Differential arrhythmogenic actions of cardiac CaMKII

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Ischemic heart disease is the leading cause of death for men and women in Australia, though the characteristics/prognoses of an ischemic event differ between sexes. Ischemia-related arrhythmic incidence is generally lower in females (*vs* males), though the risk of sudden cardiac death in women (but not men) increases substantially when there is an underlying cardiopathology. The fundamental mechanisms responsible for these sex differences are not well understood. Ca^{2+} overload is a key instigator of ischemia/reperfusion arrhythmias. Interest has hence focused on the actions of Ca^{2+}/calmodulin dependent kinase II (CaMKII) and the therapeutic potential of its inhibition in a number of myocardial disease contexts. Responsive to alterations in cellular Ca^{2+} levels, CaMKII phosphorylates and upregulates many of the ion channels/transporters centrally involved in excitation-contraction coupling. Expressed as two splice variants (δ_B and δ_C), CaMKII activity can also be maintained through post-translational modification, including autophosphorylation, oxidation and glycosylation. CaMKII activation is increased in hypertrophic and failing human hearts, and transgenic overexpression causes cardiac failure and an increased propensity for ventricular arrhythmias. Furthermore, selective activation of CaMKII by oxidation or glycosylation has been demonstrated to be pro-arrhythmic. CaMKII activity peaks very early in reperfusion (2-5min reperfusion, as evidenced by phosphorylation of phospholamban at the CaMKII-specific Thr17 residue) - a period particularly associated with ventricular arrhythmias. We have shown that CaMKII inhibition (with KN93) substantially reduces the incidence of ventricular tachycardia and/or fibrillation post-ischemia, which has subsequently been attributed to stimulatory actions on sarcoplasmic reticulum (SR) Ca^{2+} release channel opening. However, studies of the role of CaMKII in arrhythmogenesis have exclusively been performed in male animal models, despite the significant sex differences reported in cardiomyocyte Ca^{2+} handling and ischemia/reperfusion responses. As both operational Ca^{2+} levels and basal CaMKII activity are lower in female myocytes/hearts, we predicted that a relative protection from reperfusion arrhythmias in the female heart would be associated with less CaMKII activation. However, contrary to our hypothesis, our investigations showed a selective augmentation of CaMKII autophosphorylation in female hearts subjected to ischemia/reperfusion (*vs* males), despite less arrhythmias. Isolated cardiomyocyte studies indicated CaMKII-mediated actions on phospholamban and the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) were particularly prominent in females, promoting SR Ca^{2+} uptake and maintaining diastolic cytosolic Ca^{2+} levels. Our subsequent studies suggested that CaMKII splice variants are selectively modified by autophosphorylation/oxidation, and that the post-translational modification status of CaMKII may determine its substrate specificity. We propose that female hearts may be protected from reperfusion arrhythmias by a particular susceptibility of the putatively cardioprotective CaMKIIδ_B splice variant to autophosphorylation. These findings imply that, in addition to the development of global CaMKII inhibitors as a first-line defense against lethal ventricular arrhythmias, further benefit may be gained by targeting an upregulation of an autophosphorylated form of the CaMKIIδ_B splice variant as a highly selective anti-arrhythmic intervention. Importantly, the efficacy of these interventional strategies may be sex-specific and dependent on the occurrence of underlying myocardial co-pathologies.