Cardiomyocyte-specific beta3-adrenergic receptor expression reduces infarct size inhibiting the autophagic flux in mice

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Background: Since the discovery of β3-adrenergic receptor (β3AR), the third class of β-adrenergic receptors, expression in both cardiomyocytes and endothelial cells of the cardiovascular system, it has come to the focus due to it’s possible implication in cardiovascular diseases. Although it’s expression is low compared to β1 and β2 subtypes (1), its been demonstrated that β3AR agonists have a cardioprotective effect in ischemia/reperfusion (IR) injury though inhibition of mitochondrial pore opening (2).

Purpose: In this project we determined the cellular origin of the β3AR cardioprotection and its role on cellular autophagic machinery.

Methods: Mice with overexpression of the β3AR in cardiomyocytes or endothelial cells and their control littermates were subjected to left coronary artery occlusion for 45 min followed reperfusion after 24h and 7days. Left ventricular function was assessed by echocardiography at day 7. Then, heart samples were collected at baseline and 24h and 7 days after IRI. Mitochondrial number were analyzed by transmission electron microscopy. Proteins related to autophagy signaling pathways were measured by western blot and RT-qPCR.

Results: Cardiomyocyte-specific β3AR overexpression protects the heart upon IR injury, reduced cardiac fibrosis which improved cardiac function and maintained heart mass. Studying the effects at baseline to understand the molecular mechanisms of cardioprotection, we found that β3AR overexpression in cardiomyocytes showed a reduction in autophagy markers such as LC3B and Parkin, meaning there is an alteration in the autophagic flux.

Conclusions: Cardiomyocyte-specific overexpression of β3-adrenergic receptor reduces infarct size and protects the heart affecting the autophagy machinery. Our results shed light on the role of the β3AR in the mitochondrial quality control system, offering evidence of its potential use as a target to decrease IR injury in patients with acute myocardial infarction.

β3-adrenergic receptor overexpression reduces infarct size, improves cardiac function and inhibits cell-death after ischemia/reperfusion injury. Mice with overexpression of the β3AR in cardiomyocytes (c-β3tg) and their control littermates (WT) were subjected to left coronary artery occlusion for 45 min followed reperfusion after 24h. Samples were collected at baseline and 24h and 7 days after IRI (A). Histological evaluation of left ventricle (LV) AAR and IS in c-β3tg (n=8) mice compared to WT littermate controls (n=8) subjected to IR after 24h. AAR and IS were determined as previously described. Representative images of LV slices showing AAR (negative for Evans Blue) in left panels and extent of necrosis ( TTC-negative area) in right panels (B). Representative left ventricle M-mode echocardiograms 7 days after IRI (C). Echocardiographic evaluation of left ventricular ejection fraction (LVEF) and cardiac output (D). Data represented in means ± SD. t test: *, p<0.05; **, p<0.01; ***, p<0.005.
**β3-adrenergic receptor overexpression inhibits autophagy signaling pathways.** Western blot data and representation for different autophagy-related proteins: Parkin RBR E3 ubiquitin protein ligase (Parkin), ubiquitin-binding protein p62 (p62), microtubule-associated proteins 1A/1B light chain 3B (LC3B) and Beclin-1, from mice with overexpression of the β3AR in cardiomyocytes (c-hβ3tg) compared to their control littermates (WT) (A, B). Data represented in means ± SD. t test: **, p<0.01; ***, p<0.005.