

Myocardial Metabolic Adaptation and Maladaptation to Obesity: Role of Apelin

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Background/Objectives: Altered energy metabolism is the defining characteristic of obesity-related myocardial damage. The adiposity-derived peptide apelin has a role in the regulation of cardiovascular and metabolic homeostasis and may contribute to the link between obesity, energy metabolism and cardiac function. Here we investigate the role of apelin in the transition from metabolic adaptation to maladaptation of the heart in obese state.

Methods: Adult male C57BL/6J, apelin knock-out (KO) or wild-type mice were fed a high-fat diet (HFD) for 18 weeks. To induce heart failure, mice were subjected to pressure overload after 18 weeks of HFD. Long-term effects of apelin on fatty acid (FA) oxidation, glucose metabolism, cardiac function and mitochondrial changes were evaluated in HFD-fed mice after 4 weeks of pressure overload. Cardiomyocytes from HFD-fed mice were isolated for analysis of metabolic responses.

Results: In HFD-fed mice, pressure overload-induced transition from hypertrophy to heart failure is associated with reduced FA utilization ($P<0.05$), accelerated glucose oxidation ($P<0.05$) and mitochondrial damage. Treatment of HFD-fed mice with apelin for 4 weeks prevented pressure overload-induced decline in FA metabolism ($P<0.05$) and mitochondrial defects. Furthermore, apelin treatment lowered fasting plasma glucose ($P<0.01$), improved glucose tolerance ($P<0.05$) and preserved cardiac function ($P<0.05$) in HFD-fed mice subjected to pressure overload. In apelin KO HFD-fed mice, spontaneous cardiac dysfunction is associated with reduced FA oxidation ($P<0.001$) and increased glucose oxidation ($P<0.05$). In isolated cardiomyocytes, apelin stimulated FA oxidation in a dose-dependent manner and this effect was prevented by small interfering RNA sirutin 3 knockdown.

Conclusions: These data suggest that obesity-related decline in cardiac function is associated with defective myocardial energy metabolism and mitochondrial abnormalities. Furthermore, our work points for therapeutic potential of apelin to prevent myocardial metabolic abnormalities in heart failure paired with obesity.