Abstract

Cardiovascular diseases are currently one of the most common causes of morbidity and mortality in the Western world. Adaptation to chronic hypoxia can contribute to the improvement of ischemic tolerance of myocardium but exact molecular mechanisms leading to the development of a cardioprotective phenotype are still unclear. There are some indications that point to the possible role of β-adrenergic signaling in these processes.

In the first part of the thesis, we examined the effect of protective continuous (CNH; 24 h/day) and nonprotective intermittent (INH; 23 h/day hypoxia, 1 h/day reoxygenation) normobaric hypoxia on β-adrenergic signaling in the right (RV) and left ventricles (LV) of Wistar rats. Both hypoxic models led to decrease in the number of β_1-adrenergic receptors (β_1-ARs) in the RV. There were no significant changes in β-ARs in LV preparations. Although adenylyl cyclase (AC) activity stimulated through Gs proteins was decreased in the RV and increased in the LV after adaptation to CNH and INH, there were no significant changes in the expression of dominant AC 5/6 isoforms. Expression of Gs proteins was decreased in RV in both hypoxic models. These results suggest that chronic normobaric hypoxia may have a strong effect on myocardial β-adrenergic signaling without differences between protective and nonprotective model of hypoxia.

In the second part of this thesis, we studied the effect of CNH on β-adrenergic signaling and antioxidant system in the LV of spontaneously hypertensive rats (SHR) and in a conplastic SHR-mtBN strain carrying the mitochondrial genome of Brown Norway strain on the genetic background of SHR strain. The β_2-ARs proportion was significantly higher in SHR-mtBN strain than in SHR. Adaptation to CNH elevated the total number of β-ARs and proportion of β_2-ARs in SHR and decreased the total amount of β-ARs in SHR-mtBN. AC activity stimulated by isoprenaline was higher in SHR-mtBN. After exposure of rats to CNH were observed different changes in AC activity in both examined strains. Whereas AC activity in SHR strain increased, AC activity in SHR-mtBN decreased. On the other hand, the activity of MAO-A and its expression was significantly lower in SHR-mtBN than in SHR and these figures were elevated in both strains after exposure to CNH. In addition, CNH markedly enhanced the expression of catalase and aldehyde dehydrogenase-2 in both strains, and decreased the expression of Cu/Zn

superoxide dismutase in SHR. These data indicate that alterations in the mitochondrial genome can result in distinctive changes in β-adrenergic signaling, MAO-A activity and antioxidant system and may also affect the adaptive responses to hypoxia.

In the last part of this thesis, we examined the effect of chronic intermittent hypobaric hypoxia (IHH) on β-adrenergic signaling in the LV of Wistar rats. The total number of β-ARs did not change after adaptation to IHH, but the ratio of β-ARs subtypes markedly increased due to the β_2-ARs increase and β_1-ARs decrease. In parallel, adaptation to hypoxia caused decrease in expression of AC5 and increase of Gi protein levels. Our data, together with other results revealed in this study, suggest a possible role of β-ARs in the development of a cardioprotective phenotype.

Keywords: myocardium, cardioprotection, chronic hypoxia, β-adrenergic receptors, G-proteins, adenylyl cyclase, SHR, SHR-mtBN, MAO-A, antioxidant system