Melanocortin 1 receptor deficiency protects against pathological cardiac hypertrophy

A. Suominen¹, S. Ruohonen¹, Z. Szabo², E. Savontaus¹, R. Kerkela³, P. Rinne¹

¹University of Turku, Turku, Finland
²University of Oulu, Pharmacology and toxicology, Oulu, Finland
³Medical Research Center Oulu, Oulu, Finland

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Background: The melanocortin system, including adrenocorticotropic hormone, melanocyte-stimulating hormones and five melanocortin receptors (MC-R), regulates important physiological functions such as pigmentation and energy homeostasis. It has been also recently implicated in the regulation of pathological cardiac remodeling but the role of different MC-R subtypes in the heart remain unknown.

Purpose: Based on the abundant cardiac expression of MC1-R, we hypothesized that it is functionally active in the heart and regulates pathological cardiac remodeling.

Methods: Rat H9c2 cells were used to study the effects of the selective MC1-R agonist LD211 on intracellular signaling cascades, gene expression and cellular growth response by using Western blotting, quantitative RT-PCR and 3H-leucine incorporation assay, respectively. Recessive yellow mice (Mc1re/e) were used as a model of global MC1-R deficiency. Inducible cardiomyocyte-specific MC1-R knockout mouse model (Mc1r-cKO) was engineered by intercrossing MC1-R floxed mice (Mc1rfl/fl) with tamoxifen-inducible Myh6-MerCreMer transgenic mice (Myh6-MCM). Mc1re/e and Mc1r-cKO mice were subjected to transverse aortic constriction (TAC, 8 wks) or subcutaneous infusion of angiotensin II (Ang II, 4 wks) to induce pathological cardiac hypertrophy. Cardiac structure and function were measured by echocardiography and by histological examination of H&E-stained heart sections.

Results: Treatment of H9c2 cells with LD211 increased MAP-kinase p-38 phosphorylation (+53 %, P=0.005 vs control), upregulated the expression of B-type natriuretic peptide (Nppb, +40 %, P=0.03 vs control) and increased 3H-leucine incorporation (+27 %, P=0.006 vs control). Mc1re/e mice showed reduction in ventricular weight (-29 mg, P=0.03) compared to WT mice after TAC operation, and reduced left ventricular (LV) expression of atrial natriuretic peptide (Nppa) and fibrosis-related genes (Ctgf and Mmp2). In terms of LV systolic performance, TAC-operated Mc1re/e mice showed tendency towards improved LV ejection fraction (EF, +6 %, P=0.06) compared to WT mice. To further investigate whether the phenotype of Mc1re/e mice is driven by deficient MC1-R signaling in cardiomyocytes, we characterized Mc1r-cKO mice, which recapitulated the phenotypic features of Mc1re/e mice. Specifically, TAC-operated Mc1r-cKO mice displayed reduced ventricular weight (-38 mg, P=0.007) and downregulation of LV expression of Nppa and fibrosis-related genes compared to Myh6-MCM mice. Likewise, in a model of Ang II-induced cardiac hypertrophy, Mc1r-cKO mice showed reduced ventricular weight (-10 mg, P=0.015) compared to Myh6-MCM mice, indicating that the protection against pathological cardiac hypertrophy was model-independent.

Conclusion: Our studies demonstrate that MC1-R activation promotes cardiomyocyte growth in vitro, while global and cardiomyocyte-specific MC1-R deficiency protects against pathological cardiac hypertrophy induced by TAC or Ang II infusion.