Paradoxical resistance to myocardial ischemia and age-related cardiomyopathy in NHE1 transgenic mice: a role for ER stress?

Sarcolemmal Na(+)H(+) exchanger (NHE) activity, which is provided by the NHE isoform 1 (NHE1), has been implicated in ischemia/reperfusion-induced myocardial injury in animal models and humans, on the basis of studies with pharmacological NHE1 inhibitors. We generated a transgenic (TG) mouse model with cardiac-specific over-expression of NHE1 to determine whether this would be sufficient to increase myocardial susceptibility to ischemia/reperfusion-induced injury. TG mouse hearts exhibited increased sarcolemmal NHE activity and normal morphology and function. Surprisingly, they also showed reduced susceptibility to ischemia/reperfusion-induced injury, as reflected by improved functional recovery and smaller infarcts. Such protection was sustained in the presence of NHE1 inhibition with zoniporide, indicating a mechanism that is independent of sarcolemmal NHE activity. Immunoblot analysis revealed accumulation of immature NHE1 protein as well as marked upregulation of both cytoprotective (78/94 kDa glucose-regulated proteins, calreticulin, protein disulfide isomerase) and pro-apoptotic (C/EBP homologous protein) components of the endoplasmic reticulum (ER) stress response in TG myocardium. With increasing age, NHE1 TG mice exhibited increased myocyte...
apoptosis, developed left ventricular contractile dysfunction, underwent cardiac remodelling and died prematurely. Our findings indicate that: (1) Cardiac-specific NHE1 over-expression induces the ER stress response in mouse myocardium, which may afford protection against ischemia/reperfusion-induced injury despite increased NHE activity; (2) Ageing NHE1 TG mice exhibit myocyte apoptosis, cardiac remodelling and failure, likely as a result of sustained ER stress; (3) The pluripotent effects of the ER stress response may confound studies that are based on the chronic over-expression of complex proteins in myocardium.