THE DECREASE IN PPAR-ALPHA SIGNALLING IN THE FAILING HUMAN HEART – A POSSIBLE EXPLANATION FOR ENERGY SUBSTRATE PREFERENCE SWITCH

JOANNA KARBOWSKA¹,² ZDZISŁAW KOCHAN¹ and RYSZARD T. SMOLEŃSKI¹,²

¹Department of Biochemistry, Medical University of Gdansk, Debinki 1, 80-211 Gdansk, Poland, ²Heart Science Centre, National Heart and Lung Institute, Imperial College School of Medicine, Harefield Hospital, Middlesex, UK

The adult mammalian heart uses mitochondrial fatty acid oxidation (FAO) as its principal source of energy to meet the high energy demands necessary for pump function. Flux through the cardiac FAO pathway is tightly controlled in accordance with the energy demands dictated by diverse physiological and dietary conditions. Cardiac hypertrophy is associated with a decreased cardiac fatty acid oxidation and a concomitant down-regulation of the expression of the genes involved in fatty acid metabolism. It has been demonstrated that the expression of the enzymes involved in FAO in the rodent heart is controlled at the transcriptional level via the lipid-activated nuclear receptor PPAR-alpha. It was recently shown that human muscle-specific carnitine palmitoyltransferase (MCPT-I) gene expression (MCPT-I catalyses the rate-determining step in mitochondrial fatty acid oxidation) is also regulated by PPAR-alpha. We sought to delineate the molecular regulatory events involved in the energy substrate preference switch from fatty acids to glucose during cardiac hypertrophic growth in humans. In this study, we analysed the amount of PPAR-alpha protein in human cardiac tissue. PPAR-alpha protein level was measured in homogenates prepared from left ventricular biopsies taken from 5 control donor hearts and compared to the amount of this transcription factor in biopsies from 5 patients with compensated end-stage heart failure (HF) at the time of transplantation. We showed for the first time that PPAR-alpha protein concentration is decreased in human hypertrophied heart. Using Western blot analysis with a monoclonal antibody against human PPAR-alpha, we observed a significant decrease (54%) in the mean amount of PPAR-alpha in the HF group of patients compared to that in the donor tissue. Actin was used as a control for loading. This study indicates that the decrease in cardiac PPAR-alpha transcription factor gene expression observed in the failing human heart could play a significant role in the changes in fatty acid utilisation by the adult heart under conditions that are associated with a reduction in cardiac fatty acid oxidation, like cardiac hypertrophy.