Editorial

Protecting ischemic hearts by modulation of SR calcium handling

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The sarcoplasmic reticulum (SR) plays a crucial role in excitation-contraction coupling by regulating the concentration and distribution of intracellular Ca\(^{2+}\). The functions of the SR are known to be compromised by ischemia/reperfusion, but whether SR dysfunction contributes to Ca\(^{2+}\) overload and injury in cardiomyocytes during ischemia/reperfusion has been controversial for a decade. Studies using isolated cardiomyocytes subjected to simulated ischemia/reperfusion generally support the role of the SR in Ca\(^{2+}\) overload at the time of "reperfusion" [1]. However, findings in earlier studies, which examined the effects of ischemia on the SR Ca\(^{2+}\) uptake and Ca\(^{2+}\) release using isolated SR preparations from whole hearts, are contradictory. A study by Chen et al. [2] assessed the Ca\(^{2+}\) concentration in the SR by 19F-NMR in isolated beating hearts and showed that it was well maintained during a 25-min period of ischemia, while the cytosolic Ca\(^{2+}\) level was significantly increased after the onset of ischemia. Furthermore, calculation of the free energy for Ca\(^{2+}\)-ATPase and for ATP hydrolysis suggests that the ΔG\(_{ATP}\) is adequate to prevent a net release of SR Ca\(^{2+}\) during a 30-min period of ischemia [2]. However, two inhibitors of Ca\(^{2+}\)-ATPase, cyclopiazonic acid and thapsigargin, administered before ischemia or at the time of reperfusion improved recovery of mechanical function in isolated rat hearts [3], suggesting that inhibition of intracellular Ca\(^{2+}\) oscillations and/or depletion of Ca\(^{2+}\) in the SR afford the cardioprotection. These apparent inconsistencies in earlier findings in vitro and in vivo have not been explained and clearly indicate the need for better models to explore the roles of the SR in Ca\(^{2+}\) overload and ischemia/reperfusion injury.

In this issue of the Journal, Zhou et al. [4] report a study using a novel mouse model for exploring the role of SR Ca\(^{2+}\) handling in myocardial ischemia/reperfusion injury. They developed mice overexpressing histidine-rich Ca\(^{2+}\)-binding protein (HRC), which is, like calsequestrin, localizes in the SR lumen and binds Ca\(^{2+}\) with high capacity and low affinity [5]. It also binds to triadin, a regulator of SR Ca\(^{2+}\) release [6]. Although HRC only accounts for approximately 1% of junctional SR proteins, while calsequestrin is far more abundant [7], overexpression of HRC by about threefold substantially reduced Ca\(^{2+}\) uptake rate in the SR [8]. Interestingly, Ca\(^{2+}\) influx through the sarcolemma via the Na\(^{+}\)-Ca\(^{2+}\) exchanger (NCX) is also suppressed in HRC-overexpressing hearts, which would counteract the reduced SR Ca\(^{2+}\) uptake rate and result in a normal SR Ca\(^{2+}\) store [8]. In this model, myocardial necrosis and apoptosis during ischemia/reperfusion were significantly attenuated compared with those in wild-type mice [4]. These results are consistent with earlier findings in phospholamban (PLN)-knockout mice [9,10]. In the basal, dephosphorylated state, PLN inhibits Ca\(^{2+}\) uptake by the SR, and ablation of this SR protein increased SR Ca\(^{2+}\) uptake and release [9], leading to significantly augmented myocardial injury during ischemia/reperfusion [10]. The findings from these two models of SR protein modulation strongly support the notion that alterations in SR Ca\(^{2+}\) handling by ischemia/reperfusion contributes to myocardial injury in vivo.

Mechanisms by which tolerance against ischemia/reperfusion injury is increased by HRC overexpression and decreased by PLN ablation remain unclear. It is possible that the rate of SR Ca\(^{2+}\) uptake and level of SR Ca\(^{2+}\) stores are determinants of the extent of Ca\(^{2+}\) oscillation and thus cell
injury during ischemia/reperfusion. However, their relationships under the conditions of ischemia/reperfusion have not been investigated in HRC-overexpressed and PLN-ablated mice. It is also possible that anti-heart tolerance in HRC-overexpressed mice is induced, at least in part, by changes secondary to HRC overexpression such as suppressed Ca^{2+} influx through NCX and upregulation of triadin protein. Although NCX is a major route for Ca^{2+} efflux under physiological conditions, its reverse-mode operation accelerated by intracellular Na^{+} accumulation plays a major role in Ca^{2+} overload during ischemia/reperfusion [11]. Suppression of Na^{+} overload by inhibiting the Na^{+}/H^{+} exchanger (NHE) or the Na^{+} channel has been shown to attenuate Ca^{2+} overload and myocardial injury during ischemia/reperfusion [12,13]. Inhibition of NCX at the time of reperfusion [14] and cardiac-specific ablation of NCX [15] also attenuate ischemia/reperfusion injury. Thus, reduced NCX activity may be responsible for myocardial resistance to ischemia/reperfusion injury in HRC-overexpressed mice, though alteration in reverse-mode function of NCX in this mouse model has not been characterized.

The main hurdle for the clinical application of HRC up-regulation for management of coronary artery disease is the increased susceptibility of HRC-overexpressing hearts to hypertrophy and heart failure [8]. Indeed, overexpression of HRC compromised the heart’s responses to both hemodynamic overload and aging, resulting in congestive heart failure by 18 months of age. However, in contrast to 3-fold overexpression, 2-fold overexpression of HRC in hearts did not induce a cardiomyopathic phenotype during aging [8], indicating that there may be a threshold level of HRC abundance for heart failure development. On the other hand, the threshold of HRC protein level for augmentation of anti-ischemic tolerance also remains unclear. Even if a lower level of HRC overexpression protects cardiomyocytes without exposing the heart to the risk of heart failure, the development of a clinical method for controlling up-regulation of HRC is a great challenge. Nevertheless, the study by Zhou et al. [4] shed light on an interesting target in the SR for myocardial protection against ischemia/reperfusion.

References