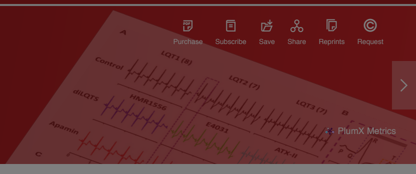

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Sex-specific I_{KAS} activation in rabbit ventricles with drug-induced QT prolongation

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Background

Female sex is a known risk factor for drug-induced long QT syndrome (diLQTS). We recently demonstrated a sex difference in apamin-sensitive small-conductance Ca^{2+}-activated K^+ current (I_{KAS}) activation during β-adrenergic stimulation.

Objective

The purpose of this study was to test the hypothesis that there is a sex difference in I_{KAS} in the rabbit models of diLQTS.

Methods

We evaluated the sex difference in ventricular repolarization in 15 male and 22 female Langendorff-perfused rabbit hearts with optical mapping techniques during atrial pacing. HMR1556 (slowly activating delayed rectifier K^+ current [I_{Ks}] blocker), E4031 (rapidly activating delayed rectifier K^+ current [I_{Kr}] blocker) and sea anemone toxin (ATX-II, late Na^+ current [I_{NaL}] activator) were used to simulate types 1-3 long QT syndrome, respectively. Apamin, an I_{KAS} blocker, was then added to determine the magnitude of further QT prolongation.

Results

HMR1556, E4031, and ATX-II led to the prolongation of action potential duration at 80% repolarization (APD_{80}) in both male and female ventricles at pacing cycle lengths of 300–400 ms. Apamin further prolonged APD_{80} (pacing cycle length 350 ms) from 187.8±4.3 to 206.9±7.1 (*P*=.014) in HMR1556-treated, from 209.9±7.8 to 224.9±7.8 (*P*=.003) in E4031-treated, and from 174.3±3.3 to 188.1±3.0 (*P*=.0002) in ATX-II–treated female hearts. Apamin did not further prolong the APD_{80} in male hearts. The Ca_i transient duration (Ca_iTD) was significantly longer in diLQTS than baseline but without sex differences. Apamin did not change Ca_iTD.

Conclusion

We conclude that I_{KAS} is abundantly increased in female but not in male ventricles with diLQTS. Increased I_{KAS} helps preserve the repolarization reserve in female ventricles treated with I_{Ks} and I_{Kr} blockers or I_{NaL} activators.

Keywords

Calcium transient • Optical mapping • Potassium and late sodium currents • Repolarization reserve • SK current

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