Mechanisms of Arrhythmogenesis:  
Focus on Long QT Syndrome (LQTS)

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CSRC-HESI-FDA  
Rechanneling the Current Cardiac Risk Paradigm:  
Arrhythmia Risk Assessment During Drug Development Without the Thorough QT Study

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Disclosures

Cellular & Molecular Arrhythmia Research Program

University of Wisconsin-Madison

Inherited Arrhythmias Clinic

Cellular Dynamics International
The Heart Beat: A Remarkable Feat!

- Your heart is an electrically driven pump.
- It usually beats 60-80 times a minute,
  or about 100,000 times a day,
  or about 35 million times a year,
  or about 3 billion times in a normal life span.
- If the normal pumping rhythm or function is severely disrupted for more than a few minutes, irreversible multi-organ damage and death occur.
Organization of Talk

• Background
  – Congenital (Inherited) LQTS
  – Acquired (Drug-induced) LQTS
    • Anti-arrhythmic drugs
    • Non-cardiovascular drugs

• Cellular Mechanisms of Drug Action
  – Effects on ion channels
  – Effects on protein trafficking

• Cellular and Tissue Consequences

• Summary
Definitions and History

- **Cellular/tissue Mechanisms of Cardiac Arrhythmias**
  - Triggered activity
    - Early afterdepolarizations (EADs): Trigger for Torsades de Pointes
    - Delayed afterdepolarizations (DADs): Ca$^{2+}$ overload
  - Reentry (most common arrhythmia mechanism)
    - Monomorphic (fixed circuit): The more common reentrant mechanism
    - Polymorphic (varying circuit): LQTS related Torsades de Pointes
  - Abnormal (accelerated) automaticity
  - Parasystole (rare)

- **Long QT syndromes first characterized >50 yrs ago**
  - Autosomal recessive congenital LQTS with deafness (Jervell and Lange-Nielsen, 1957)
  - Autosomal dominant congenital LQTS (Romano et al, 1963; Ward, 1964)
  - Quinidine syncope with drug-induced LQTS (Selter and Wray, 1964)
  - Ventricular arrhythmia Torsades de Pointes – TdS (Dessertenne, 1966)
Background: Proarrhythmia and Antiarrhythmic Drugs

**Block of Na\(^+\) channels**: Not LQTS related

**Block of K\(^+\) channels**: Proarrhythmia associated with QT interval lengthening
- Mixed channel blockers (Quinidine, etc) shown in 1960-70’s to cause ↑APD, ↑QRS, ↑QT, and EADs and TdS. Meta-analyses later showed ↑mortality. *Circ*, 1991.
Proarrhythmia and Non-antiarrhythmic Drugs

The “founder” drug terfenadine (Seldane)


- Antihistamines were the first non-cardiovascular agents linked to drug-induced QT interval prolongation and TdS.

- FDA first became concerned in 1991 about non-sedating antihistamines (primarily terfenadine but also astemizole).
Many drugs interact with $I_{Kr}$ but other channels/currents may also be important.
Action Potential Prolongation (AP)

- Lengthens Refractoriness (>Purkinje, M-cell)
- Increases Heterogeneity of Repolarization
- Induce Early Afterdepolarizations (EADs)

EAD mechanism: Recovery of L-Ca$^{2+}$ channel window current at the AP plateau voltage range.

### Acquired (Congenital) LQTS: APD/EAD/QT Interval Prolonging Models

<table>
<thead>
<tr>
<th>Drug (Gene Defect)</th>
<th>Principal Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veratridine, ATX II, anthopleurin A, alfuzosin, (<em>mutations in Na(^+) channels</em>)</td>
<td>Enhance late I(_{\text{Na}})</td>
</tr>
<tr>
<td>Bay K 8644 (<em>mutations in Ca(^{2+}) channels</em>)</td>
<td>Enhance I(_{\text{Ca-L}}) (mode 2)</td>
</tr>
<tr>
<td>Cs(^+), quinidine, procainamide, bepridil</td>
<td>Suppress K(^+) currents</td>
</tr>
<tr>
<td>E-4031, dofetilide, ibutilide, sotalol, terfenadine, astemizole, desmethylastemizole, cisapride, haloperidol, droperidol, halofantin, erythromycin, fluoxetine, etc. (<em>mutations in hERG/Kv11.1 K(^+) channels</em>)</td>
<td>Suppress I(_{\text{Kr}})</td>
</tr>
<tr>
<td>Chromanol 293B (<em>mutations in KCNQ1/Kv7.1 K(^+) channels</em>)</td>
<td>Suppress I(_{\text{Ks}})</td>
</tr>
<tr>
<td>Depolarizing current</td>
<td>No direct channel effects</td>
</tr>
<tr>
<td>Ischemia, reperfusion, acidosis, hypertrophy</td>
<td>Multiple effects</td>
</tr>
</tbody>
</table>

**Conclusions:**
- **Congenital LQTS:** Multiple channels but K\(^+\) channels dominant
- **Acquired LQTS:** Most drugs cause rapid *direct channel block* of I\(_{\text{Kr}}\)
**hERG\textsubscript{I\textsubscript{Kr}} Channel Protein Trafficking:**
Indirect mechanism to reduce \textit{I\textsubscript{Kr}}

Drug-induced disruption of WT hERG channel protein trafficking

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**I. As\textsubscript{2}O\textsubscript{3}**

![As\textsubscript{2}O\textsubscript{3} experiment (A) and normalized image densities (B) and normalized surface expression (C)]

**II. Pentamididine**

![Pentamididine experiment (A) and normalized image densities (B) and normalized surface expression (C)]

**III. Celastrol**

![Celastrol experiment (A) and normalized image densities (B) and normalized surface expression (C)]

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Yang et al, *JBC*. 2006

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# Direct vs Indirect hERG Effects: Complex Drug Interactions to Reduce $I_{Kr}$

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT</th>
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</thead>
<tbody>
<tr>
<td>Probucol</td>
<td>trafficking only</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>trafficking only (↑conc)</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>trafficking &gt; block</td>
</tr>
<tr>
<td>Celastrol</td>
<td>trafficking &gt; block</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>trafficking &gt; block</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>trafficking ~ block</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>trafficking ~ block</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>block &gt; trafficking</td>
</tr>
<tr>
<td>Verapamil</td>
<td>block &gt; trafficking (↑conc)</td>
</tr>
<tr>
<td>Cisapride</td>
<td>block only</td>
</tr>
<tr>
<td>E-4031</td>
<td>block only</td>
</tr>
</tbody>
</table>

Findings support separate drug binding domains for direct and indirect block

Additional potential drug mechanisms: Drug transporters, signaling & adrenergic pathways, secondary genes/proteins, genomic associations
EAD Mechanism: The same in iPS-CMs
EAD amplitude varies inversely with its take off potential

Adult Canine Purkinje Fiber APs

Bay k 8644

Slope -1.87±0.26 mV/mV


iCell CM APs

Slope -2.28±0.11 mV/mV

Mechanism of Torsades de Pointes (TdS)

EADs excite polymorphic reentry in the ventricles

Block of $I_{Kr}$ → ↓Repolarizing current

$\uparrow$APD (greater in Purkinje, M-cell relative to epi & endo)

$\uparrow$Heterogeneity of repolarization

Variable unidirectional block and reentry

Triggered activity (excite neighboring myocytes/tissue)

TdS

Nonsustained. Palpations and syncope

Sustained. Sudden cardiac death

Modified from Yap and Camm. *Heart*, 2003
Long QT Syndrome (LQTS): A Long Journey

LQTS and Torsades de Pointes with the antihistamine astemizole (Hismanal®)

In 1999 Hismanal was withdrawn from the marketplace for drug-induced LQTS

81 y.o. female

Summary

- LQTS has been a “cardiology problem” for >50 years.
- AP prolongation lengthens refractoriness, increases tissue heterogeneity of repolarization, and triggers arrhythmogenic EADs to initiate Torsades de Pointes.
- Direct drug block of $I_{Kr}$ (hERG channels) is the dominant mechanism for both cardiovascular and non-cardiovascular drug related LQTS.
- Additional channels and additional cellular mechanisms may infrequently also cause non-cardiovascular drug related LQTS.
- New screening approaches including iPS-derived human cardiomyocytes offer innovative ways forward.