Introduction

Precise evaluation of cardiac safety in an early preclinical stage is essential for developing novel drugs. In particular, it is important to predict a possible risk for proarrhythmia in safety pharmacology testing. Since life-threatening drug-induced arrhythmia like torsades de pointes is well correlated with QT prolongation, which can be caused by blockade of the hERG potassium channels, electrophysiological assays on the hERG channel has been indispensable. Recently, QT prolongation associated with blockade of other cardiac ion channels has also been discussed. In this study, we implemented a mechanistic approach for understanding how individual human cardiac ion channels are affected along with QT prolongation by the IQ-CSRC drugs.

Materials & Methods

- Drugs: 6 drugs used in the IQ-CSRC perspective study
  - Ondansetron
  - Quinine
  - Dofetilide
  - Moxifloxacin
  - Levocetirizine (QT-negative)

- In vitro multi-channel assay:
  Whole-cell voltage-clamp recordings at RT
  - Cell lines

<table>
<thead>
<tr>
<th>Transfected gene</th>
<th>host</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>hNaV1.5, hCaV1.2/β2/α2δ1</td>
<td>HEK</td>
<td>ICa, INa,P, INa,L</td>
</tr>
<tr>
<td>hERG</td>
<td>HEK</td>
<td>IKr</td>
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<tr>
<td>hKVLQT1/mink</td>
<td>CHO</td>
<td>IKs</td>
</tr>
<tr>
<td>hKV1.2</td>
<td>CHO</td>
<td>IKur</td>
</tr>
<tr>
<td>hKV4.3</td>
<td>CHO</td>
<td>Ito</td>
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</tbody>
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- Voltage protocol (step pulses)

- Evaluations:
  - Suppression rate after 3 to 5 min-administration
  - IC50* hill slope, etc

Results

- Dofetilide (I_{K_{o}} >> I_{Ca}, I_{Na})

- Ondansetron (I_{K_{o}} >> I_{Ca}, I_{Na})

- Moxifloxacin (I_{K_{o}} > I_{Ca} > I_{Na})

- Quinine (multichannel blocker)

- Levocetirizine (multichannel blocker, I_{po} > other channels)

Conclusion

In the present study, we evaluated the blocking profiles of the IQ-CSRC drugs against human cardiac ion channels, serving for proarrhythmic risk prediction in the drug development process.