Abstract

The cardiovascular disease, particularly acute myocardial infarction, is the most common cause of death worldwide. It is well documented that adaptation to chronic hypoxia increases resistance to ischemia-reperfusion (I/R) injury in heart tissue. Reactive oxygen species (ROS) play an important signalling role by the activation of the protective pathways during I/R, although, the excess of ROS during reperfusion leads to cardiac tissue injury. As the cellular antioxidant system is responsible for the maintenance of redox homeostasis, the main aim of this thesis was to investigate the relationship between myocardial tolerance to I/R injury and regulation of main components of antioxidant systems, related transcription factors and their target genes in protective and non-protective regimens of chronic hypoxia. We found differences in cardioprotective phenotype in rats exposed to three regimens of chronic normobaric hypoxia (FiO₂ 0.1, 3 weeks). The adaptation to continual (CNH) and intermittent (CNH-8; 8 h/day) regimen of hypoxia increased myocardial resistance to I/R damage, whereas 1-hour daily interruption of hypoxic adaptation (INH-23) abolished cardioprotective effect and decreased the ratio of reduced and oxidized glutathione (GSH/GSSG). Both cardioprotective regimens significantly increased mRNA expression of mitochondrial antioxidants (manganese superoxide dismutase, MnSod; glutathione reductase, Gsr; thioredoxin, Txn2; thioredoxin reductase, Txnrd2) and cytosolic isoform of peroxiredoxin (Prx2). Contrary to that, INH-23 increased only Prx5, which was not sufficient to induce cardioprotective phenotype. We also analysed cardioprotective regimen of severe intermittent hypobaric hypoxia (IHH-8; 7,000 m, 8h/day, 5 weeks) which surprisingly did not stimulate most of antioxidant enzymes. Only antioxidants related to the metabolism of iron and TXN1 were elevated. Interestingly, we observed activation of pro-inflammatory transcription factors and cytokines.

We can conclude that antioxidants associated with mitochondria contribute to the modulation of the cardioprotective phenotype conferred by adaptation to chronic well tolerable normobaric hypoxia. On the other hand, the antioxidant system is not able to compensate oxidative stress induced by severe hypobaric hypoxia. Therefore, other signalling pathways promoting myocardial protection against I/R injury are activated.