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Chloride current in mammalian ventricular cells

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Background & Aim: Calcium activated Cl^- current (ICl(Ca)) mediated by TMEM16A and/or Bestrophin-3 may contribute to cardiac arrhythmias. Our goal was to study the ICl(Ca) profile during an actual ventricular Action Potential (AP) under normal calcium cycling as well as in case of altered intracellular calcium concentration ($[Ca^{2+}]_i$). The expression of TMEM16A and/or Bestrophin-3 in canine and human left ventricular myocytes was examined.

Methods: Whole-cell configuration of the patch-clamp technique and Action Potential voltage-clamp were used to monitor $I_{Cl(Ca)}$, detected as 9 anthracene carboxylic acid (9 AC)-sensitive current. FURA-2-AM dye was used to measure $[Ca^{2+}]_i$. Expression and cellular localization of Cav1.2, Bestrophin-3 and TMEM16A was analyzed with immunocytochemistry and confocal microscopy.

Results: Under AP voltage-clamp conditions the profile of ICl(Ca) contained an early fast outward (1.62±0.06 A/F) and a late inward component (-0.16±0.02 A/F). Both components were reduced by ryanodine (1.05±0.03 A/F; -0.07±0.03 A/F), while fully abolished by BAPTA, but not EGTA (1.17±0.09 A/F; −0.13±0.02 A/F). Setting $[Ca^{2+}]_i$ to 1.1 μM decreased $I_{Cl(Ca)}$, while application of Bay K8644, isoproterenol increased the amplitude of ICl(Ca). Both L-type Ca^{2+} current and $I_{Cl(Ca)}$ were eliminated by nisoldipine. TMEM16A and Bestrophin-3 showed strong co-localization with one another and also with Cav1.2 channels both canine myocytes and human ventricular myocardium.

Conclusions: Activation of ICl(Ca) in canine ventricular cells requires calcium entry through neighboring L-type Ca^{2+} channels and is only augmented by SR Ca^{2+}-release. Substantial activation of ICl(Ca) requires high Ca^{2+} in the dyadic clefts which can be effectively buffered by BAPTA, but not EGTA.

Biography

Janos Magyar has completed his PhD from University of Debrecen and Postdoctoral studies from University of Virginia and University of Kentucky. He is the Head of Division of Sport Physiology of University of Debrecen. He has published more than 80 papers in reputed journals.

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