Group 3
Stony Brook University
BME 301

Long QT Syndrome Type 2 (LQT2)

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Long QT Syndrome (LQTS)

- Comprises a number of disorders, all of which involve an elongated QT interval
- In this case, caused by delayed ventricular repolarization
- Not a problem per se, but is a risk factor for more dangerous complications, such as ventricular arrhythmias
A specific type of LQTS caused by mutations of HERG gene, which codes for Kv11.1, the α-subunit that makes up the pores of I_{kr} channels.
\( I_{kr} \) Channels & Kv11.1

- \( I_{kr} \) is notable for its slow activation/deactivation, and fast inactivation/recovery
- Kv11.1 is the \( \alpha \)-subunit of \( I_{kr} \)
- The \( I_{kr} \) channel consists of 4 identical \( \alpha \)-subunits that together form the pore
- Each \( \alpha \)-subunit comprises 6 transmembrane \( \alpha \) helices labeled S1-S6
- S4 is most important domain for voltage sensing (+AA every ~3 residues)
Comparing Missense Mutations in hERG

- Depending on the region affected, mutations can be pathological or benign
- Most likely harmful mutations are the ones on transmembrane/linker/pore region
- Mutations may also be nonsense, but these usually never leave the ER

*N-terminus, Transmembrane/Linker/Pore, and C-Terminus Domains*
Refresher on the Cardiac AP

0. $I_{Na}$ depolarizes the cell

1. $I_{to}$ sets the plateau voltage

2. $I_{Ca-L}$ & $I_{Ks}$ balance to create the plateau

3. $I_{Kr}$, $I_{Ks}$, and $I_{K1}$ repolarize

4. $I_{k1}$ enforces negative $V_m$

What kinds of loss in function?

- Reduction in number of channels in the cell membrane (changes effective $g_{kr}$)
  - Due to reduced protein trafficking since quality control mechanisms prevent departure from ER
- Decreasing single channel conductance
  - Pore forming domains are mutated
- Changing probability of channel gates to be open
  - E.g. Deactivation can be accelerated by N or C-terminal mutations (these help regulate gating)
Reduced $I_{kr}$ Conductance - So What?

- Reduction in $g_{kr}$ means a reduction in current.
- With a reduction in $I_{kr}$, the slope of phase 3 of the AP is drastically reduced.
- If repolarization is too slow (i.e. delayed)... EADs are possible!!!
What about Altered Gating?

Recall that Two Things Characterize $I_{kr}$:
1. Slow activation and deactivation
2. Fast inactivation and recovery from inactivation

Mutations affecting the function of either one of these gates could affect $I_{kr}$ in numerous ways, including these that we found in the literature:

- Accelerated deactivation
- Voltage-shifted inactivation
- Voltage-shifted activation

Any of these can also lead to EADs!
Early Afterdepolarizations

- Any depolarization that happens too early and interrupts another AP phase
- Can be caused by delayed repolarization as in LQT2 (slope not steep enough)
- Calcium channels have a limited refractory period - if repolarization is delayed, they can fire again or even create a self-sustaining wave
- Ventricular tachyarrhythmias!!!
MATLAB Code Manipulations

Input parameters

\[ I_k \text{ splitting and scaling factor in } I_{kr} \text{ conductance} \]

\[
\begin{align*}
g_{kr} &= \frac{g_{kr\text{scale}}}{100} \times 0.02614 \times (\sqrt{K_o/5.4}) \\
g_{ks} &= 0.057 + 0.19 \times \left(\frac{1}{1 + \exp((-7.2 + pCa)/0.6)}\right) \\
E_{kr} &= \text{nernst} \times \log((K_o)/(K_i)) \\
E_{ks} &= \text{nernst} \times \log((K_o + PR_nak*Na_o)/(K_i + PR_nak*Na_i)) \\
i_{kr} &= g_{kr} \times i_{ir} \times (v - E_{kr}) \\
i_{ks} &= g_{ks} \times x_s \times (v - E_{ks}) \\
itot &= i_{na} + i_{si} + i_{ks} + i_{kr} + i_{k1} + i_{kp} + i_b
\end{align*}
\]
MATLAB Code Manipulations Cont’d

Voltage shift in activation (vshift_a) and scaling factor in deactivation (Bp)

\[
\begin{align*}
\alpha_{xr} &= 0.00138*(v + 14.2 - vshift_a)/(1.0 - \exp(-0.123*(v + 14.2 - vshift_a))); \\
\beta_{xr} &= (Bp/100)*0.00061*(v + 38.9 - vshift_a)/(\exp(0.145*(v + 38.9 - vshift_a))-1);
\end{align*}
\]

Voltage shift in inactivation (vshift_n)

\[
x_{ir} = 1/(1+\exp((v+9-vshift_n)/22.4));
\]
Effect of $g_{kr}$ Changes on AP

Comparing Varying Conductance %

Fun With Bifurcations

<table>
<thead>
<tr>
<th>Conductance</th>
<th>100%</th>
<th>85%</th>
<th>70%</th>
<th>55%</th>
<th>40%</th>
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<tr>
<th>EADs</th>
<th>0 EADs: 100%</th>
<th>1 EAD: 48.9%</th>
<th>2 EADs: 46.6815%</th>
<th>3 EADs: 46.681472%</th>
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V(t) in mV against Time (ms)
Effects of Voltage Shifting Gates on AP
Effect of Accelerated Deactivation

Comparing Percent Acceleration of Deactivation

Volts (mV)

Time (ms)
# Member contributions

<table>
<thead>
<tr>
<th></th>
<th>Research/Background</th>
<th>MATLAB code</th>
<th>PPT presentation</th>
<th>Website</th>
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<td>Hui Zheng</td>
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Website: [http://you.stonybrook.edu/bmeswagyolo/](http://you.stonybrook.edu/bmeswagyolo/)


