Abstract

The mortality of cardiovascular diseases remains high and it likely tends to increase in the future. Although many ways how to increase the resistance against myocardial ischemia-reperfusion damage have been described, few of them were transferred into clinical practice. Cardioprotective effect of chronic hypoxia has been described during 60s of the last century. Its detailed mechanism has not been elucidated, but a number of components has been identified. One of these components presents protein kinase C (PKC). The role of PKC was described in detail in the mechanism of ischemic preconditioning, but its involvement in the mechanism of cardioprotection induced by chronic hypoxia remains unclear. One reason is the amount of PKC isoforms, which have often contradictory effects, and the diversity of hypoxic models used. The most frequently mentioned isoforms in connection with cardioprotection are PKCδ and PKCε. The aim of my thesis was to analyze changes in these PKC isoforms at two different cardioprotective models of hypoxia – intermittent hypobaric (IHH) and continuous normobaric hypoxia (CNH). We also examined the target proteins of PKCδ and PKCε after the adaptation to IHH, which could be involved in the mechanism of cardioprotection. These included proteins associated with apoptosis and autophagy, mitochondrial dynamics, removal of toxic aldehydes, metabolism of sphingolipids and gap junctional communication. We have shown that while adaptation to IHH leads to PKCδ activation, the adaptation to CNH leads to activation of PKCε. The use of PKCε inhibitory peptide KP-1633 confirmed that PKCε is a key isoform in cardioprotection induced by CNH. The analysis of PKC target proteins showed that although IHH led to an increase of proapoptotic proteins of Bcl-2 family, the number of apoptotic cells was lower. Simultaneously, the adaptation to IHH activated autophagy, through which it could lead to a faster removal of damaged organelles, and thus might contribute to of IHH-induced cardioprotection. Elucidation of signaling pathways associated with cardioprotection induced by adaptation to chronic hypoxia could help in the treatment of ischemic heart disease.