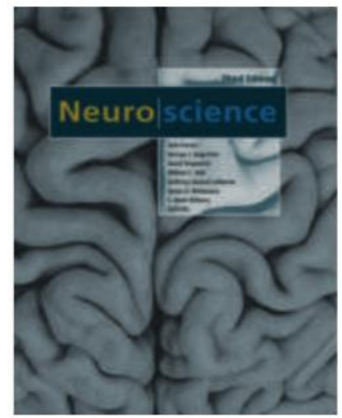
Voltage Gated Ion Channels

The Machines That Make It Possible...

Topics I	Topics II
Introduction & Electrochemical Gradients	Synaptic Transmission
Passive Membrane Properties	Electrophysiology Techniques
Action Potentials	Basic Circuits (Spinal Cord)
Voltage-Gated Ion Channels	Sensory Systems Overview
Ligand-Gated Ion Channels	Synaptic Plasticity

Study Material

- NEUROSCIENCE Third Edition
  - Dale Purves
- Chapter 4 pages 69-85



THE COVER
Dorsal view of the human brain.
(Courtesy of S. Mark Williams.)

NEUROSCIENCE: Third Edition

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Aims for this Lecture

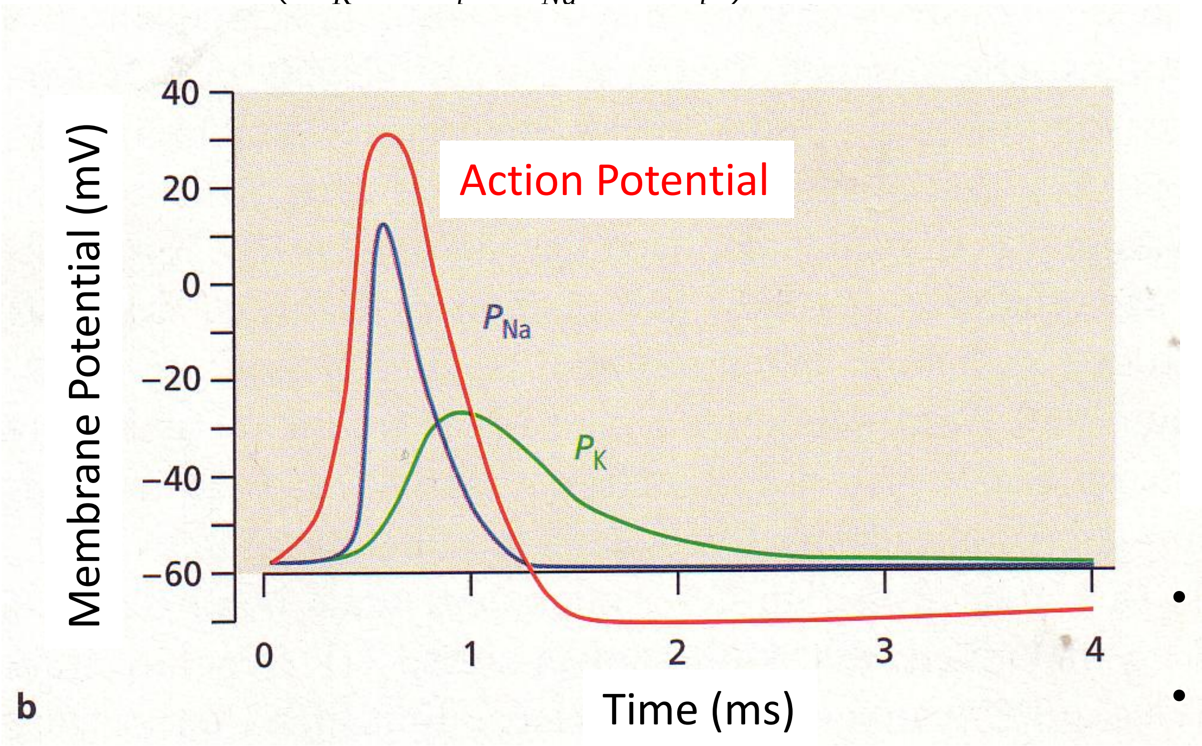
- Get an idea of the molecular structure of voltage-gated ion channels.
- Understand mechanisms for ion selectivity.
- Understand channel opening and closing and its stochastic nature.
- Understand activation and inactivation curves.

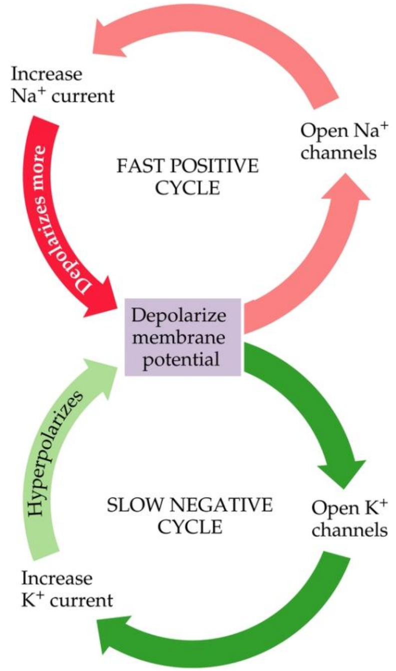
Recapitulation L4

- Action potentials are fast stereotypical signals produced by neurons when depolarized above a threshold.
- Na conductances open and let Na flow into the neuron. The neuron further depolarizes. The Na conductances rapidly inactivate.
- K conductances open with a delay and cause an outflow of K ions and a repolarization of the neuron.

Recapitulation L4

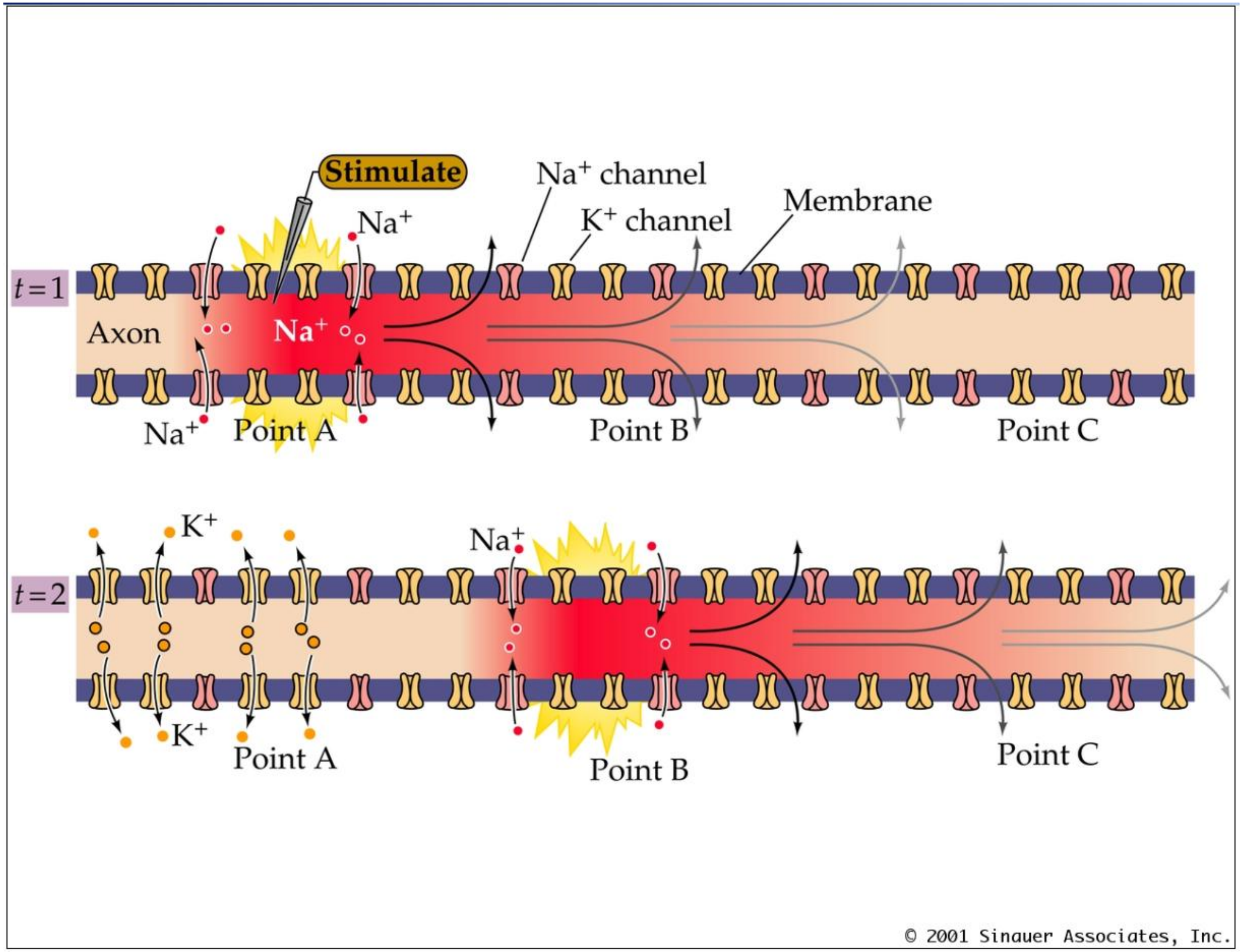
$$E_i = \frac{RT}{F}\ln\left(\frac{P_K[K^+]_a + P_{Na}[Na^+]_a}{P_K[K^+]_i + P_{Na}[Na^+]_i}\right)$$



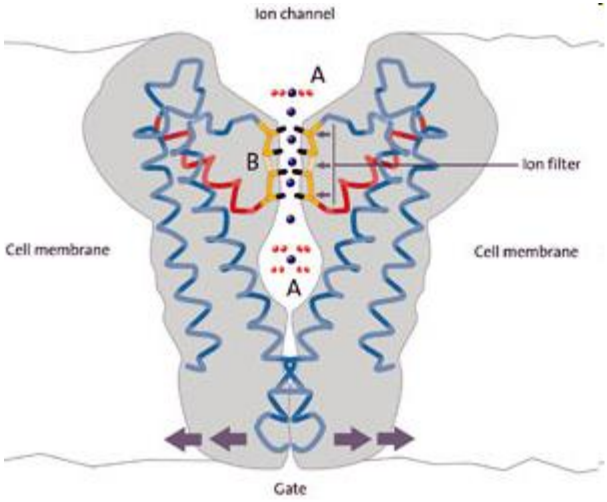


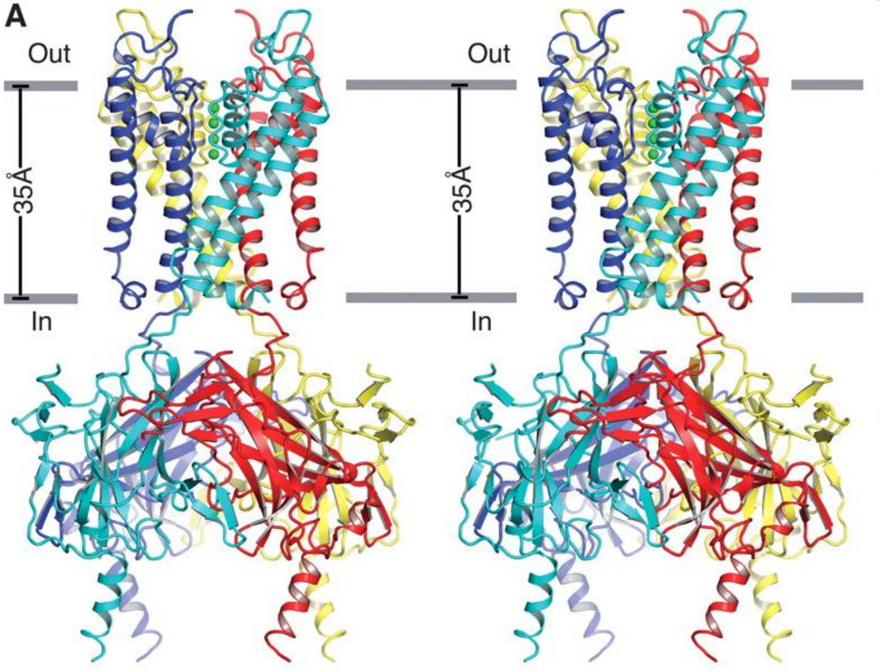
- Positive feedback of voltage dependent Na-conductance
- Negative feedback of voltage dependent K-conductance
- Explosive depolarization and subsequent repolarization..

Recapitulation L4

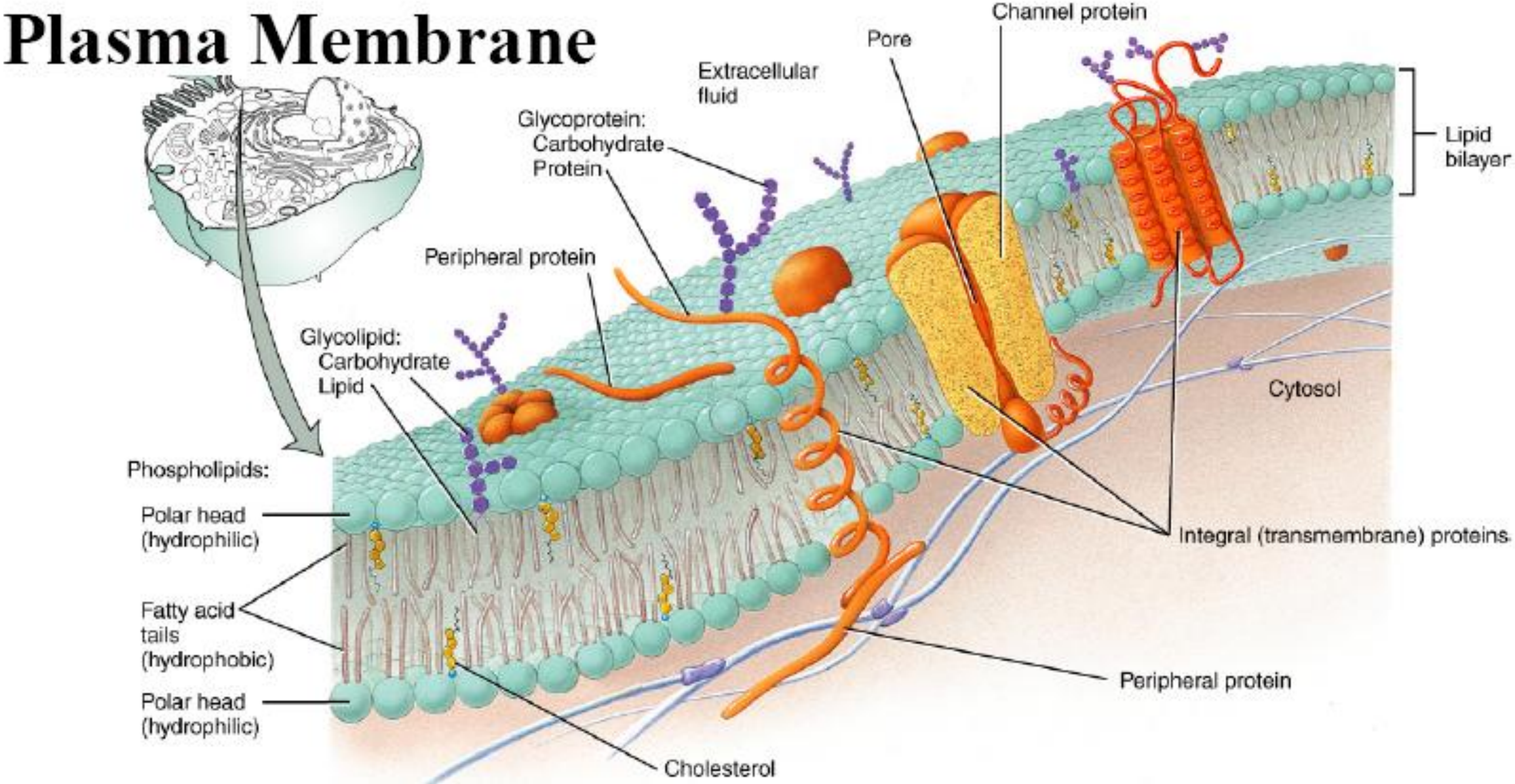


Ion Channels

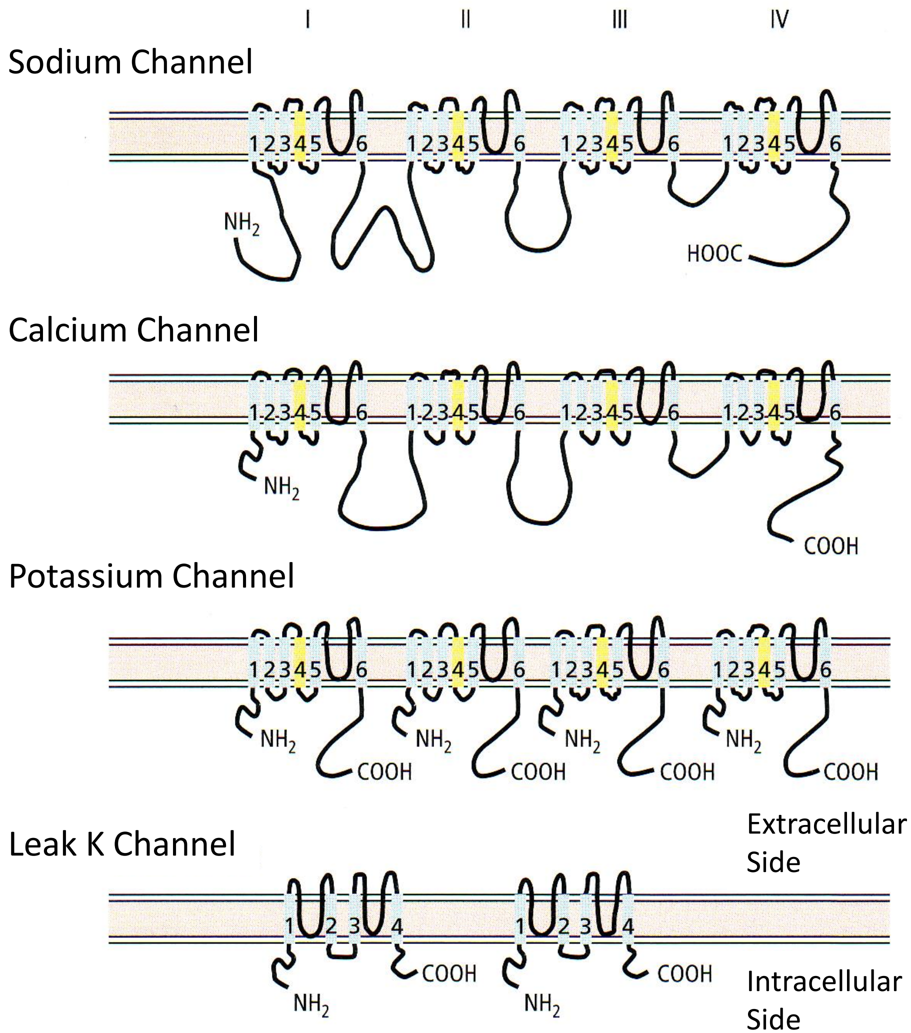


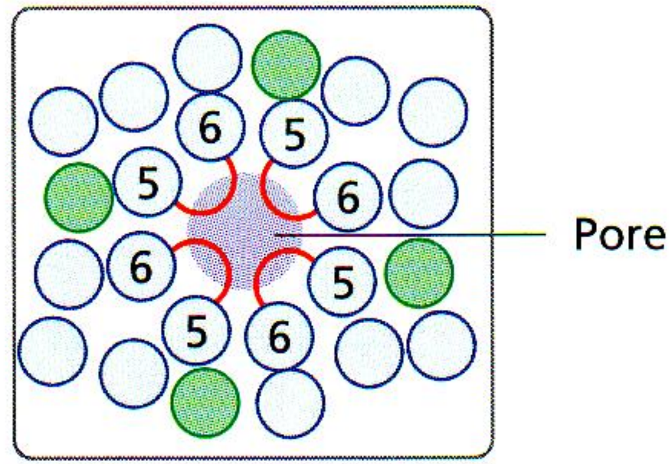


The Cell Membrane

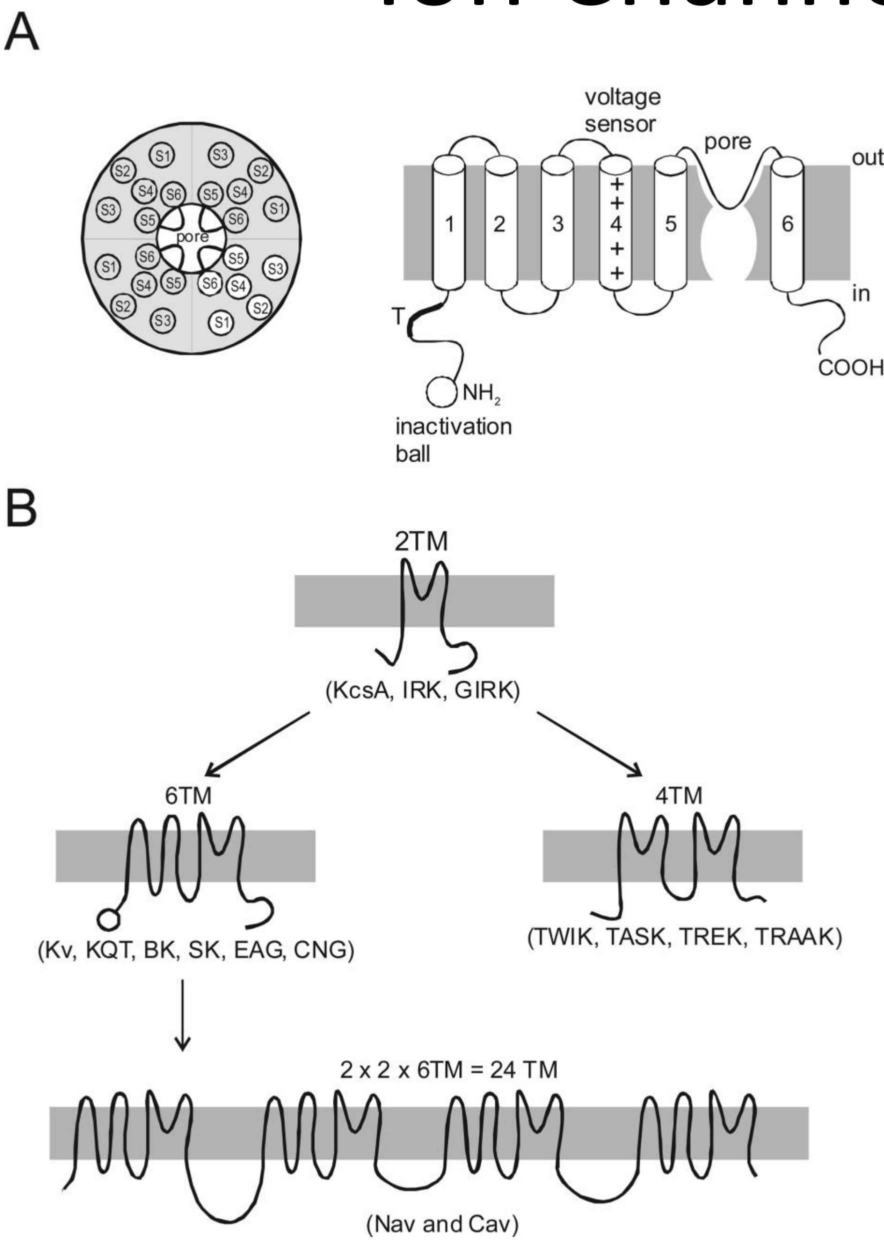


Ion Channels - Structures

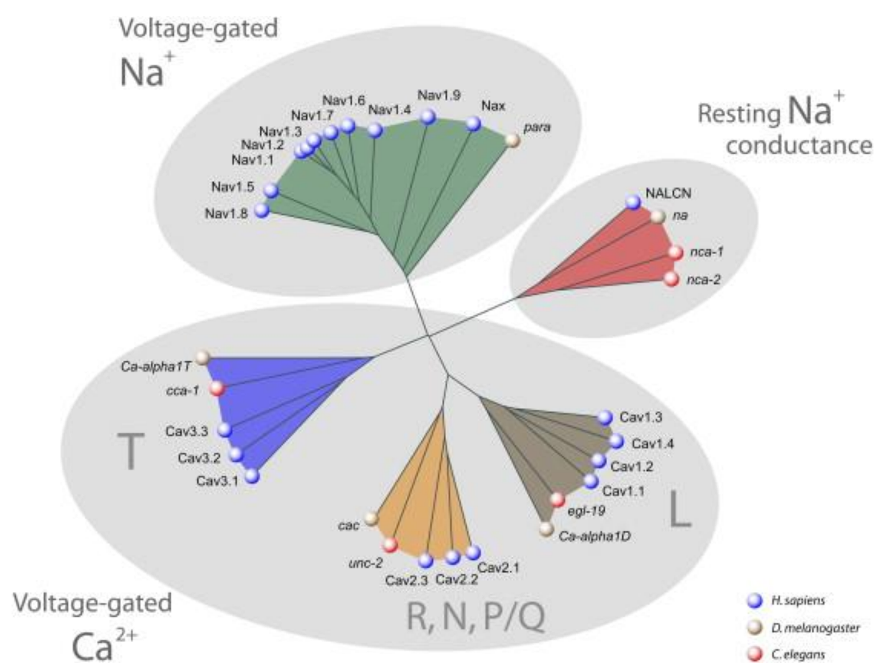




Ion Channel Evolution



Four-Domain Channels



Potassium Channels

- The most diverse and most ancient class of ion channels.
- All sequenced genomes contain at least one, most contain many genes for potassium channels.
- Voltage-gated potassium channels are members of this class of channels

K Channels

TABLE 1
K_v channel families

Gene names shown are those assigned by the IUPHAR (Catterall et al., 2002) and HGNC (http://www.gene.ucl.ac.uk) in addition to some other commonly used names.

IUPHAR	HGNC	Other
$K_v1.1$	*KCNA1*	*Shaker*-related family
$K_v1.2$	*KCNA2*	
$K_v1.3$	*KCNA3*	
$K_v1.4$	*KCNA4*	
$K_v1.5$	*KCNA5*	
$K_v1.6$	*KCNA6*	
$K_v1.7$	*KCNA7*	
$K_v1.8$	*KCNA10*	
$K_v2.1$	*KCNB1*	*Shab*-related family
$K_v2.2$	*KCNB2*	
$K_v3.1$	*KCNC1*	*Shaw*-related family
$K_v3.2$	*KCNC2*	
$K_v3.3$	*KCNC3*	
$K_v3.4$	*KCNC4*	
$K_v4.1$	*KCND1*	*Shal*-related family
$K_v4.2$	*KCND2*	
$K_v4.3$	*KCND3*	
$K_v5.1$	*KCNF1*	Modifier
$K_v6.1$	*KCNG1*	Modifiers
$K_v6.2$	*KCNG2*	
$K_v6.3$	*KCNG3*	
$K_v6.4$	*KCNG4*	
$K_v7.1$	*KCNQ1*	*KVLQT*
$K_v7.2$	*KCNQ2*	*KQT2*
$K_v7.3$	*KCNQ3*	
$K_v7.4$	*KCNQ4*	
$K_v7.5$	*KCNQ5*	
$K_v8.1$	*KCNV1*	Modifiers
$K_v8.2$	*KCNV2*	
$K_v9.1$	*KCNS1*	Modifiers
$K_v9.2$	*KCNS2*	
$K_v9.3$	*KCNS3*	
$K_v10.1$	*KCNH1*	*eag1*
$K_v10.2$	*KCNH5*	*eag2*
$K_v11.1$	*KCNH2*	*erg1*
$K_v11.2$	*KCNH6*	*erg2*
$K_v11.3$	*KCNH7*	*erg3*
$K_v12.1$	*KCNH8*	*elk1, elk3*
$K_v12.2$	*KCNH3*	*elk2*
$K_v12.3$	*KCNH4*	*elk1*

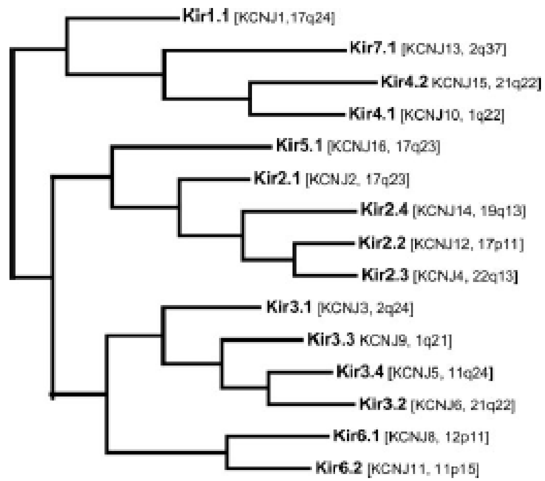


FIG. 1. Phylogenetic tree of K_{ir} channels. Amino acid sequence alignments and phylogenetic analysis for the 15 known members of the human K_{ir} family were generated as described in the legend for Fig. 1 of "LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassiuim Channels". No new channels have been added to this topology since it appeared in the earlier edition of this compendium. International Union of Pharmacology and HUGO Gene Nomenclature Committee names of the genes are shown together with their chromosomal localization.

TABLE 1
K_{Ca} channels

IUPHAR names of the members of the K_{Ca} group of potassium channels are shown, together with their HGNC designations and other commonly used names.

IUPHAR	HGNC	Other
$K_{Ca}1.1$	*KCNMA1*	Slo, Slo1, BK
$K_{Ca}2.1$	*KCNN1*	$SK_{Ca}1$
$K_{Ca}2.2$	*KCNN2*	$SK_{Ca}2$
$K_{Ca}2.3$	*KCNN3*	$SK_{Ca}3$
$K_{Ca}3.1$	*KCNN4*	$IK_{Ca}1$
$K_{Ca}4.1$	*KCNT1*	Slack, Slo2.2
$K_{Ca}4.2$	*KCNT2*	Slick, Slo2.1
$K_{Ca}5.1$	*KCNU1*	Slo3

BK, big-conductance K^+ channel; SK, small-conductance K^+ channel; IK, intermediate-conductance K^+ channel.

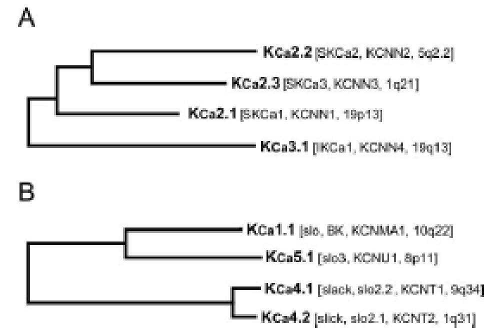
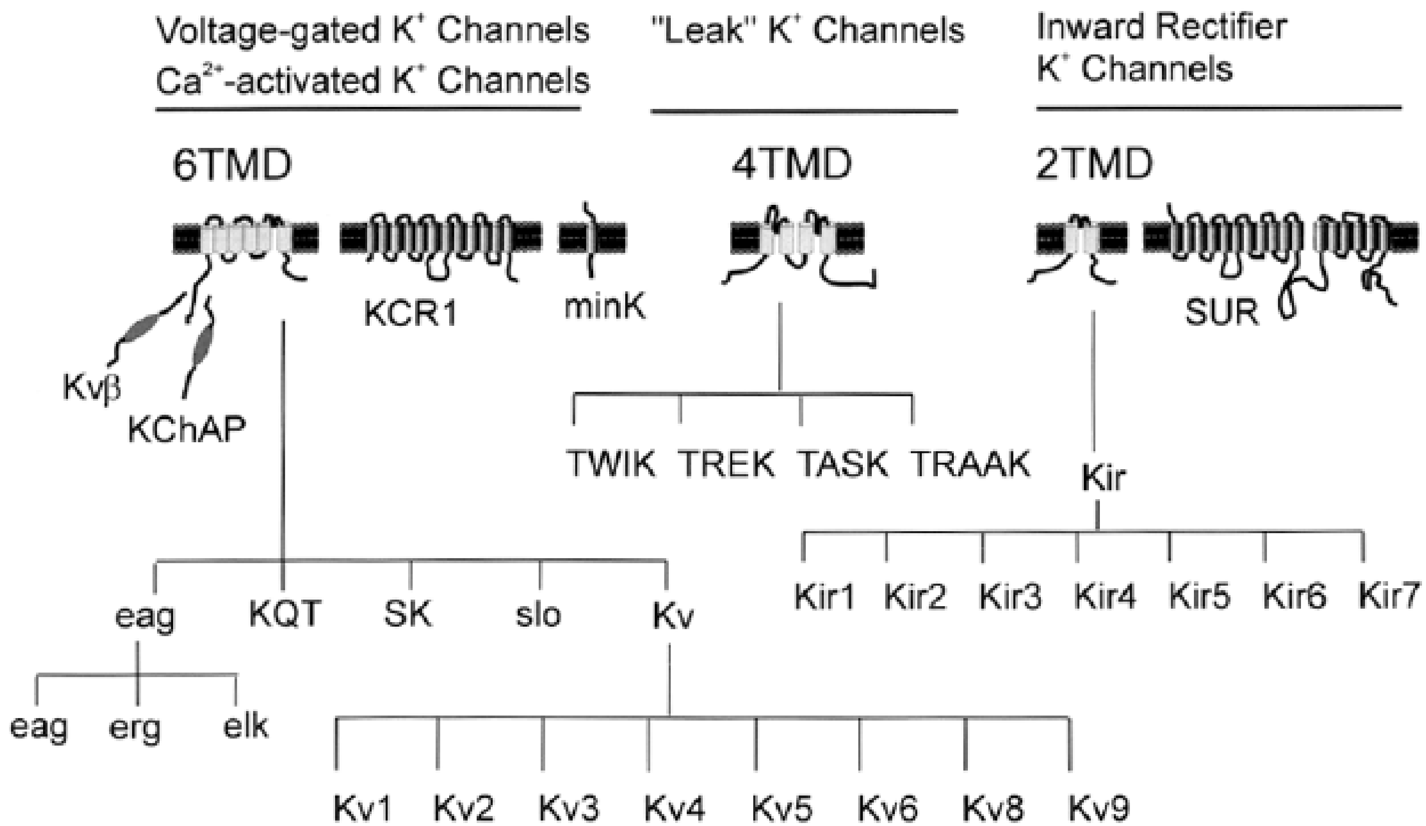


FIG. 1. Phylogenetic tree for K_{Ca} channels. A, $K_{Ca}2/3$ group. B, $K_{Ca}1/4/5$ group. Amino acid sequence alignments and phylogenetic analysis for these two groups of four human K_{Ca} channels were generated as described in the legend for Fig. 1 of "International of Union of Pharmacology LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassium Channels." No new channels have been added to these topologies since they appeared in the earlier edition of this compendium. IUPHAR and HGNC names of the genes are shown together with other commonly used names and their chromosomal localization.

Pharmacol Rev. 2005 Dec;57(4):463-72.
Pharmacol Rev. 2005 Dec;57(4):473-508.
Pharmacol Rev. 2005 Dec;57(4):509-26.

Found in all fully sequenced genomes (Archaea, Eubacteria, Eucaryotes).
70 genes in vertebrates code for potassium channels.
Other channels probably evolved from potassium channels.

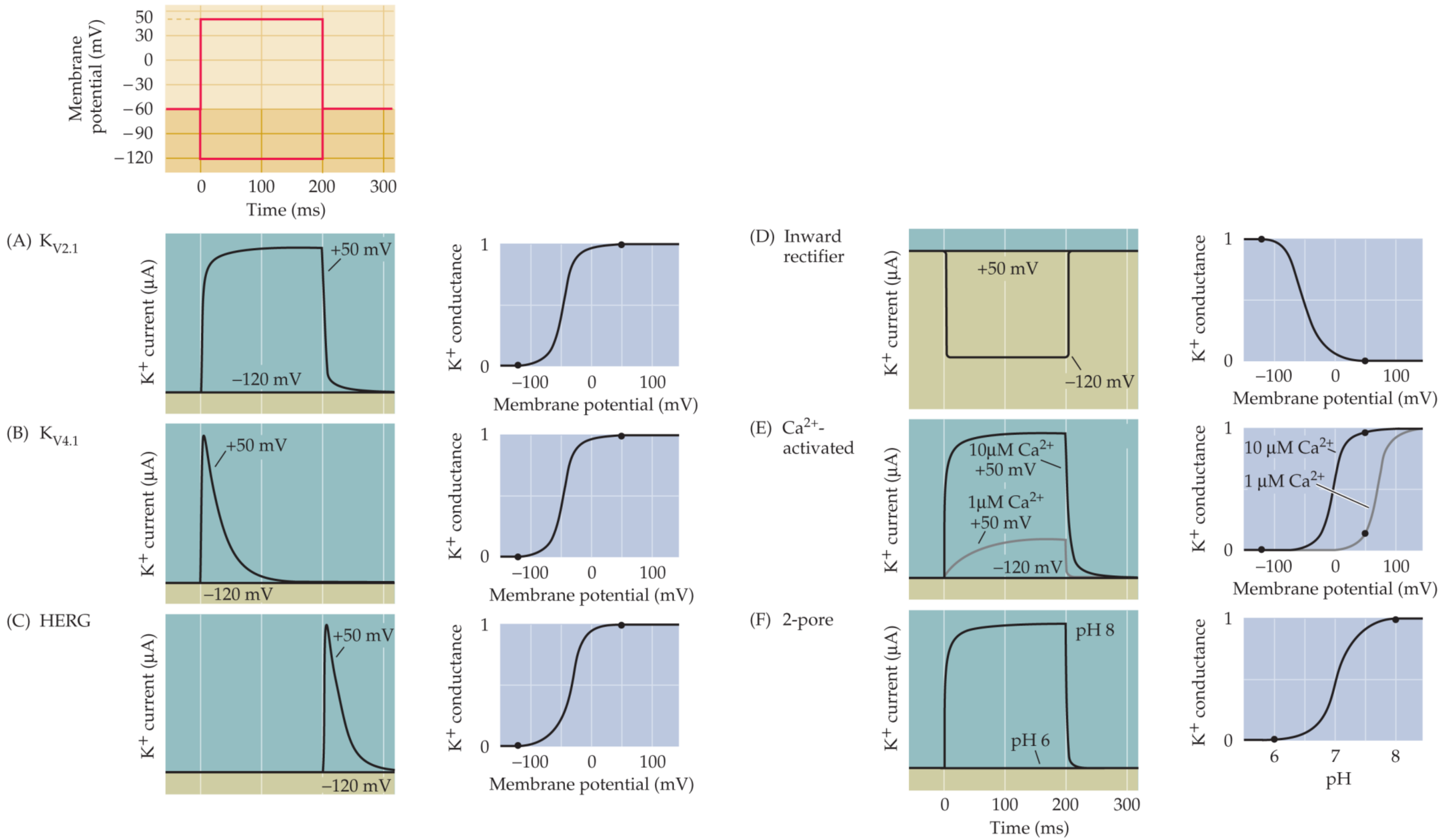
Potassium Channel Classes



Molecular Diversity of K^+ Channels

ANNALS NEW YORK ACADEMY OF SCIENCES

Different K Channels



Voltage-Gated Sodium Channels

- Less diverse – most prominent in excitable tissue that can produce action potentials.
- Four six-transmembrane domain units strung together.
- Prominent inactivation.

Na Channels

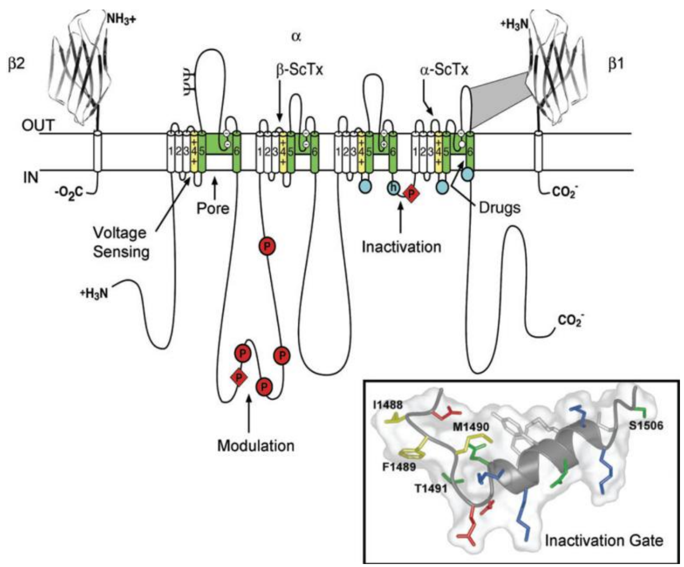


Table 1. Mammalian sodium channel α subunits

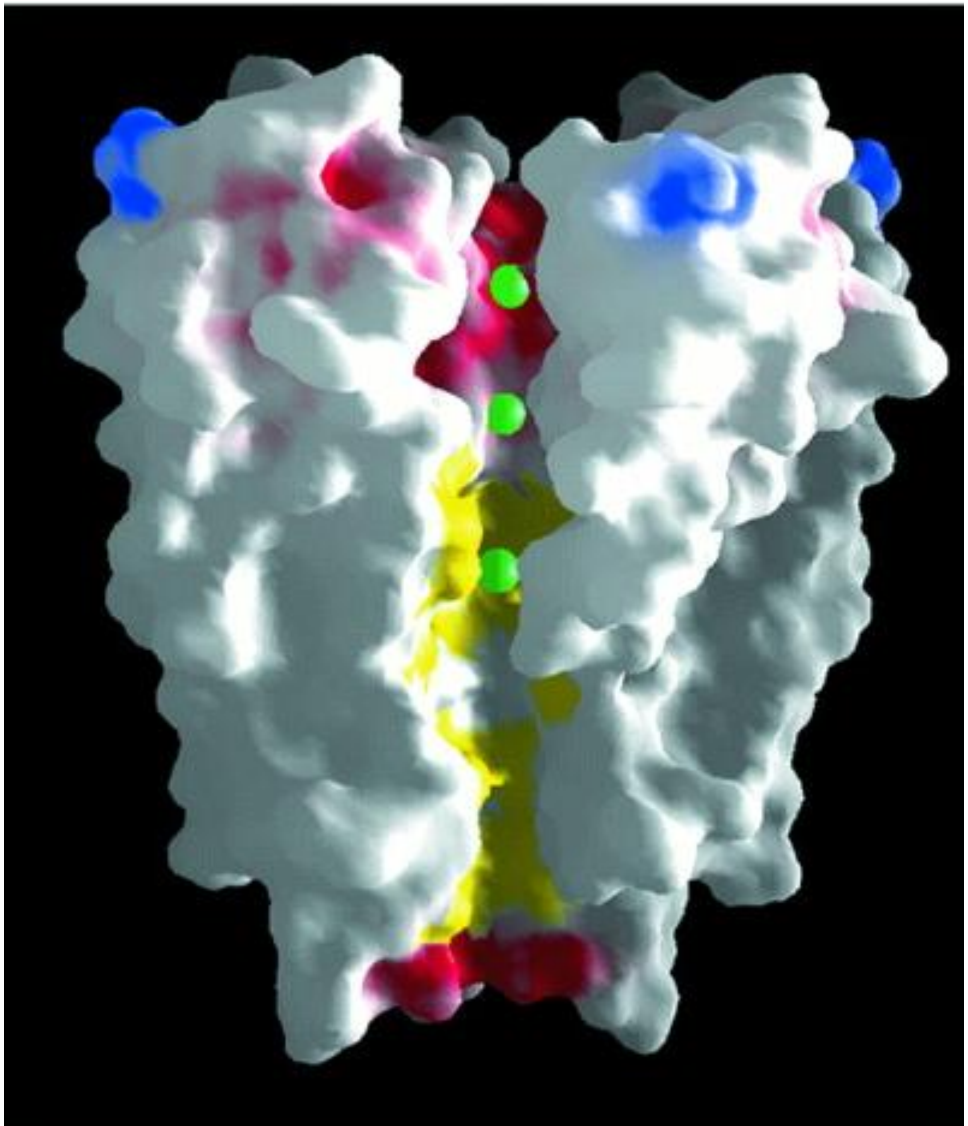
Type	Gene symbol	Chromosomal location	Primary tissues
$Na_V1.1$	*SCN1A*	Mouse 2 Human 2q24	CNS neurons
$Na_V1.2$	*SCN2A*	Mouse 2 Human 2q23–24	CNS neurons
$Na_V1.3$	*SCN3A*	Mouse 2 Human 2q24	CNS neurons
$Na_V1.4$	*SCN4A*	Mouse 11 Human 17q23–25	SkM
$Na_V1.5$	*SCN5A*	Mouse 9 Human 3p21	Uninnervated SkM, heart
$Na_V1.6$	*SCN8A*	Mouse 15 Human 12q13	CNS neurons
$Na_V1.7$	*SCN9A*	Mouse 2 Human 2q24	PNS neurons
$Na_V1.8$	*SCN10A*	Mouse 9 Human 3p22–24	DRG neurons
$Na_V1.9$	*SCN11A*	Mouse 9 Human 3p21–24	DRG neurons
Na_x	*SCN7A* *SCN6A*	Mouse 2 Human 2q21–23	uterus, astrocytes, hypothalamus

TOPICAL REVIEW

Voltage-gated sodium channels at 60: structure, function and pathophysiology

William A. Catterall

Ion Selectivity



Blue - positive charges
Red - negative charges
Yellow - hydrophobic

Rough structure of a potassium channel (fourth subunit removed). Negatively charged mouth repels neagtively charged ions.

Pore Structure

Gruppen	1	2	3
Perioden	s^1	s^2	d^1
1	1,00 $_1$H		
2	6,94 $_3$Li	9,01 $_4$Be	
3	22,99 $_{11}$Na	24,31 $_{12}$Mg ←	
4	39,10 $_{19}$K	40,08 $_{20}$Ca	44,96 $_{21}$Sc
5	85,47 $_{37}$Rb	87,62 $_{38}$Sr	88,91 $_{39}$Y
6	132,91 $_{55}$Cs	137,33 $_{56}$Ba	138,91 $_{57}$La*
7	223,02 $_{87}$Fr	226,83 $_{88}$Ra	227,03 $_{89}$Ac#

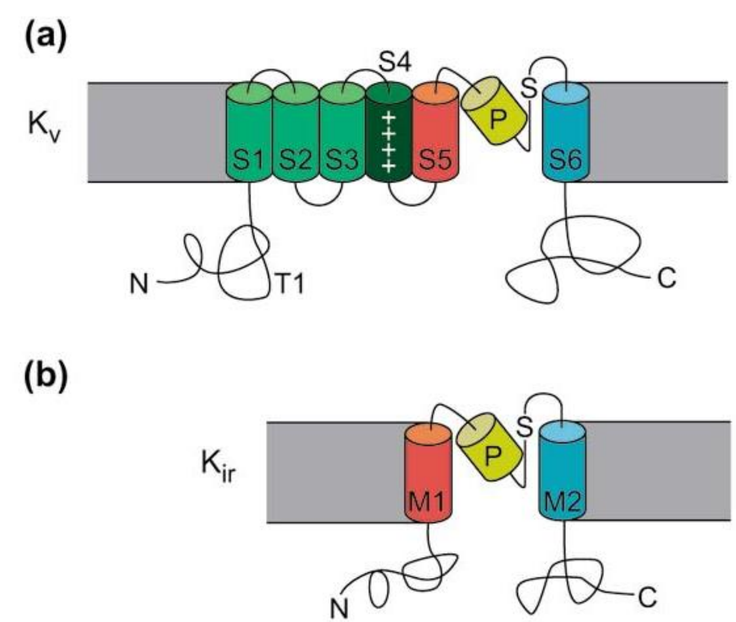
s-Block

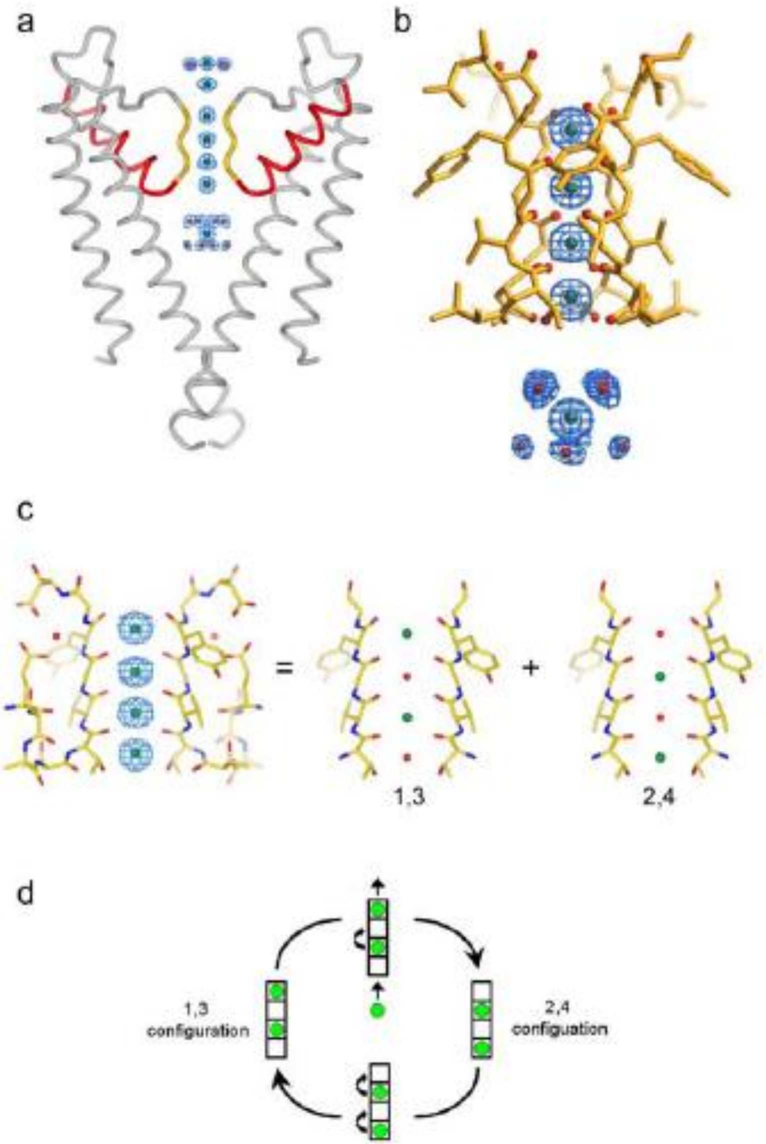
Minireview

Potassium channels

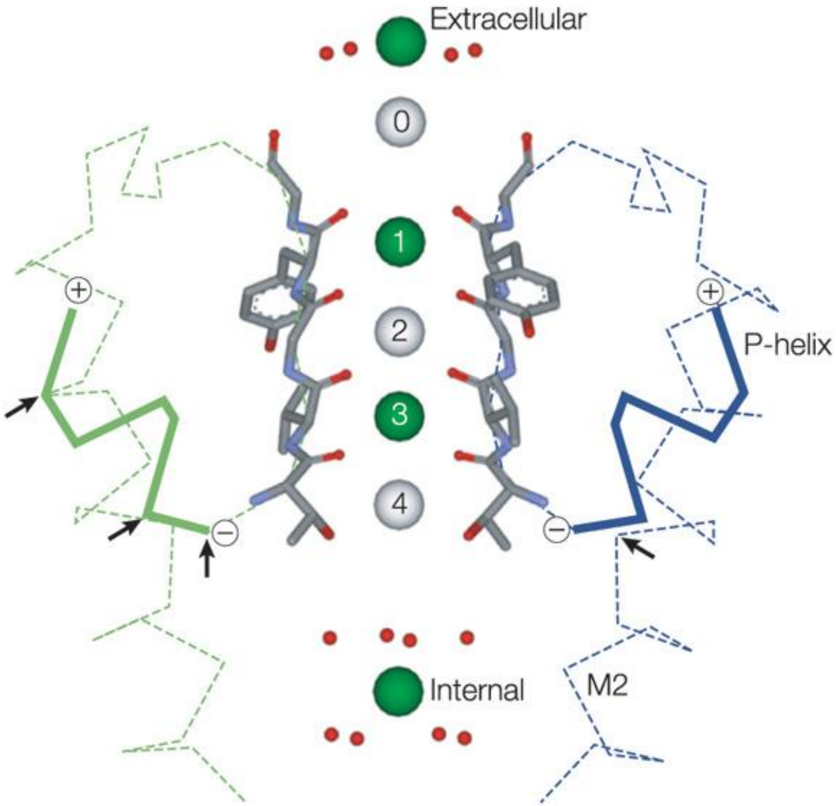
Roderick MacKinnon*

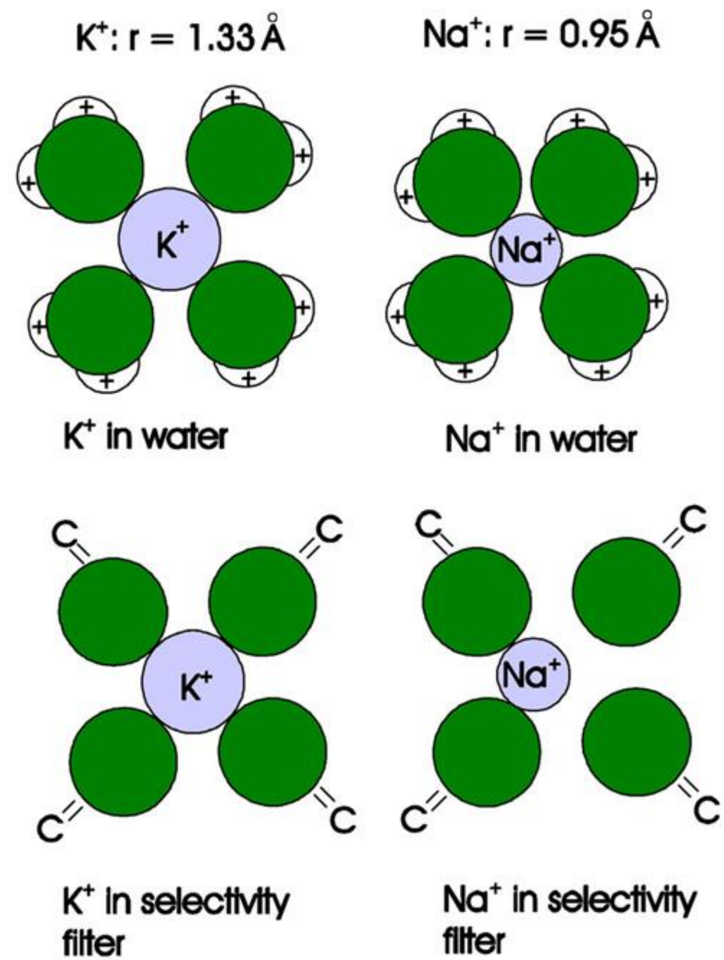
FEBS Letters 555 (2003) 62–6



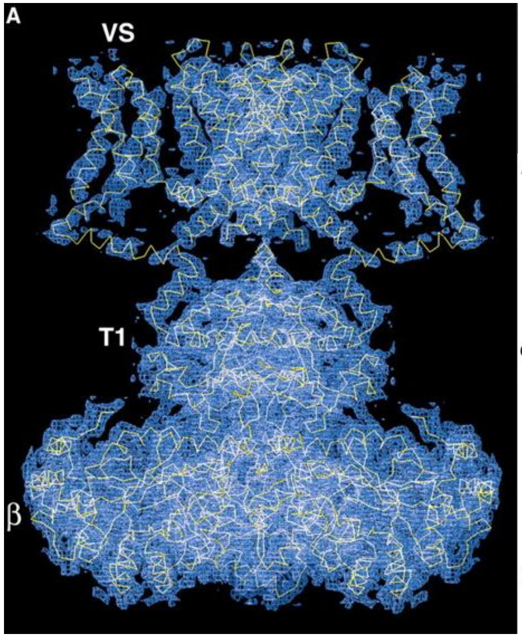


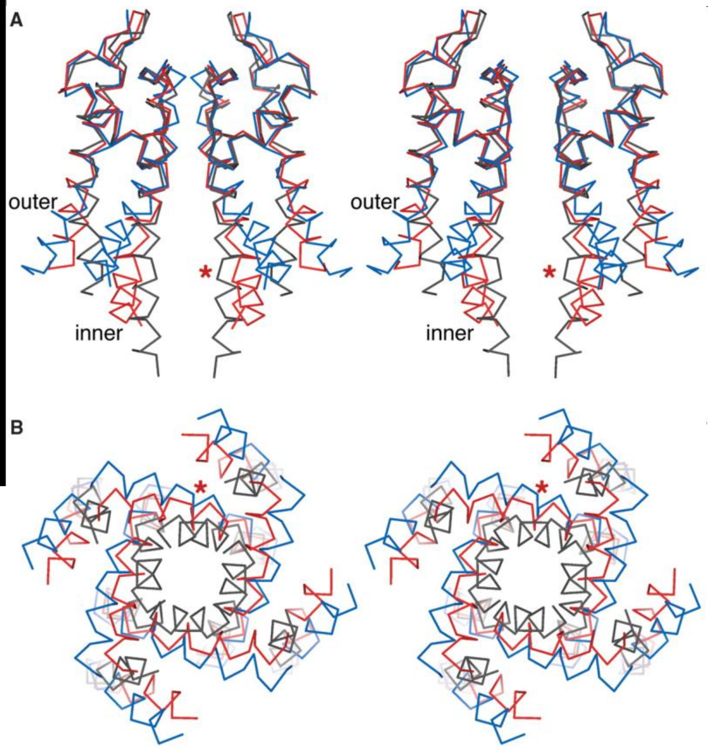
Selectivity Filter

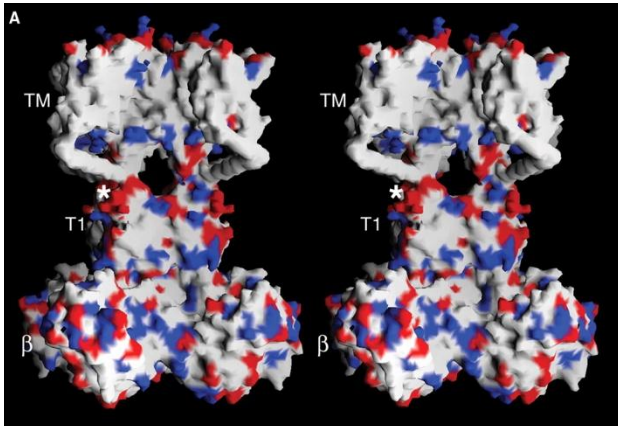




Mammalian K-Channel







Science 5 August 2005:
Vol. 309. no. 5736, pp. 897 - 903

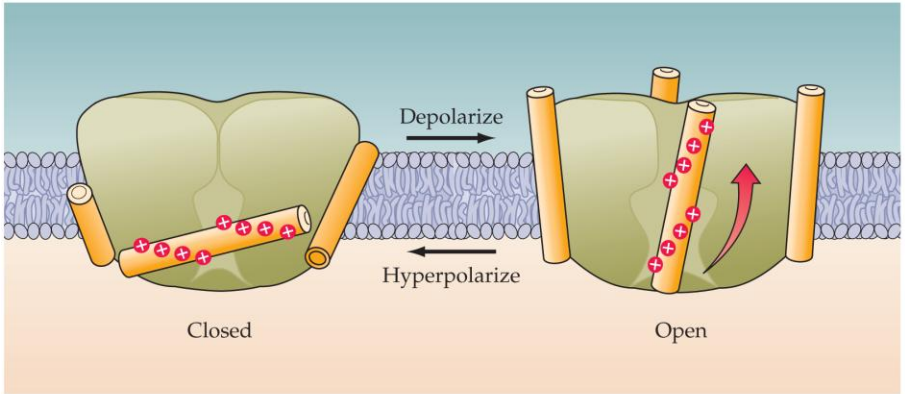
Crystal Structure of a Mammalian Voltage-Dependent *Shaker* Family K+ Channel

Stephen B. Long, Ernest B. Campbell, Roderick MacKinnon*

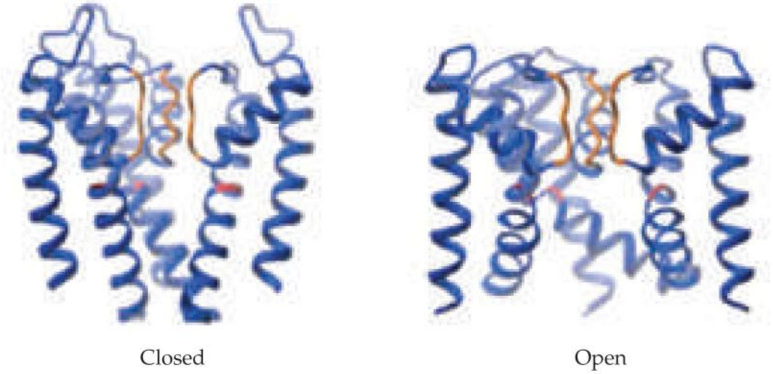
3D if watched cross-eyed

K Channel Gating

(A)



(B)

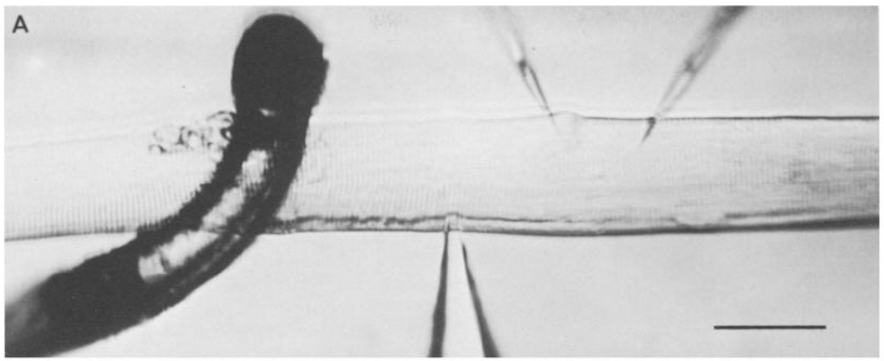


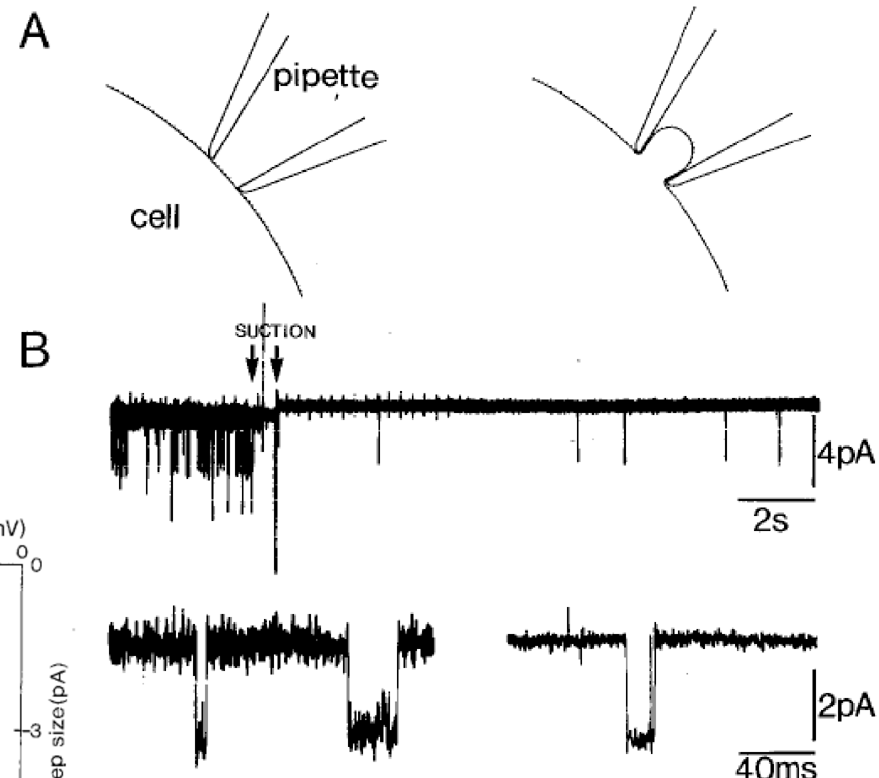
Measuring Individual Channels

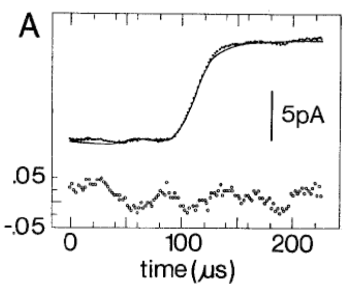
Pflügers Arch (1981) 391 : 85 – 100

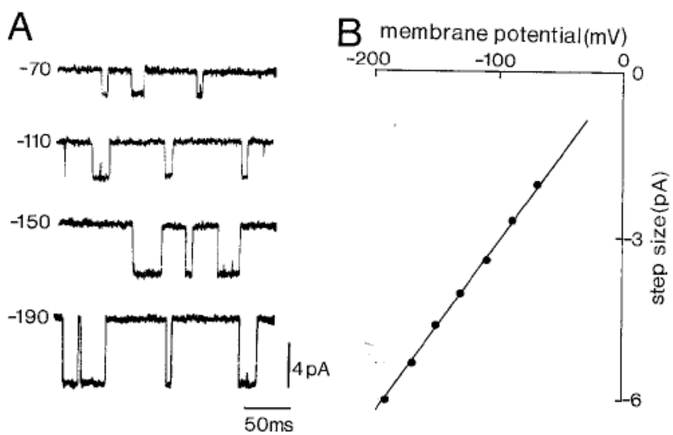
Improved Patch-Clamp Techniques for High-Resolution Current Recording from Cells and Cell-Free Membrane Patches

O. P. Hamill, A. Marty, E. Neher, B. Sakmann, and F. J. Sigworth
Max-Planck-Institut für biophysikalische Chemie, Postfach 968, Am Fassberg, D-3400 Göttingen, Federal Republic of Germany

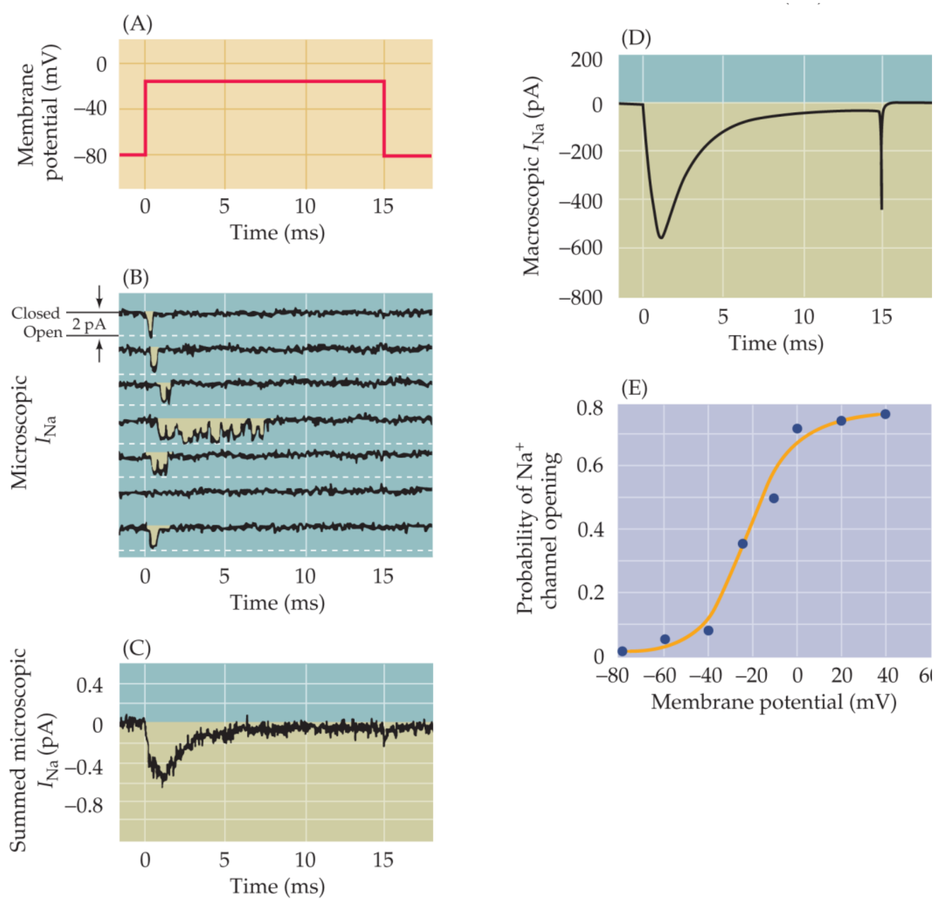






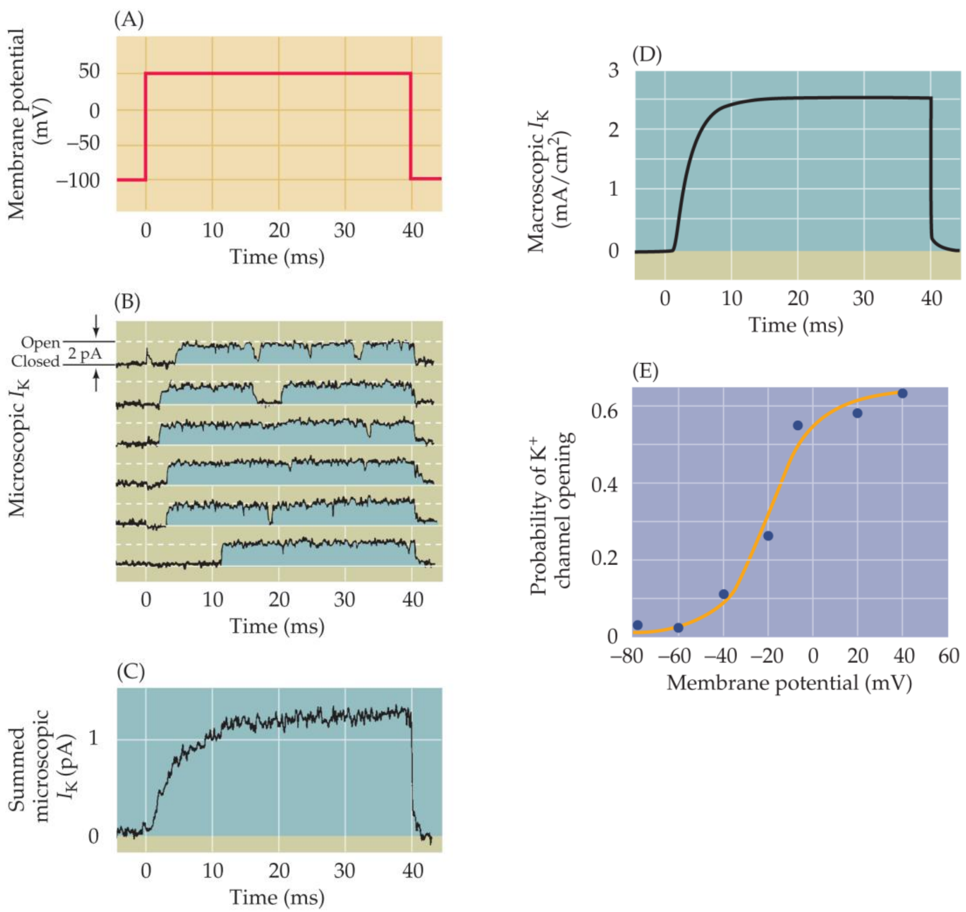


Na Channel Behavior



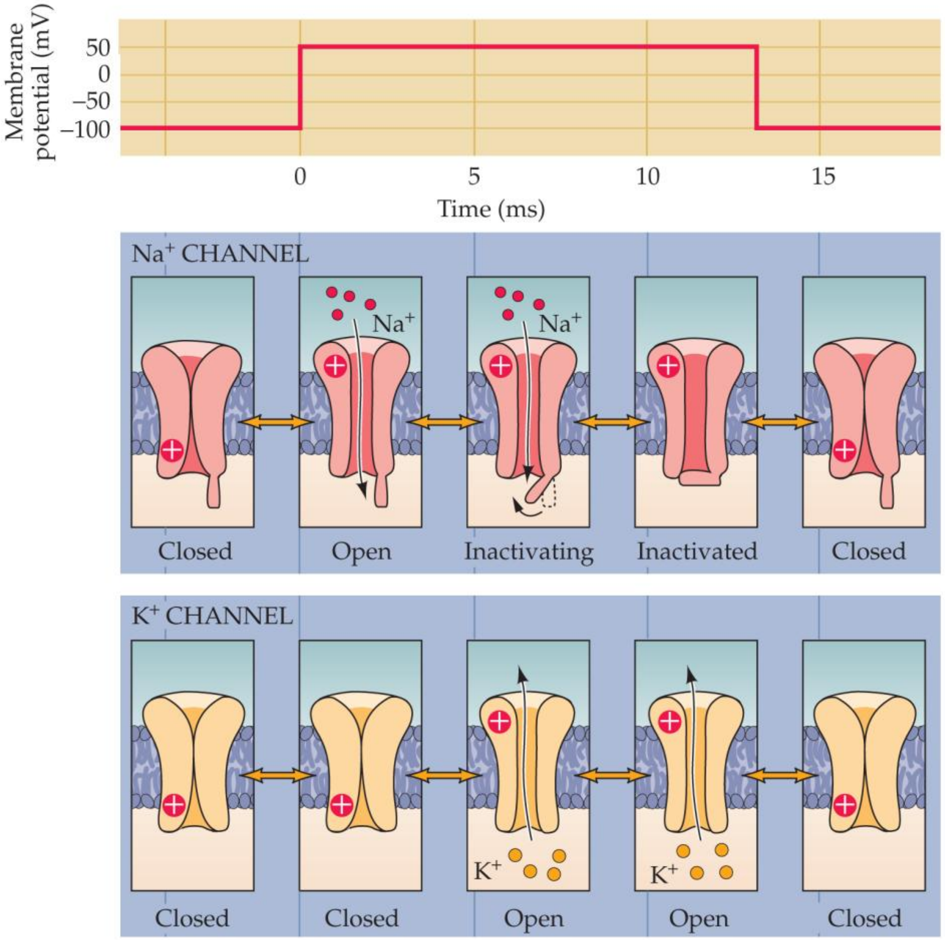
Individual channels behave stochastically – only the probability of their opening can be predicted. Because many channels are typically involved the macroscopic current can still be predicted with high accuracy

K Channel Behavior

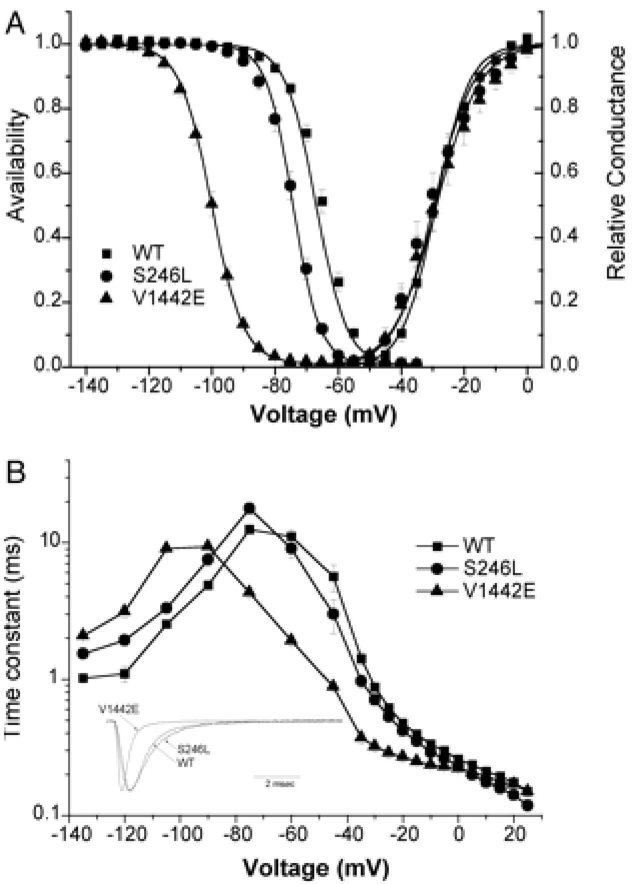


Individual channels behave stochastically – only the probability of their opening can be predicted. Because many channels are typically involved the macroscopic current can still be predicted with high accuracy

AP and Channel States



Activation and Inactivation Curves



Myasthenic syndrome caused by mutation of the *SCN4A* sodium channel

PNAS June 10, 2003 vol. 100

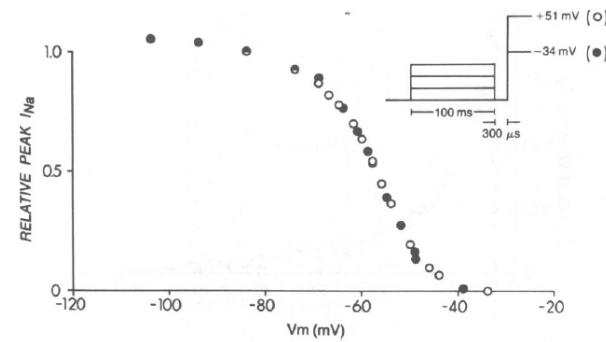


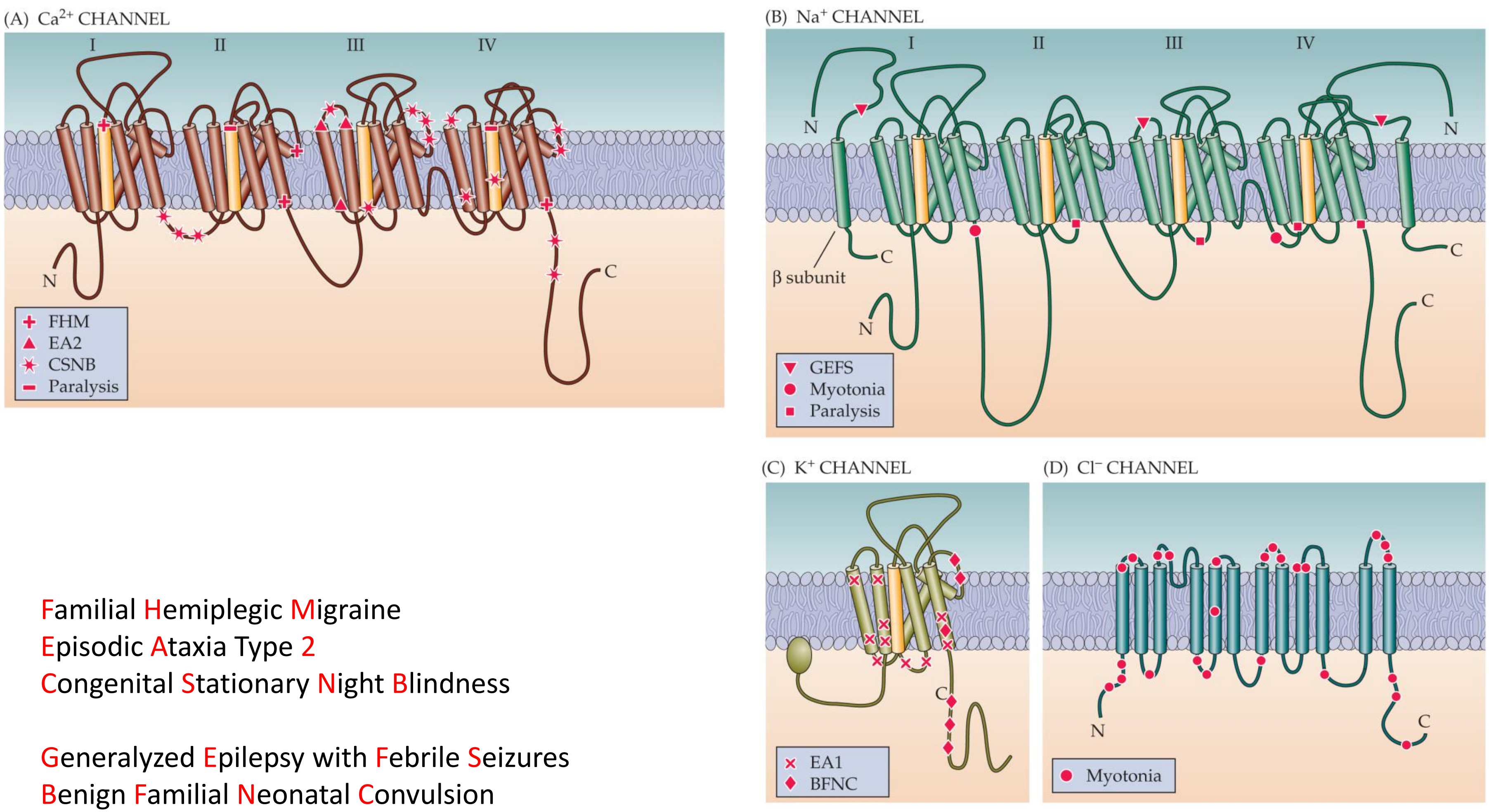
FIGURE 9 Absence of shift in steady-state activation curve with test-pulse height. Steady-state inactivation curves were obtained by giving a 100-ms prepulse to a variable potential, returning to the holding potential for 300 μs, and stepping to the test-pulse potential. The peak currents during the test pulses are plotted as a function of the prepulse potential, normalized to the value for a step from −84 mV, the holding potential. The data points for −94 and −104 mV for the −34-mV test pulse show that there was virtually no inactivation at −84 mV; peak current was about 5% increased by the 100-ms prepulse to −104 mV, and much of this may have been due to removal of slow inactivation. Peak conductance at −34 mV was 0.19 of that at +51 mV. ¼ Na, ½ K, 1 mM 4-AP, 3.3–3.5°C.

SODIUM CHANNEL INACTIVATION IN THE CRAYFISH GIANT AXON

MUST CHANNELS OPEN BEFORE INACTIVATING?

BIOPHYS. J. © Biophysical Society · 0006–3495/09/81/595/20 $1.00
Volume 35 September 1981 595–614

Channelopathy



Familial Hemiplegic Migraine
Episodic Ataxia Type 2
Congenital Stationary Night Blindness

Generalyzed Epilepsy with Febrile Seizures
Benign Familial Neonatal Convulsion

What Do You Want To Know....

- ... about a channel?
- How is it opened (activation curve)?
- How is it closed (de-activation, inactivation curve)?
- Which ion type(s) go through?
- What are its kinetics?
- What is its single channel conductance?

These parameters may vary depending on subunit assembly, phosphorylation, ion-, cAMP-, ATP-binding, ...