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Beta3-adrenergic receptor stimulation reduces ischemia/reperfusion injury through inhibition of the mitochondrial transition pore opening (mPTP) and subsequent apoptotic inhibition

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Background: Beta3-adrenergic receptor (b3AR) stimulation reduces myocardial ischemia/reperfusion injury (IRI) in vivo. The aim of this study was to assess whether this effect is exerted directly on the cardiomyocytes and to investigate the role of the mPTP in this protection.

Methods: Adult isolated and HL-1 cardiomyocytes were subjected to hypoxia/reoxygenation (H/R) in the presence or absence of BRL (5μM). To study the effect on the mPTP, adult cardiomyocytes were subjected to tetramethyl-rhodamine methyl ester laser-induced oxidative stress-mediated mPTP opening in the presence or absence of BRL. WT and CyclophilinD-KO mice underwent myocardial IRI and were randomized to receive the b3AR agonist BRL37344 (BRL, 5μg/kg) or saline 5 min before reperfusion.

Results: Viability evaluation in cardiomyocytes showed consistent 25% cell death reduction when treated with BRL. Western blot revealed AKT signalling pathway implication and BCL2-mediated apoptotic inhibition. Susceptibility to (mPTP) opening assay resulted in a significant delay to mPTP opening in BRL37344 (5μmol/L) treated cardiomyocytes. Finally, infarct size evaluation revealed 33% reduction in the WT treated animals, while cyclophilinD-KO mice presented same extent of infarction suggesting mPTP as a key player in BRL protective effect.

Conclusion: b3AR stimulation cardioprotection appear to be directly on the cardiomyocytes by inhibiting the opening of the mPTP and promoting anti apoptotic signalling pathways.