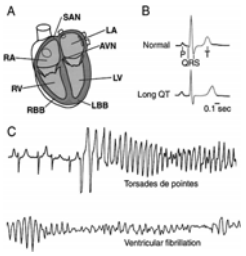
Regulation of Ion Channels by Drugs and Hormones

- Roles of local signaling complexes
- Lessons from Investigation of Human Disease
- Pharmacology Unique to Voltage-Gated Ion channels

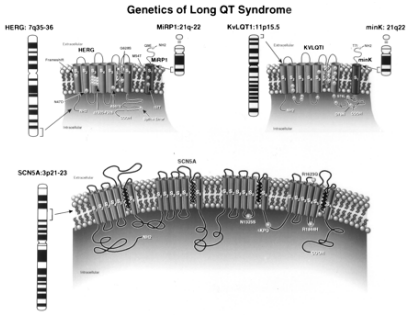
Adrenergic Regulation of Cardiac Electrical Activity:

Lessons from Human Disease

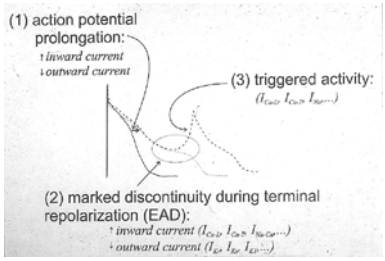


Keating & Sanguinetti, *Cell*, 2001.

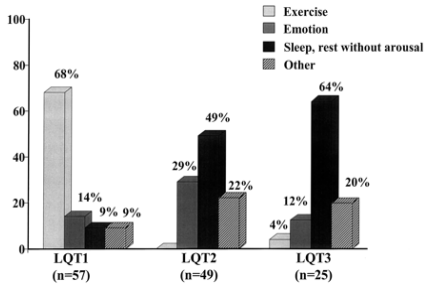
LQTS: Genetic Linkage to Multiple Ion Channel Genes



AP Prolongation Can Trigger Arrhythmias

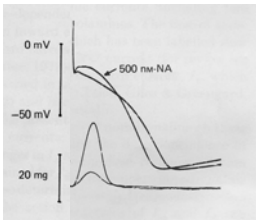


Triggers Are Gene-specific



Circ 2001;103:89-95

β-Adrenergic Stimulation Shortens AP Duration

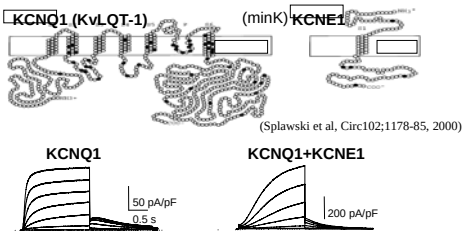


(Kass & Wiegers, *J Physiol*. 1982)

β-AR Regulation of Cardiac AP: A Balance of Inward and Outward Current

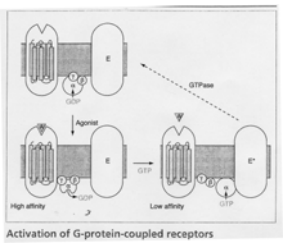
- *L-type Calcium Channel current Increased*
- *Slow I_{Ks} potassium channel Current Increased*

Molecular Architecture of I_{KS} Channel Revealed Through LQTS studies

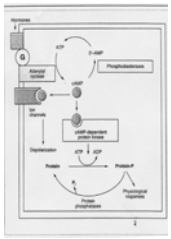


Receptor stimulation to Local Signaling

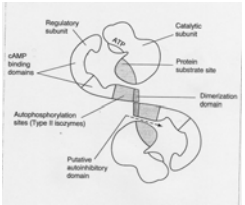
Agonist Binding and Receptor Activation



cAMP Pathway: Receptor Activation Increases cAMPi

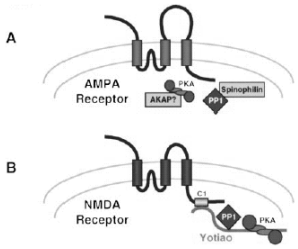


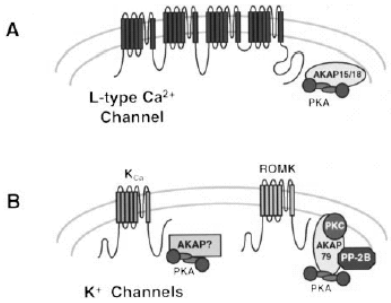
cAMP Bindng:
Dissociation of Regulatory and Catalytic PKA subunits



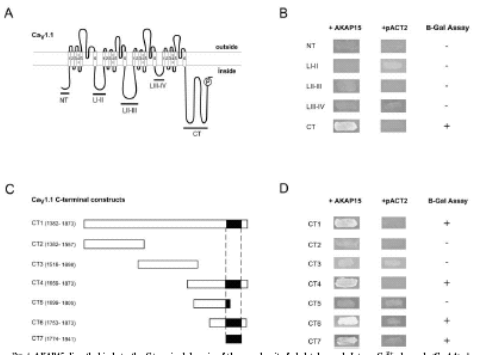
Adaptor Proteins:

Molecular Basis for Receptor/Substrate Diversity: Channel as ***Macromolecular Complexes***





Calcium Channel Complex

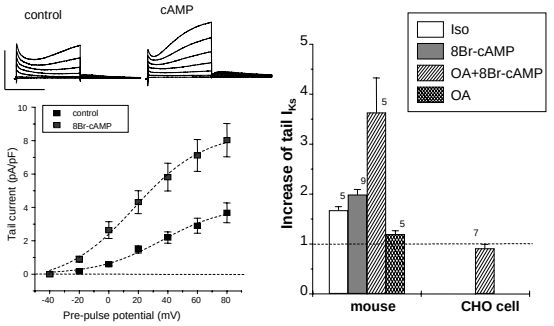


Channels as ***Macromolecular*** Signaling Complexes

- Signaling ***Microdomains*** exapnd diversity of receptor-mediated cellular responses
- Disruption of ***Microdomains*** in disease can unbalance physiological responses

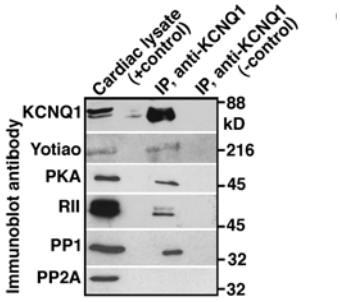
K Channel Complex

Functional regulation in TG$^+$ Myocytes but not in CHO cells: Phosphatase and Kinase activity

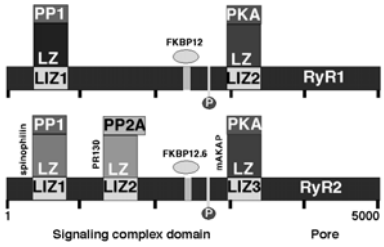


KCNQ1 forms a macromolecular complex

Human Heart

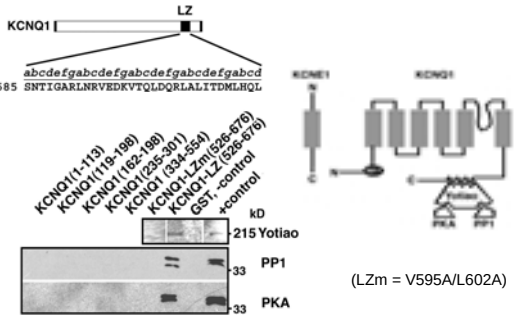


RyR macromolecular complexes are held together by leucine/isoleucine zippers (**LZ**s)



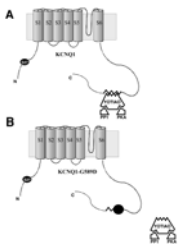
Marx, et al., (2001). ***The Journal of Cell Biology***, **153**: 699-708.

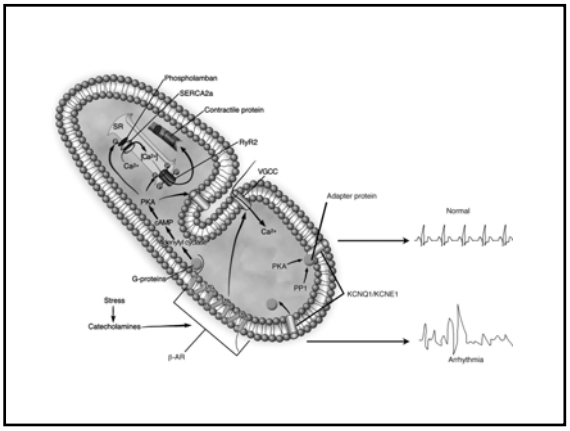
A leucine zipper motif in KCNQ1 C-terminus : Coordination of protein-protein interactions



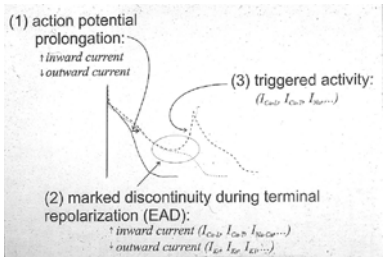
(LZm = V595A/L602A)

The K channel Complex can be Disrupted in Disease





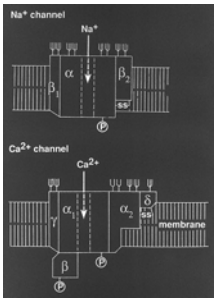
AP Prolongation Can Trigger Arrhythmias

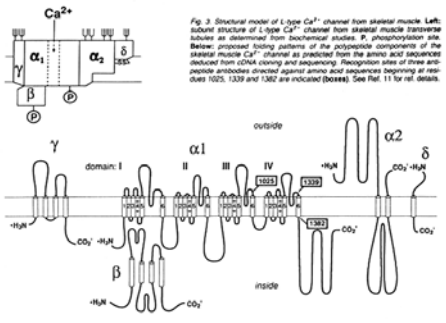


State-dependent Block of Ion Channels by drugs

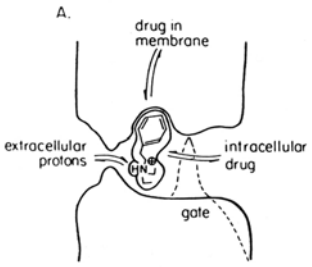
- The Modulated Receptor Hypothesis
- Hille, B. (1977). Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. *Journal of General Physiology* **69**, 497-515.

Sodium and Calcium Channels are Targets of Voltage-Regulated Drugs

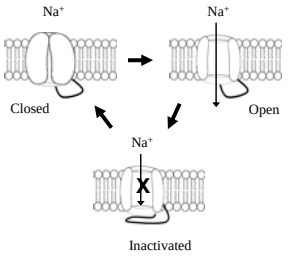




Drug Ionization Restricts Access to Drug Receptor



Na+ channel open state inactivation

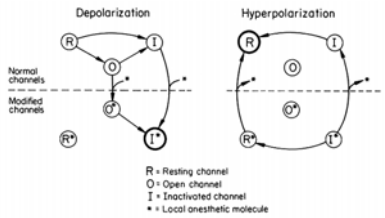


Use-Dependent Block

- Pulse-dependent channel availability depends on recovery from inactivation;
- Drug-Bound Channels recovery slower than drug-free channels;
- Channels are not available for excitation when drug-bound.

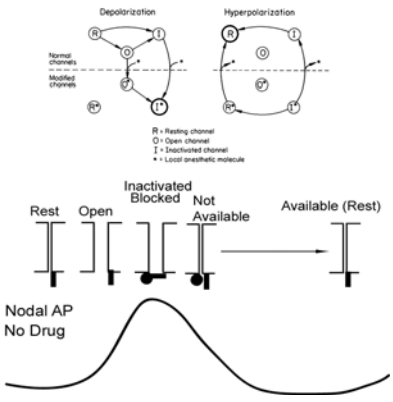
Drug binding is influenced by the state of the channel:

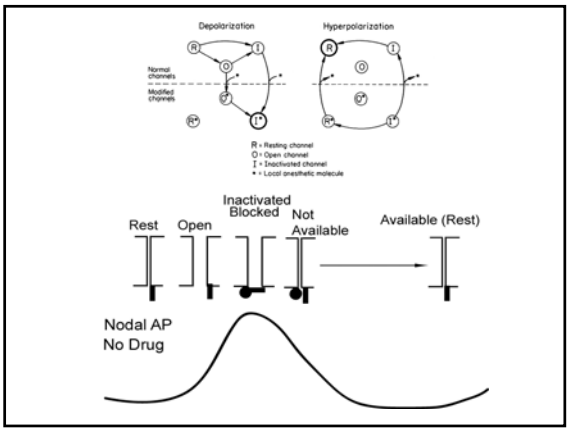
Preferential binding to and Stabilization of the Inactivated State



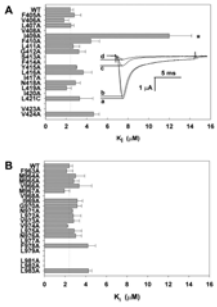
Block Develops During Repetitive electrical Activity

- Block During Depolarization (systole)
- Unblock During Repolarization (Diastole)

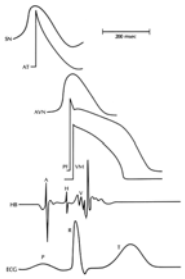


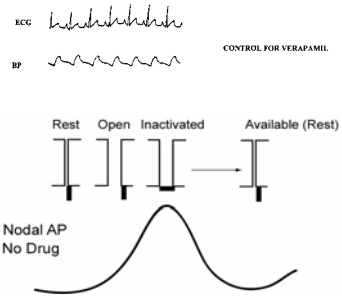


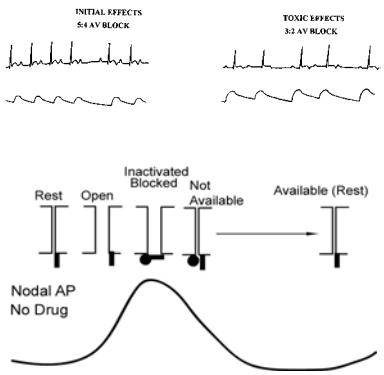
Mapping a drug receptor via Alanine Scanning



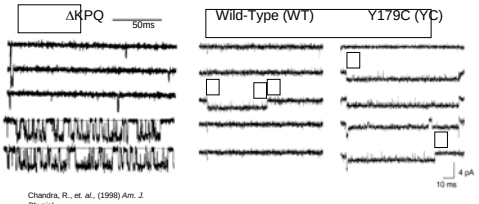
Targeting Different Channels for Distinct Therapeutic Goals:







Novel Pharmacology of Inherited Sodium Channel Mutations



Chandra, R., *et. al.*, (1998) *Am. J. Physiol.* **274**, H1643-H1654.

The Local Anesthetic Receptor for Voltage-Gated Sodium Channels