Safety Pharmacological Approach for Proarrhythmic Risk Prediction Using IQ-CSRC Drugs (I) – Patch-clamp Study –

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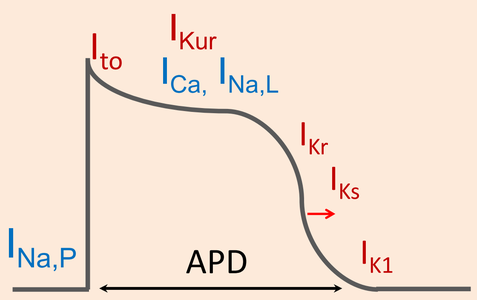
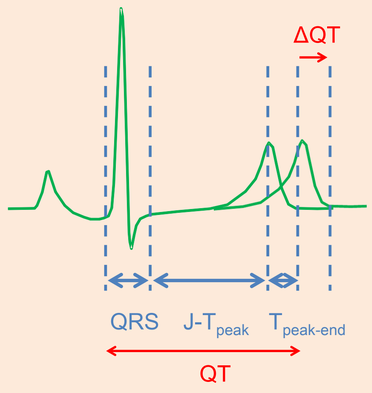
Introduction

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.

In vitro : Patch-clamp



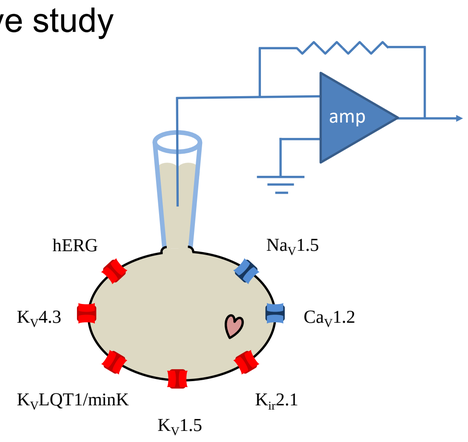
In vivo : ECG, Langendorff



Materials & Methods

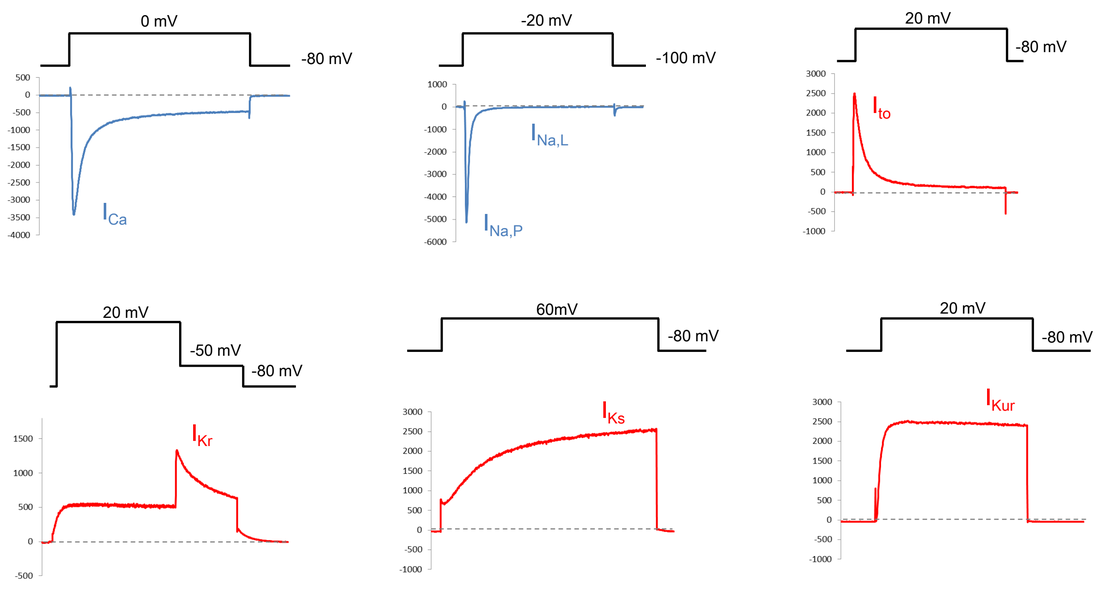
- Drugs: 6 drugs used in the IQ-CSRC perspective study
  - Ondansetron
  - Quinine
  - Dolasetron
  - Moxifloxacin
  - Dofetilide
  - Levocetirizine (QT-negative)

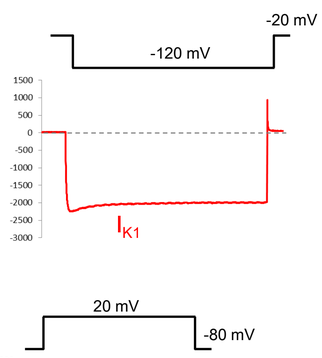
- In vitro multi-channel assay:
  Whole-cell voltage-clamp recordings at RT
  - Cell lines



Transfected gene	host	Current
hNa$_V$1.5	HEK	$I_{Na,P}$, $I_{Na,L}$
hCa$_V$1.2/β2/α2δ1	CHO	I_{Ca}
hERG	HEK	I_{Kr}
hK$_V$LQT1/mink	CHO	I_{Ks}
hK$_V$1.5	CHO	I_{Kur}
hK$_V$4.3	CHO	I_{to}
hK$_{ir}$2.1	CHO	I_{K1}

- Voltage protocol (step pulses)

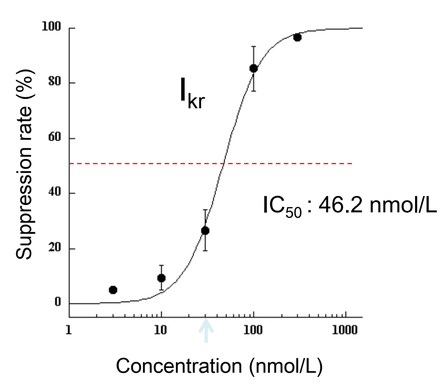


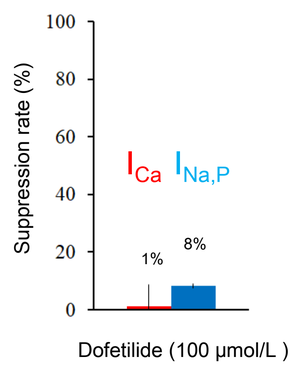


- Evaluations:
  - Suppression rate after 3 to 5 min-administration
  - IC_{50}, hill slope , etc

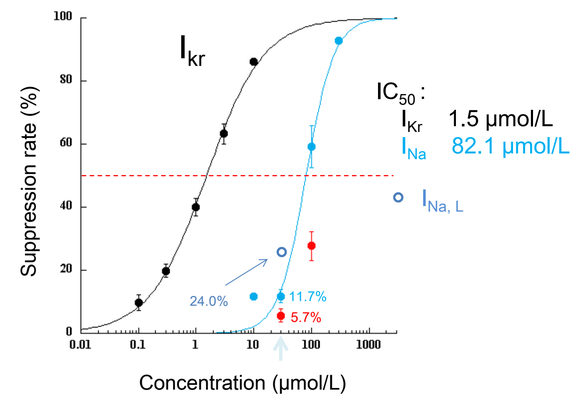
Results

- Dofetilide (I_{Kr} >>> I_{Na}, I_{Ca})

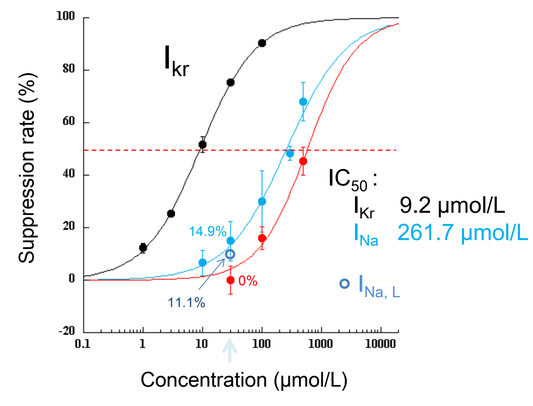




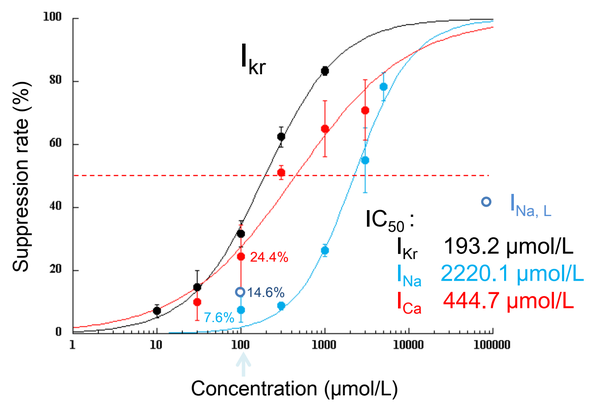
- Ondansetron (I_{Kr} >> I_{Na}, I_{Ca})



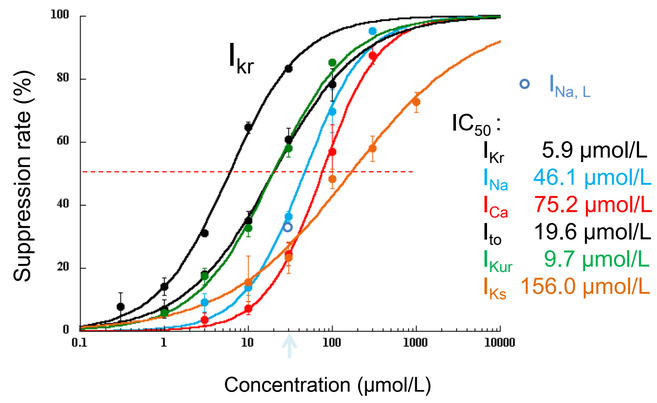
- Dolasetron (I_{Kr} >> I_{Na}, I_{Ca})

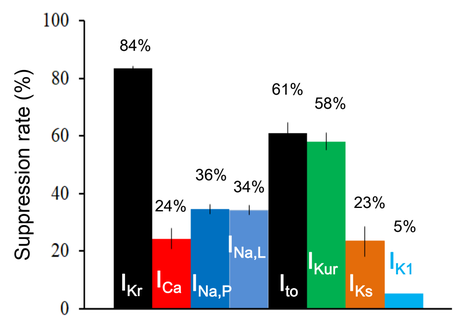


- Moxifloxacin (I_{Kr} > I_{Ca} > I_{Na})

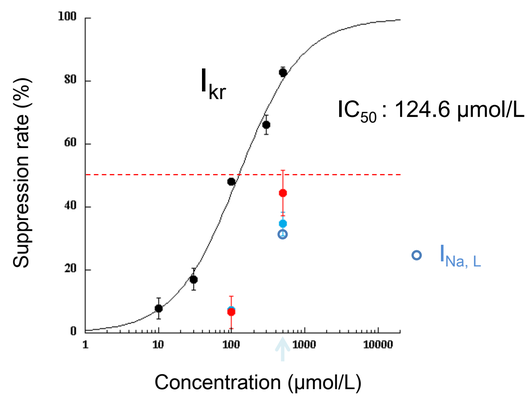


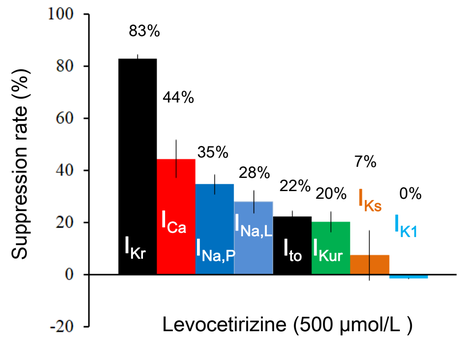
- Quinine (multichannel blocker)





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





- hERG channel was strongly blocked by all 6 drugs while inward currents through Na$_V$1.5 and Ca$_V$1.2 channels were less frequently inhibited.

- **Dofetilide**, **ondansetron**, and **dolasetron** showed highly selective hERG channel inhibition with little or small inhibitory effects on Na$_V$1.5 and Ca$_V$1.2 channels.

- **Moxifloxacin** moderately blocked hERG and Ca$_V$1.2 channels and weakly Na$_V$1.5 channel.

- **Quinine** and a QT-negative drug of **levocetiridine** showed strong inhibition of hERG channel and moderate inhibition of the other 6 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.