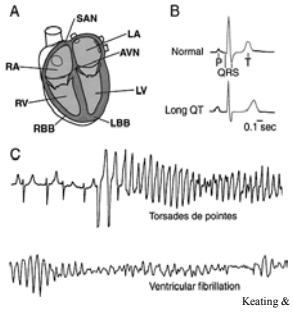
Beta Adrenergic Signaling in Heart

- Roles of local signaling complexes

The Long QT Syndrome: Dysfunction in Ventricular Repolarization



Keating & Sanguinetti, *Cell*, 2001.

Decrease in K Channel Activity or Increase in Na Channel Activity Can Prolong ADP (QT Interval)

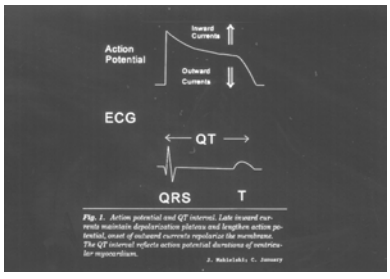
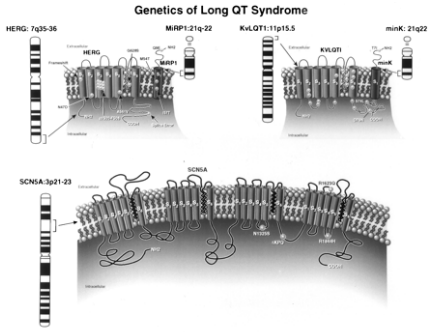


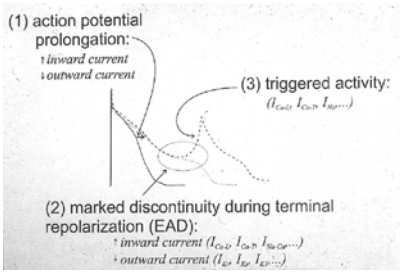
Fig. 1. Action potential and QT interval. Late inward currents maintain depolarization plateau and lengthen action potential, onset of outward currents repolarize the membrane. The QT interval reflects action potential durations of ventricular myocardium.

J. Kubalski, C. January

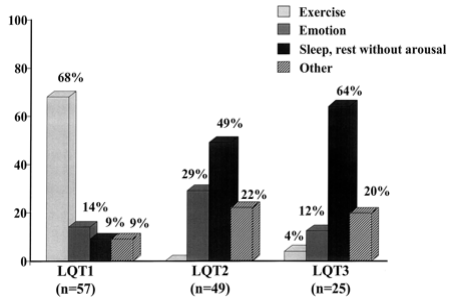
LQTS: Genetic Linkage to Multiple Ion Channel Genes



AP Prolongation Can Trigger Arrhythmias

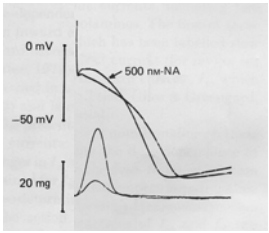


Triggers Are Gene-specific



Circ 2001;103:89-95

β-Adrenergic Stimulation Shortens AP Duration

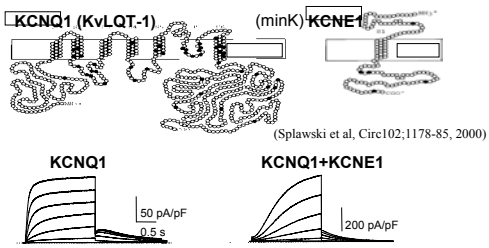


(Kass & Wiegers, *J Physiol*. 1982)

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

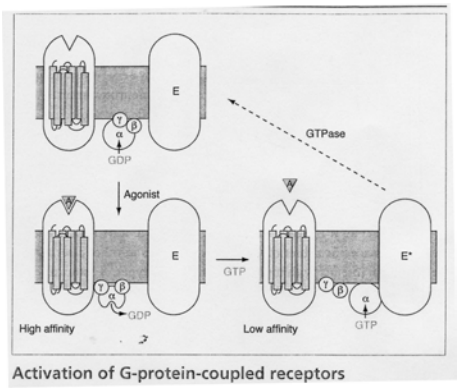
- *L-type Calcium Channel current Increased*
- *Slow I_{Ks} potassium channel Current Increased*

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

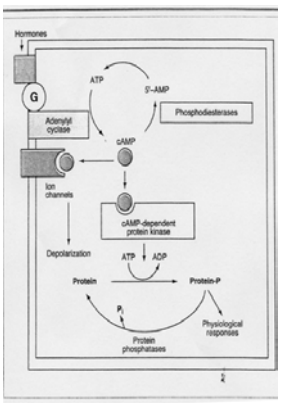


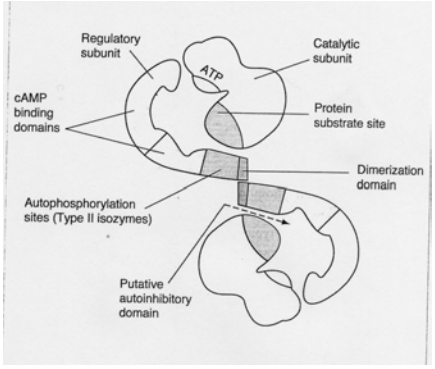
(Splawski et al, Circ102;1178-85, 2000)

Receptor stimulation to Local Signaling



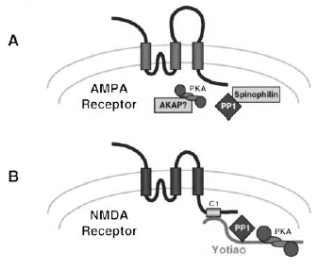
Activation of G-protein-coupled receptors

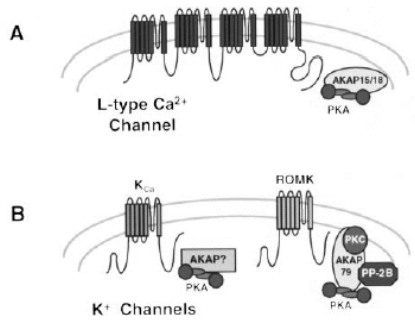




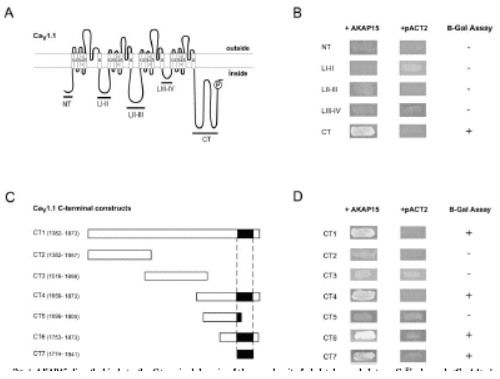
Adaptor Proteins:

Channel Microsignaling Domains:
Macromolecular Complexes





Calcium Channel Complex

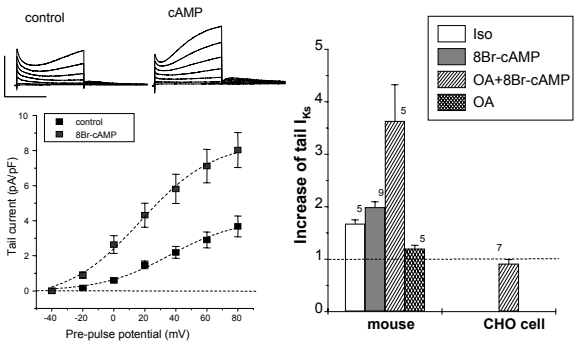


Channels as ***Macromolecular*** Signaling Complexes

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

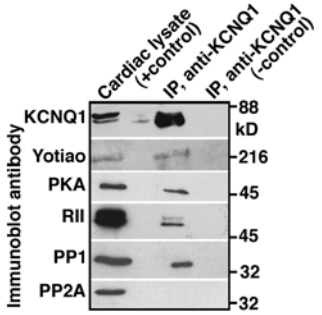
K Channel Complex

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

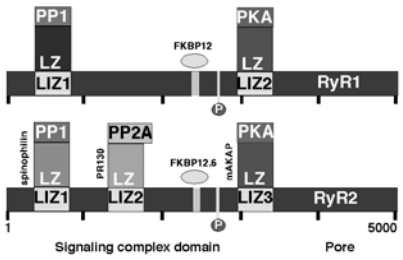


KCNQ1 forms a macromolecular complex

Human Heart

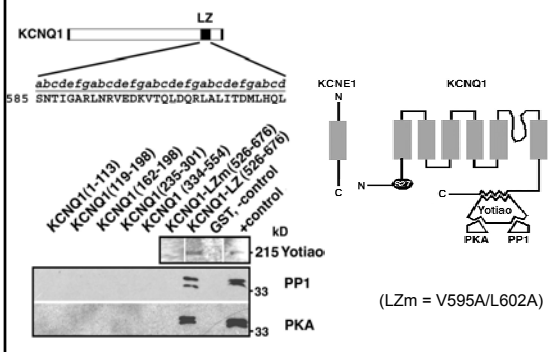


RyR macromolecular complexes are held together by leucine/isoleucine zippers (**LZ**s)



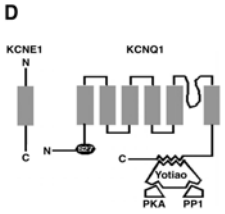
Marx, et al., (2001). ***The Journal of Cell Biology***, **153**: 699-708.

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

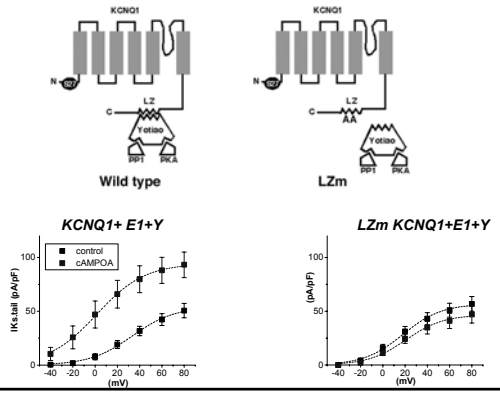


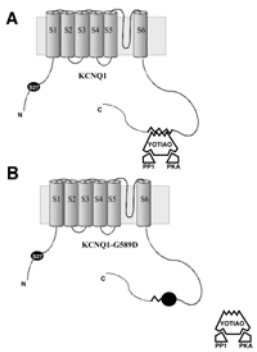
(LZm = V595A/L602A)

The KCNQ1 Macromolecular Complex



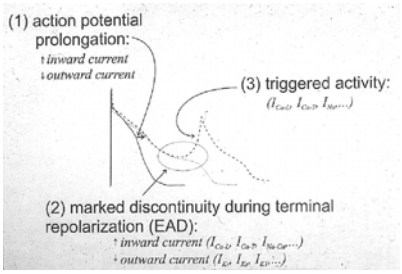
LZ mutation ablates functional up regulation





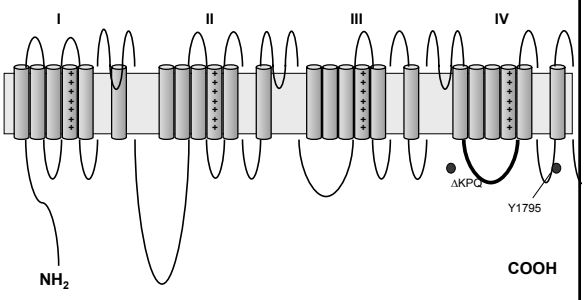
Disruption of Macromolecular Complexes in Disease

AP Prolongation Can Trigger Arrhythmias

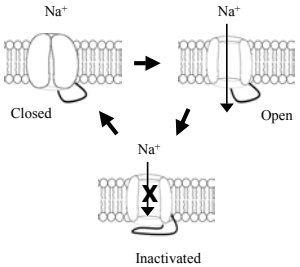


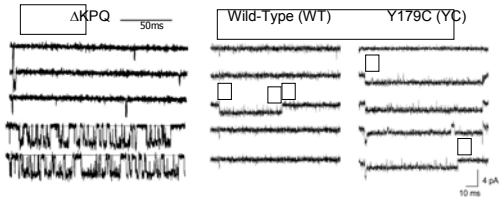
State-dependent Block of Ion Channels by drugs

- 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.

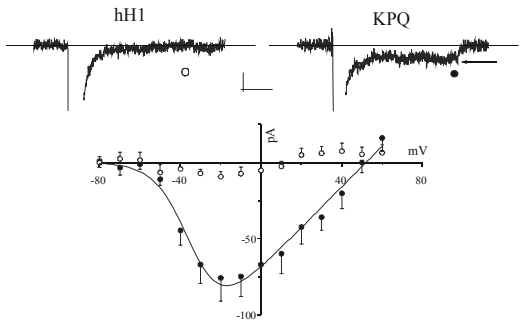


Na+ channel open state inactivation





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

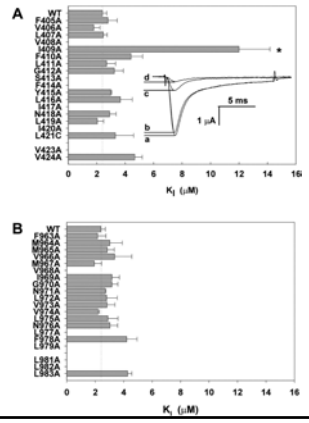


Binding Sites of LA's in Na channels:

Vladimir Yarov-Yarovoy, Jancy C. McPhee, Diane Idsvoog, Caroline Pate,

Todd Scheuer, and William A. Catterall

J. Biol. Chem., Vol. 277, Issue 38, 35393-35401, September 20, 2002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I417A
N418A
L419A
I420A
L421C
V423A
V424A
d
c
b
a
5 ms
1 μA
0 2 4 6 8 10 12 14 16
K_I (μM)
B
WT
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M964A
M965A
M966A
M967A
V968A
G969A
I970A
V971A
V972A
V973A
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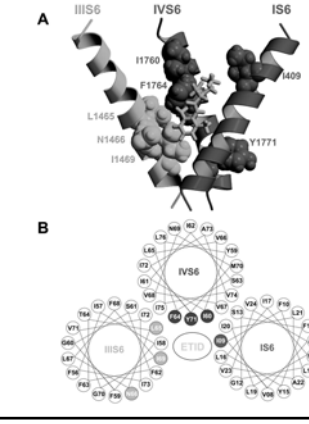
K_I (μM)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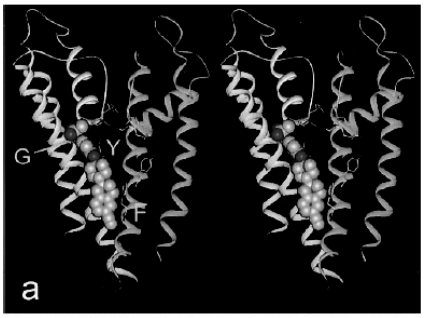
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Y
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a