ABSTRACT

Cardiovascular intervention studies are a very important issue given that the ischaemic heart disease is one of the main mortality and morbidity causes in the Western world. Cardioprotection is mediated through a variety of signalling pathways in the cell that may directly or indirectly affect energy metabolism and mitochondria. Ischaemia-reperfusion injury of the heart significantly affect mitochondrial function revealing a potential therapeutic target. The role of mitochondria in the myocardium is not only in the field of energy homeostasis, but also in mediating the cellular response to reduced oxygen supply and in apoptosis regulation.

This thesis aims to elucidate the response of the hypertrophied heart of the spontaneously hypertensive rat (SHR) and the derived conplastic strain with mitochondrial genome of normotensive Brown Norway (SHR-mt^{BN}) to the cardioprotective regime of adaptation to chronic normobaric hypoxia (CNH, Fi 0.1). The adaptive changes were studied at the cellular, protein and gene levels using Real-time RT-PCR, Biomark Chip Analysis, Western Blot, spectrophotometric measurements of enzyme activity and quantitative immunofluorescence analyses.

The present thesis was based on a different cardioprotective phenotype between SHR and SHR-mt^{BN} strains, i.e. a significantly smaller infarct size was observed in the SHR-mt^{BN} strain after CNH. Partial analyses focused on the mitochondrial function revealed a decrease in 4.1 and 4.2 subunits of cytochrome c oxidase mRNA expression. The subsequent analyses of HIF-dependent protein kinase B/glucose transporter/hexokinase (Akt/GLUT/HK) pathway displayed this pathway to be upregulated by more than 50% larger protein expression of the individual components after CNH in both strains. The difference between strains was observed at the level of increased Akt2 and HK activity in SHR-mt^{BN} with simultaneous higher translocation of GLUT to sarcolemma. The data also suggest a higher HK translocation to mitochondria associated membranes after CNH in the conplastic strain.

The Biomark Chip Analysis of 48 mRNA transcripts revealed expression changes after CNH in genes associated with metabolism and oxidative stress in both strains. In SHR, a decrease in lipid metabolism transcripts and in genes involved in mitochondrial biogenesis was observed that was compensated in SHR-mt^{BN}. The analysis of hypoxic clusters data uncovered candidate genes that might be responsible for the phenotypic difference between the strains manifested up to the CNH adaptation (*Acer2, Cd36, Aco1, Pparg, Hmox2, Ppl2g2a, Drp, Pk, Sgms2, Casp3, Mfn1, Pla2g5, Cat*).

There were no changes in the level of *Adrb1* and *Adrb2* mRNA expression suggesting no alterations in adrenergic signalling, however, these proteins may be regulated post-translationally. Adenylate cyclase expression (*Ac5* and *Ac6*) decreased after CNH in SHR-mt^{BN} as well as selected mitochondrial antioxidants. In contrast, CNH evoked an increase in MAO A mRNA expression in SHR that is a known reactive oxygen species producer.

In conclusion, the mitochondrial genome positively modulates the cardioprotective effect of CNH in the hypertensive rat. This effect is associated with the enhancement of glucose metabolism, lipid metabolism and antioxidant modulation. The pleiotropic effect of the Akt2 signalling pathway can play a significant role in the observed changes. The obtained results deepened the characteristics of the more resistant, conplastic strain SHR-mt^{BN}, demonstrating the notable role of the mitochondrial genome in myocardial protection in the hypertrophied heart.

Key words: Spontaneously hypertensive rat, heart, mitochondria, chronic hypoxia