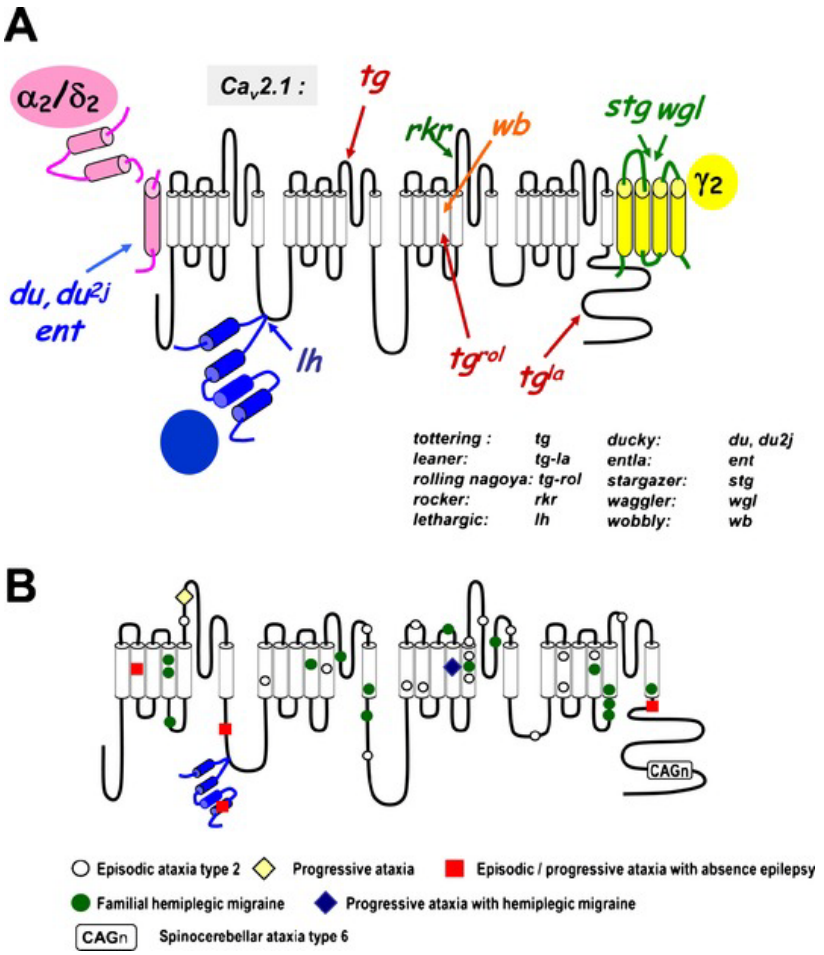


Neuronal α_1 subunits

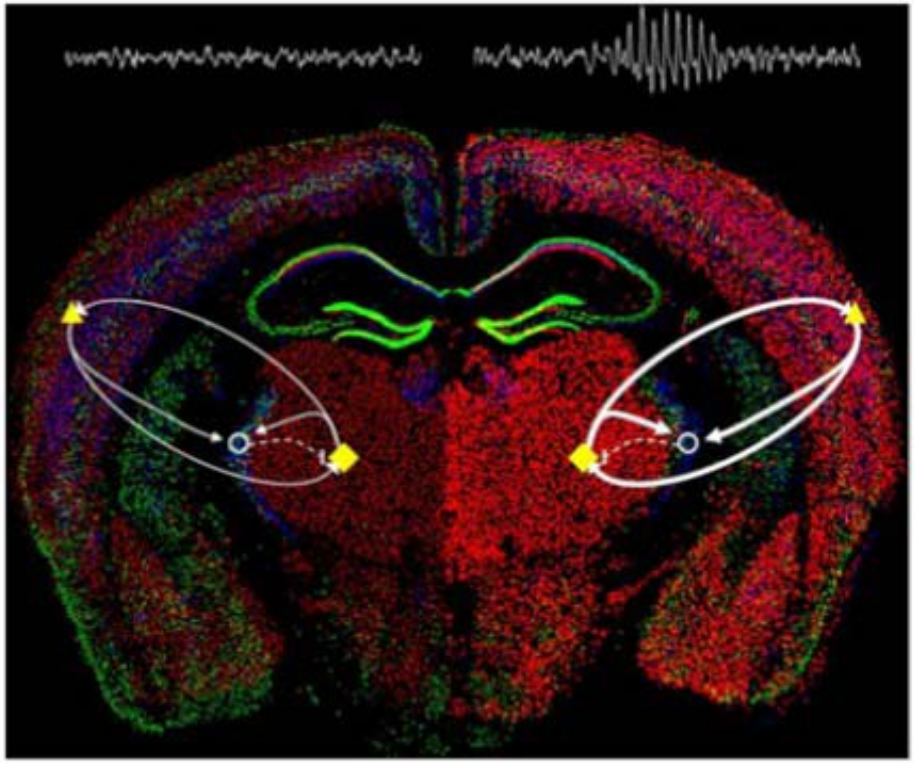
HVA	$Ca_v1.2$	L-type
	$Ca_v1.3$	L-type
	$Ca_v1.4$	L-type
	$Ca_v2.1$	P/Q-type
	$Ca_v2.2$	N-type
	$Ca_v2.3$	R-type
LVA	$Ca_v3.1$	T-type
	$Ca_v3.2$	T-type
	$Ca_v3.3$	T-type

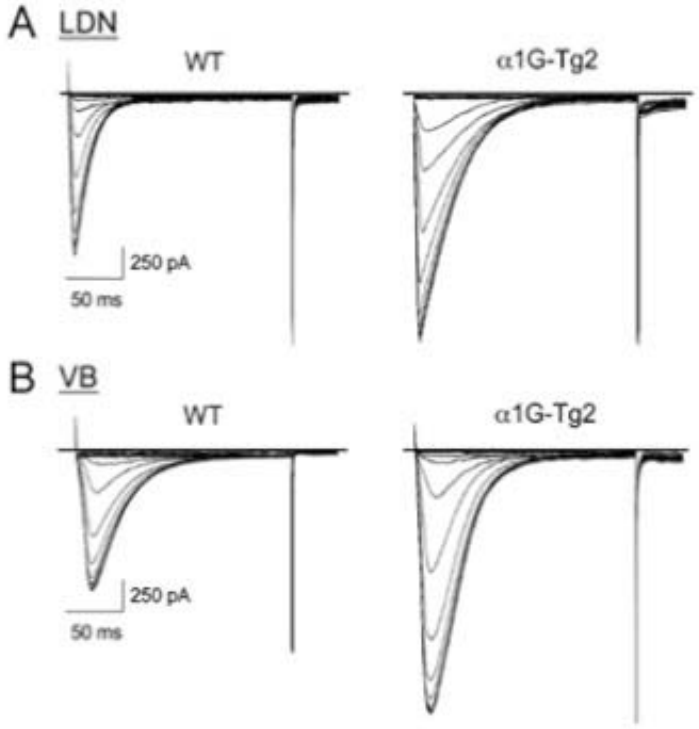
Epilepsy: Voltage-gated Ca^{2+} Channel





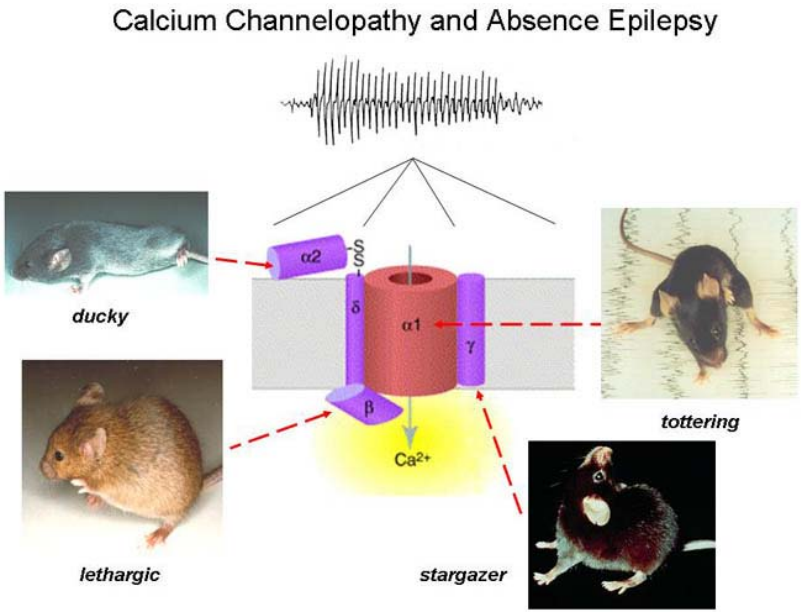
Enhancement of T-type Ca current in thalamocortical networks produces spike wave absence epilepsy





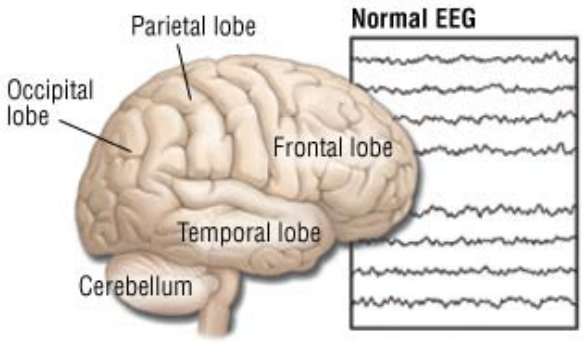
gain-of-function

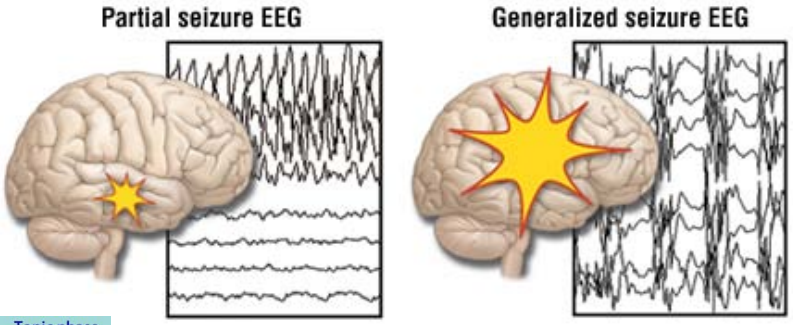
Epilepsy: Pathology and Symptom

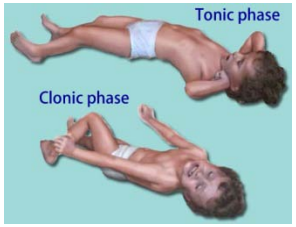


In mice

In human







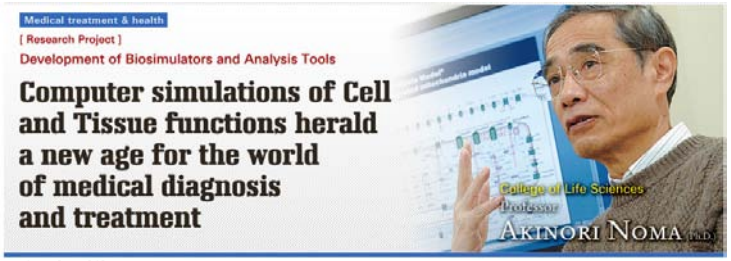
Electroencephalogram (EEG)

disturbed electrical rhythms

Example 4:

ATP-Sensitive K^+ Channel and Diabetes

Discovery of K_{ATP} Channel



Nature. 1983 Sep 8-14;305(5930):147-8.

ATP-regulated K+ channels in cardiac muscle.

Noma A.

Abstract

An outward current of unknown nature increases significantly when cardiac cells are treated with cyanide or subjected to hypoxia, and decreases on intracellular injection of ATP. We report here that application of the patch-clamp technique to CN-treated mammalian heart cells reveals specific K+ channels which are depressed by intracellular ATP (ATPi) at levels greater than 1 mM. For these channels, conductance in the outward direction is much larger than the inward rectifier K+ channel which is insensitive to ATP. AMP had no effect on the ATP-sensitive K+ channel, and ADP was less effective than ATP. Thus, the ATP-sensitive K+ channel seems to be important for regulation of cellular energy metabolism in the control of membrane excitability.

Saalland大学三人組と三内三人組

Nature. 1983 May 19-25;303(5914):250-3.

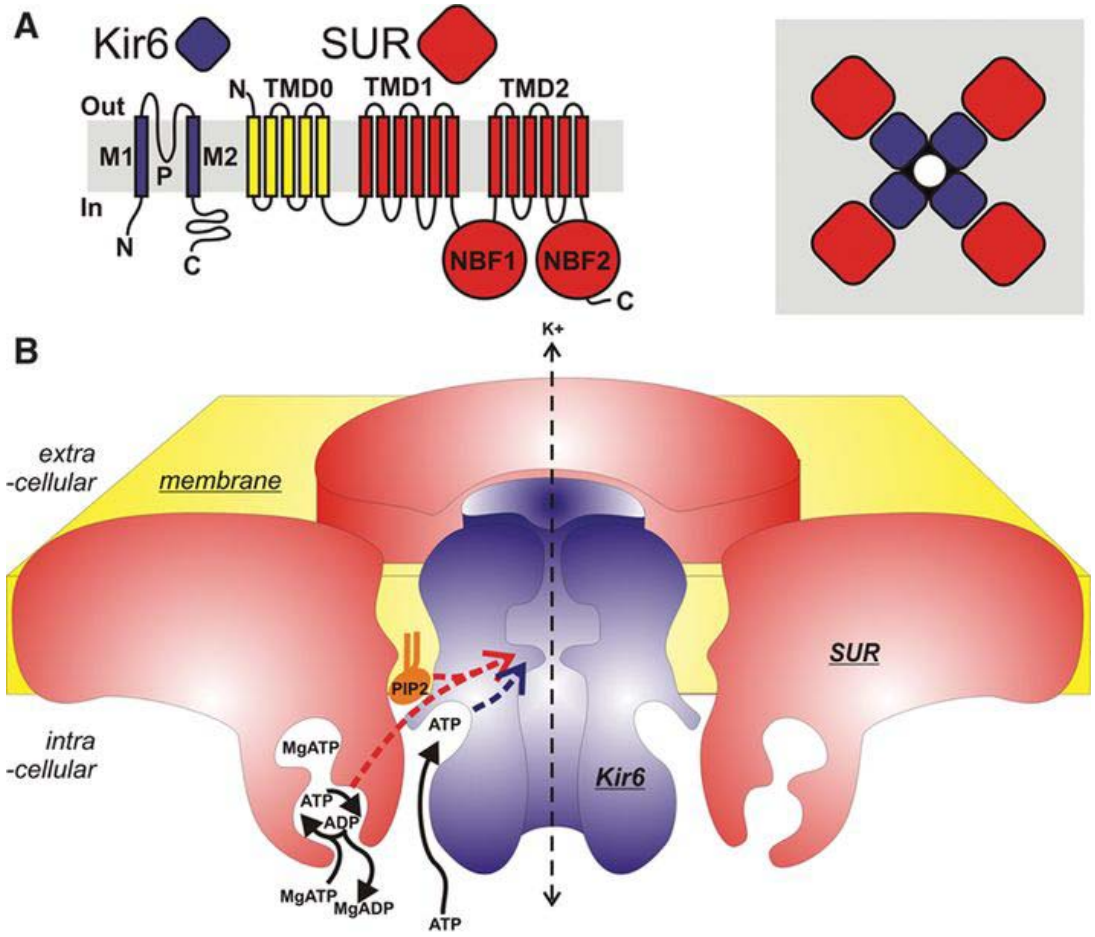
Acetylcholine activation of single muscarinic K+ channels in isolated pacemaker cells of the mammalian heart.

Sakmann B, Noma A, Trautwein W.

Abstract

Acetylcholine (ACh) released on vagal stimulation reduces the heart rate by increasing K+ conductance of pacemaker cells in the sinoatrial (S-A) node. Fluctuation analysis of ACh-act currents in pacemaker tissue showed this to be due to opening of a separate class of K+ chann

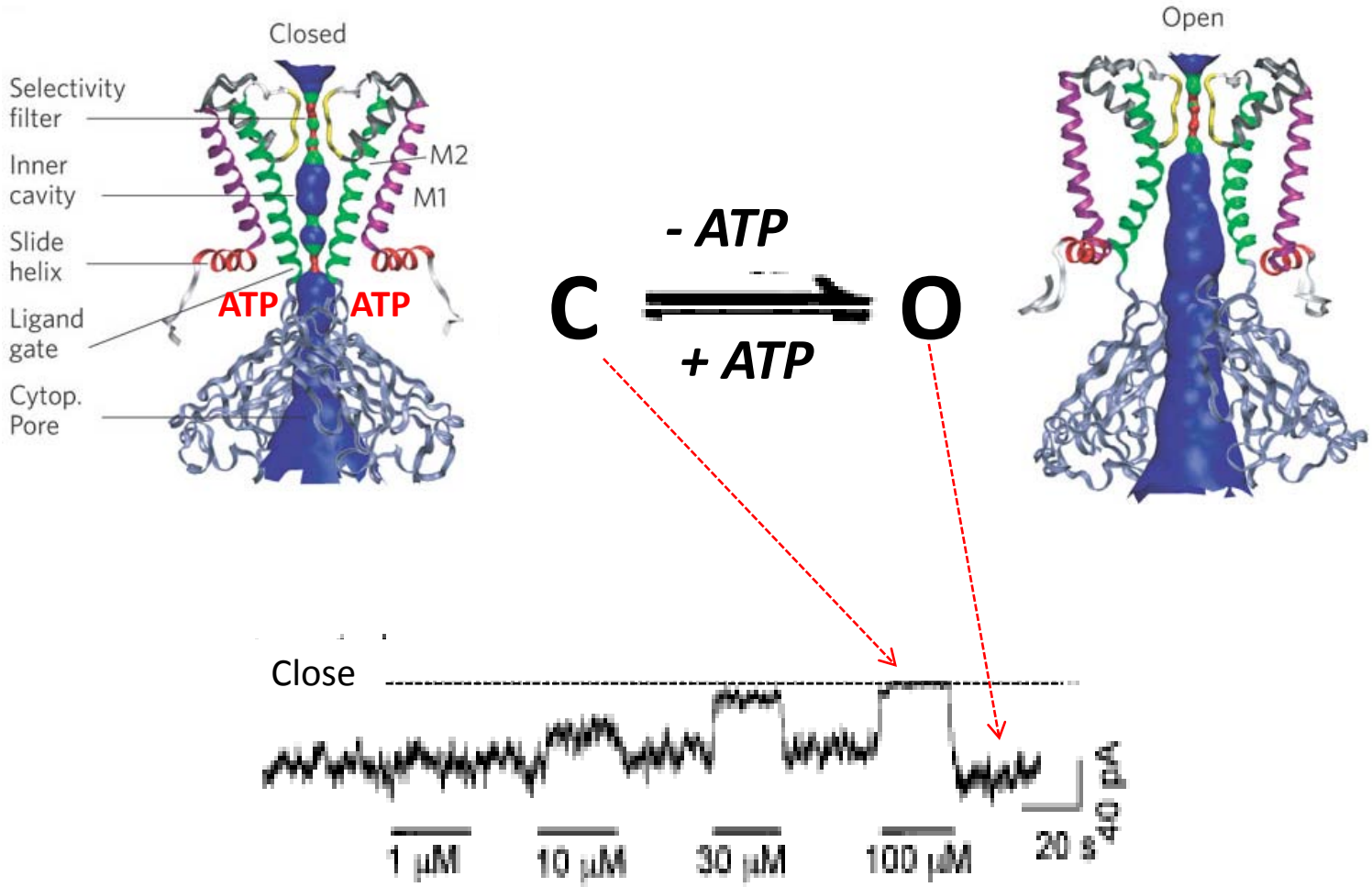
ATP-Sensitive Potassium Channel



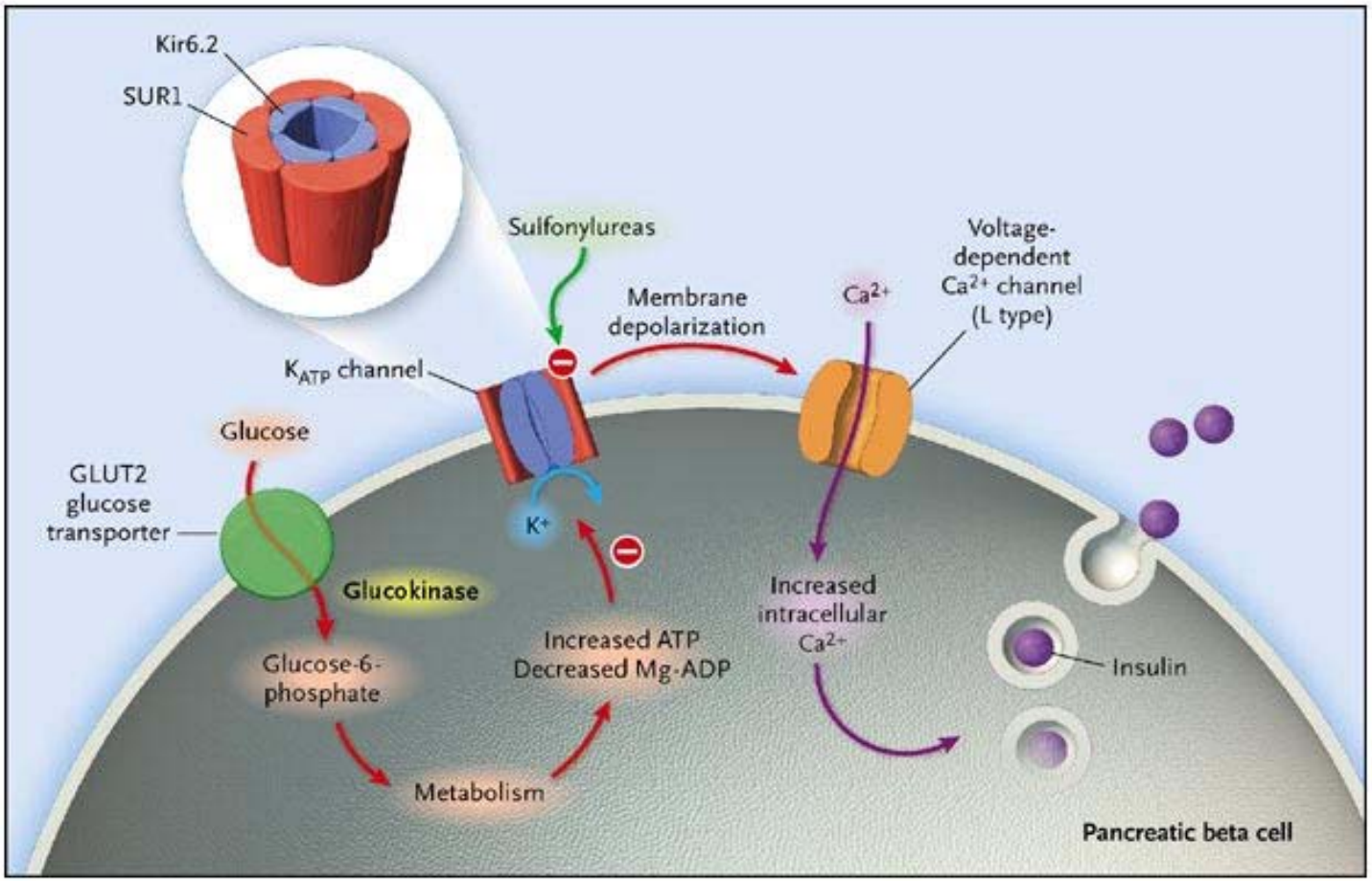
Is composed of Kir6.x and sulfonylurea receptors (SURs)

- Inhibited by ATP
- Inhibited by sulfonylurea via SURs

ATP-Sensitive K channel Inhibited by ATP



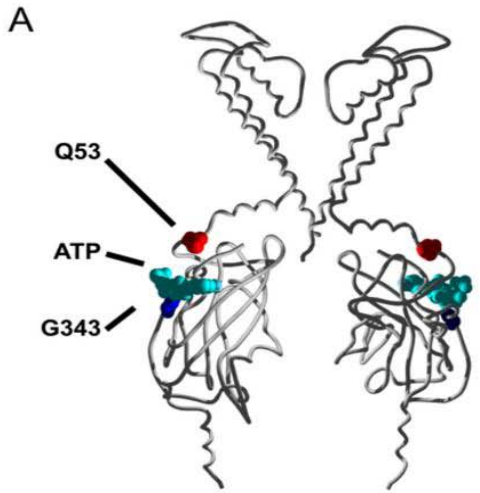
Role of the K_{ATP} Channel in Insulin Secretion in Pancreatic β Cell

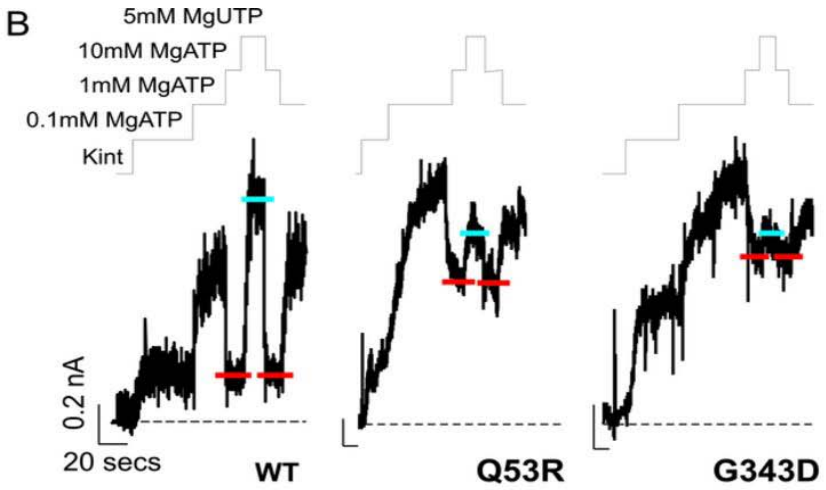


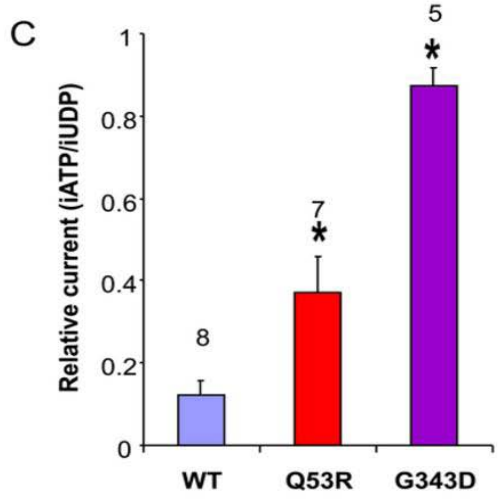
- Glucose enters the cell via the GLUT2 transporter
- Glycolytic and mitochondrial metabolism leads to an increase in ATP
- This results in K_{ATP} channel closure, membrane depolarization,
- Opening of voltage-gated Ca^{2+} channels, Ca^{2+}influx,
- Exocytosis of insulin granules (insulin secretion).

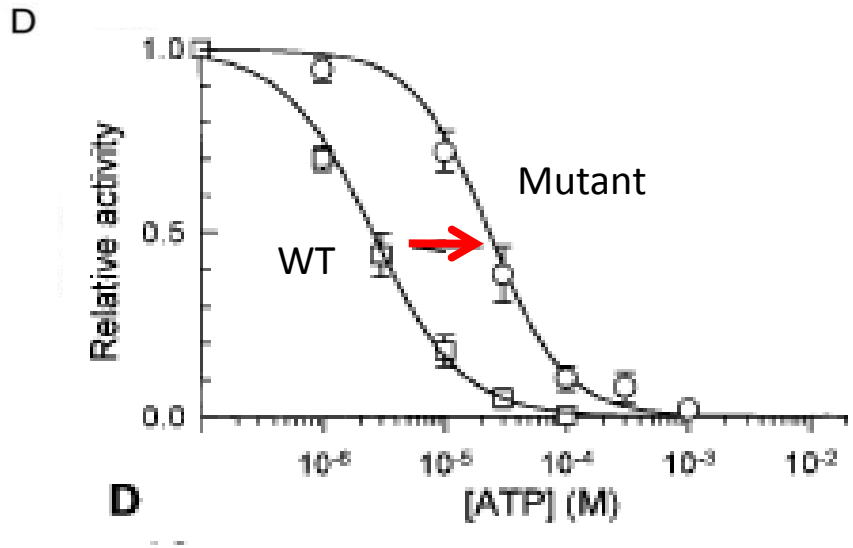
Gloyn AL et al. N Engl J Med 2004;350:1838-1849.

K_{ATP} Channel Mutations Causing Lower ATP Sensitivity and Diabetes

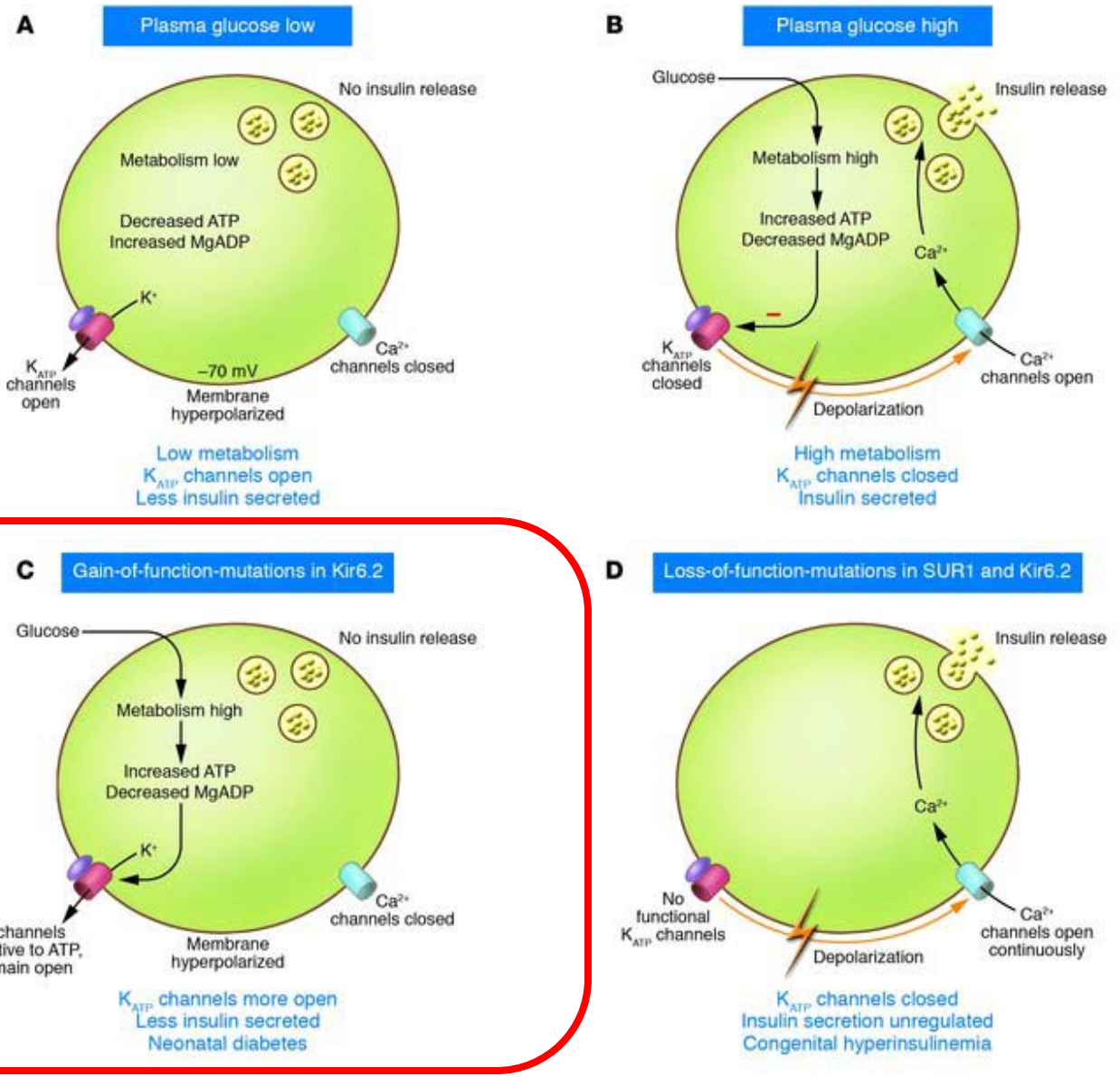








The K_{ATP} Channel Couples Glucose Metabolism to Insulin Secretion



Example 5:

Cystic Fibrosis: Cl^- Channel Disease

Cystic Fibrosis: Facts

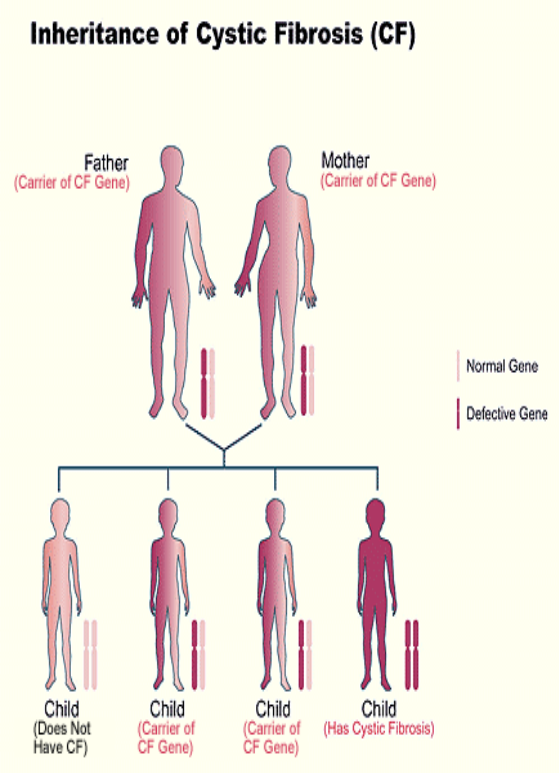
- Cystic fibrosis (CF) is autosomal recessive disease

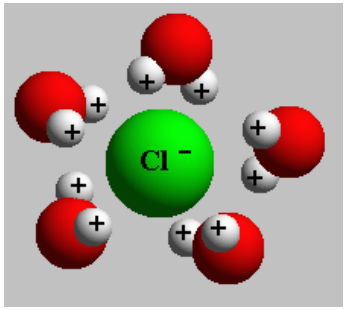
- CF is a chronic, progressive, life threatening genetic disorder of pediatrics.

- It affect white population (1 in 3200 live births) but is uncommon among Asian and African population

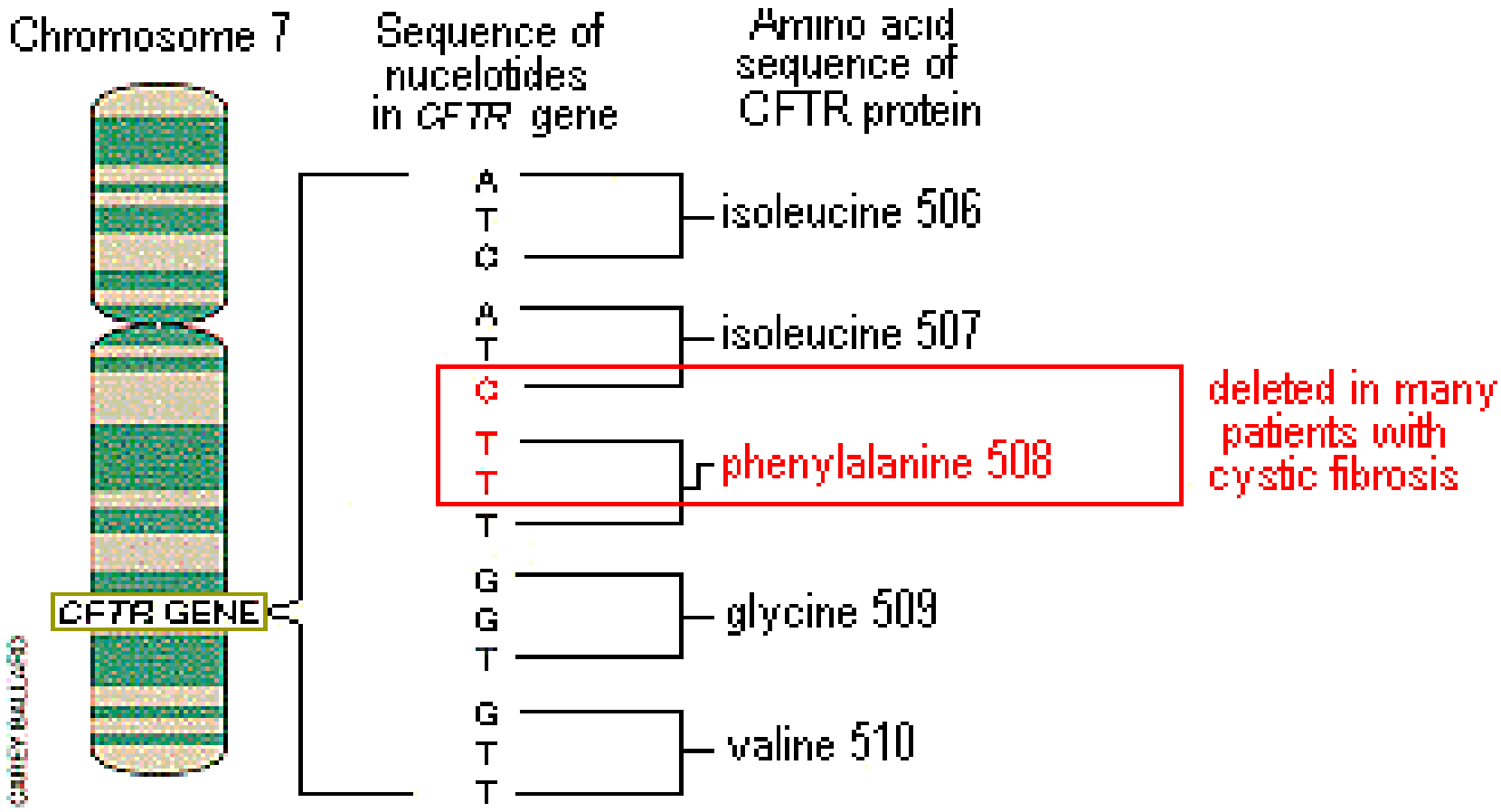
- It affects exocrine glands (mainly sweat glands) and mucus gland present on the epithelial lining of lungs, pancreas, intestine, and reproductive system.

- CF is a defect in epithelial chloride channel protein, causes membrane to become impermeable to Chloride ion.





CFTR gene encode for the CFTR protein channel



CF occurs due to the deletion of 3 nucleotides which code for the phenylalanine from the CFTR (cystic fibrosis transmembrane conductance regulator) gene located on chromosome no.7 at position 508. This mutation is known as ΔF 508

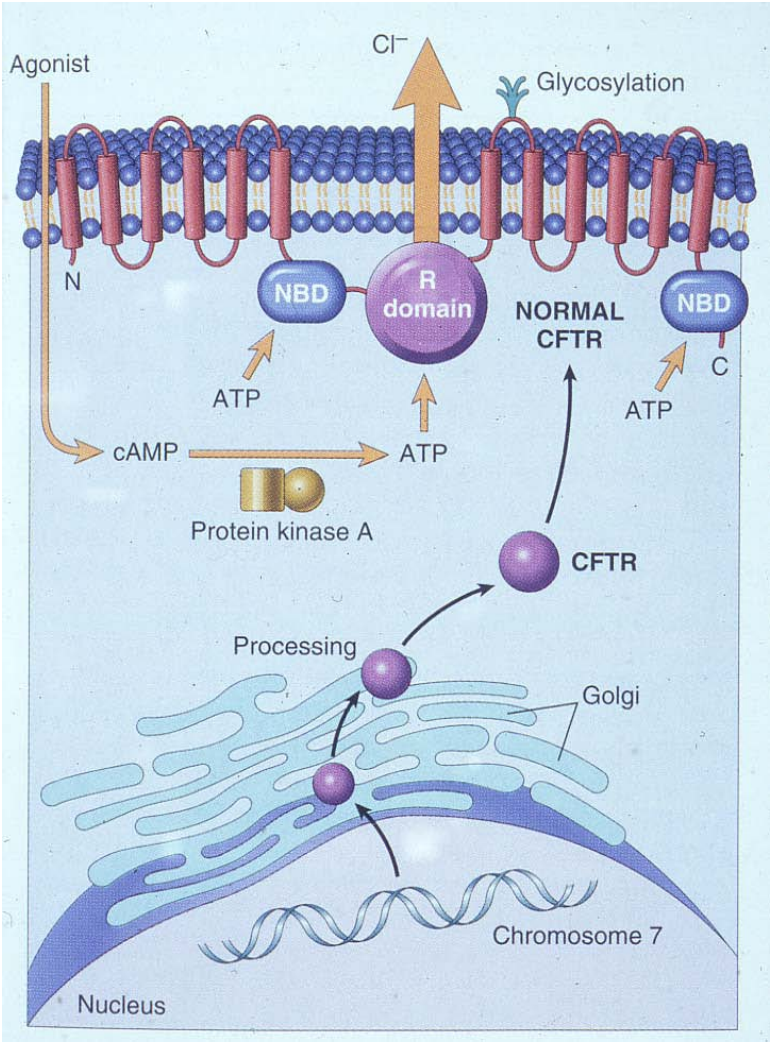
Structure of the CFTR protein

CFTR protein is a cAMP induced Channel made up of five domains:

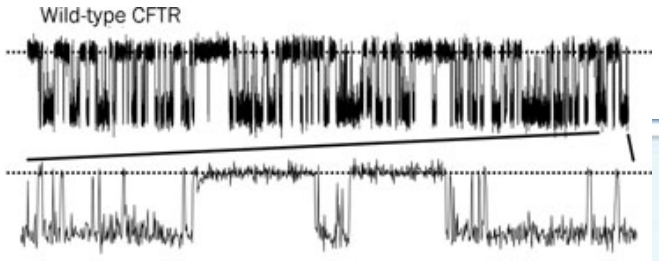
Two membrane-spanning domain (MSD1 & MSD2) that form Cl^- ion channel.

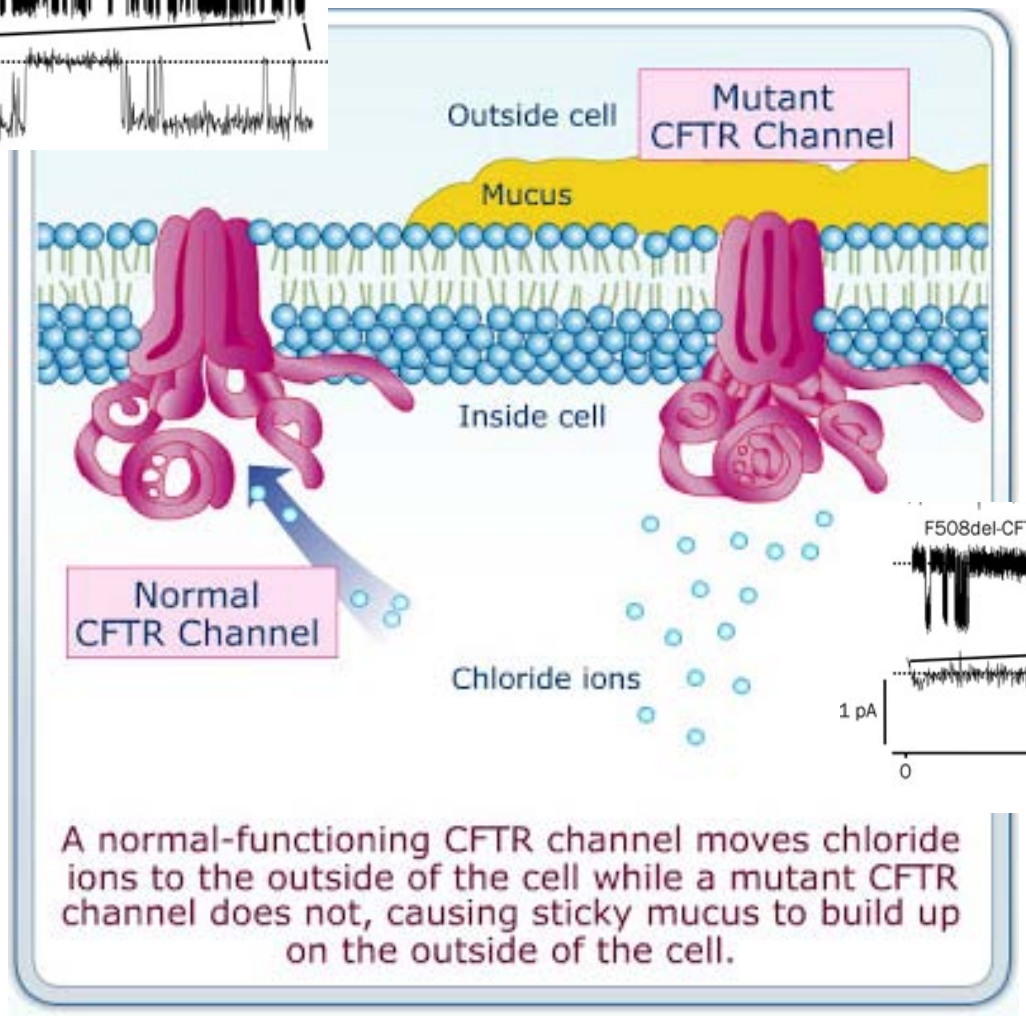
Two nucleotide binding domains (NBD1 & NBD2) that bind and hydrolyze ATP.

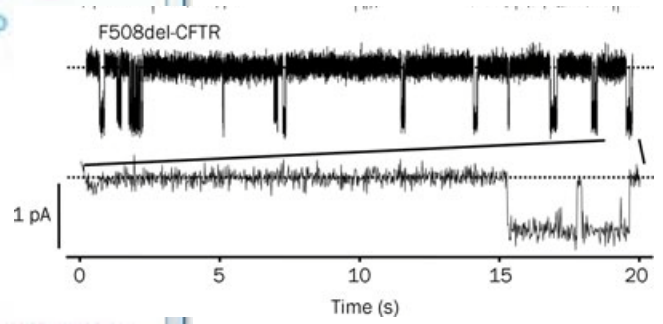
A regulatory R domain.



CFTR mutation: Loss of Cl^- Channel Function





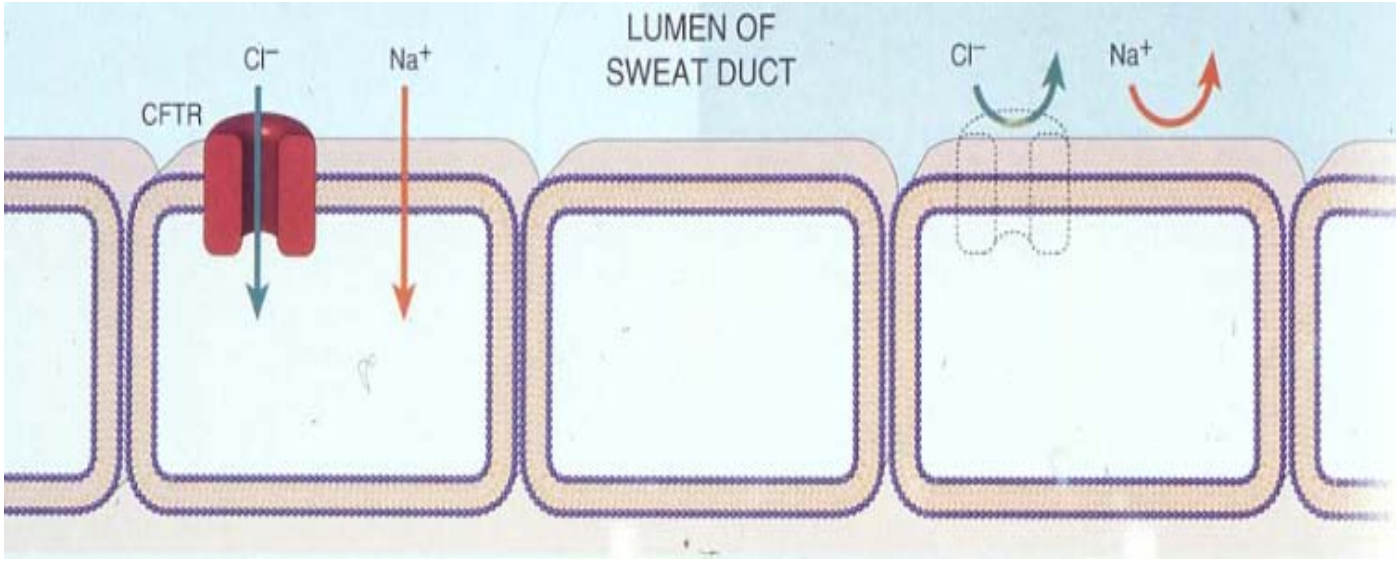


Pathology of Cystic Fibrosis - 1

In sweat glands:

CFTR is responsible for re-absorption of Cl^- along with Na^+ through epithelial Na channel (ENaC).

Impaired function of CFTR cause the production of hypertonic salty sweat, and ultimately dehydration.

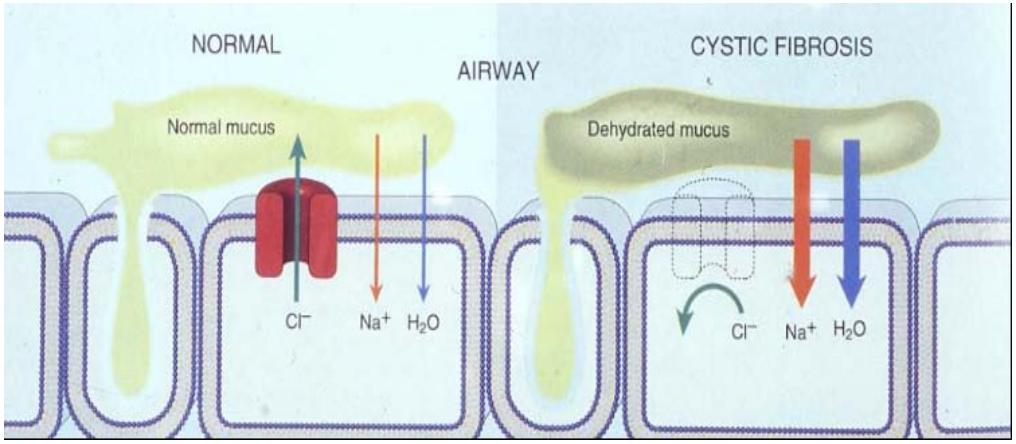


SWEAT GLANDS

Pathology of Cystic Fibrosis - 2

In lung mucus glands:

- Loss of CFTR function to secrete chloride ion →
- Loss or reduction of Cl^- ion in luminal secretion →
- Followed by active luminal Na^+ absorption through ENaC →
- Increases passive water absorption from the lumen →
- Impaired mucociliary action, accumulation of thick, viscous, dehydrated mucus
- Obstruction of air passage and recurrent pulmonary infections



Channelopathies: Summary

- Channel mutations are an increasingly recognized cause of disease.
- Many channelopathies are episodic despite persistently abnormal channel.
- Abnormalities in same channel may present with different disease states
- Mutations/ abnormalities in different channels may lead to same disease e.g. periodic paralysis or epilepsy
- Disease mechanism often unclear despite identification of mutation.

Thank you!

FYI: Human Channelopathies

Protein	Gene	Disease	Functional defect
$Na_v1.1$	*SCN1A*	Generalized epilepsy with febrile seizures plus (GEFS+)	Hyperexcitability
$Na_v1.2$	*SCN2A*	Generalized epilepsy with febrile and afebrile seizures	Hyperexcitability
$Na_v1.4$	*SCN4A*	Paramyotonia congenita, potassium-aggravated myotonia, hyperkalemic periodic paralysis	Hyperexcitability
$Na_v1.5$	*SCN5A*	LQTS/Brugada syndrome	Heart action potential
SCN1B	*SCN1B*	Generalized epilepsy with febrile seizures plus (GEFS+)	Hyperexcitability
KCNQ1	*KCNQ1*	Autosomal-dominant LQTS with deafness	Heart action potential/inner ear K^+ secretion
		Autosomal-recessive LQTS	Heart action potential
KCNH2	*KCNH2*	LQTS	Heart action potential
Kir2.1	*KCNJ2*	LQTS with dysmorphic features	Heart action potential
HERG	*KCNH2*	Congenital and acquired LQTS	Heart action potential and excessive responses to drugs
Ankyrin-B	*ANKB*	LQTS	Heart action potential
$Ca_v1.2$	*CACNA2*	Timothy syndrome	Multisystem disorders
Kir6.2	*KCNJ11*	Persistent hyperinsulinemic hypoglycemia of infancy	Insulin hypersecretion
		Diabetes mellitus	Insulin hyposecretion
SUR1	*SUR1*	Persistent hyperinsulinemic hypoglycemia of infancy	Insulin hyposecretion
SUR2	*SUR2*	Dilated cardiomyopathy	Metabolic signaling
KCNE1	*KCNE1*	Autosomal-dominant LQTS with deafness	Heart action potential
		Autosomal-dominant LQTS	Heart action potential
KCNE2	*KCNE2*	LQTS	Heart action potential
CFTR	*ABCC7*	Cystic fibrosis	Epithelial transport defect
ClC-1	*CLCN1*	Myotonia (autosomal-recessive or -dominant)	Defective muscle repolarization
ClC-5	*CLCN5*	Dent disease	Defective endosome acidification
ClC-7	*CLCN7*	Osteopetrosis (recessive or dominant)	Defective bone resorption
ClC-Kb	*CLCNKB*	Bartter syndrome type III	Renal salt loss
RyR1	*RyR1*	Central core disease, malignant hyperthermia	Abnormal muscle activity
RyR2	*RyR2*	Catecholaminergic polymorphic tachycardia	Exercise-related cardiac arrhythmias

J Clin Invest. 2005;115(8)

and MORE…