Recent advances in research of cardiac calcium-activated chloride channels

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TMEM16A and/or Bestrophin-3 mediated Ca^{2+}-activated Cl^- current ($I_{Cl(Ca)}$) may cause cardiac arrhythmias but others showed $I_{Cl(Ca)}$ to be antiarrhythmic. True profile of $I_{Cl(Ca)}$ during an actual ventricular action potential (AP) is poorly understood.

Profile of $I_{Cl(Ca)}$ (studied as 0.5 mM 9-anthracene carboxylic acid (9-AC)-sensitive current under whole-cell AP voltage-clamp (APVC) conditions) contained an early fast outward and a late inward component in canine left ventricular cells. Both components were reduced by ryanodine, while fully abolished by nisoldipine and BAPTA. Setting $[Ca^{2+}]_i$ to 1.1 μM decreased, while Bay K8644, isoproterenol (ISO), and faster stimulation increased $I_{Cl(Ca)}$. The early outward component of $I_{Cl(Ca)}$ was larger in *subepicardial* than in *subendocardial* cells.

9-AC generated early afterdepolarizations (EAD) recorded with sharp electrodes at low stimulation rates and their incidence was higher in ISO. 9-AC increased short-term variability of repolarization and reduced phase-1 repolarization. 9-AC increased AP duration in a reverse rate-dependent manner in all cell types except *subepicardial* ones.

Whole-cell $I_{Cl(Ca)}$ density and normalized protein expressions of TMEM16A and Bestrophin-3 did not differ significantly among left ventricular cells of various origin. TMEM16A and Bestrophin-3 showed co-localization with one another and also with $Ca_v1.2$ channels in both canine and human left ventricular myocytes.

$I_{Cl(Ca)}$ activation requires Ca^{2+}-entry through neighbouring L-type Ca^{2+} channels but augmented by sarcoplasmic reticulum Ca^{2+}-release. $I_{Cl(Ca)}$ can be protective against cardiac arrhythmias by reducing spatial and temporal heterogeneity of cardiac repolarization and EAD formation.