Role of membrane phospholipid remodeling, oxidative stress and PKC- δ upregulation in cardioprotection induced by chronic hypoxia

Introduction: Cardiovascular disease is the main cause of morbidity and mortality in industrially developed countries. Therefore, a number of experimental and clinical studies deal with the issue of how to increase tolerance to myocardial ischemia/reperfusion (I/R) injury. The present studies are concerned with mechanisms involved in the induction of endogenous cardioprotection after adaptation to intermittent altitude (IHA) hypoxia and influence of fat diets enriched with different fatty acids (FA) composition. We focused on changes in the composition of serum and heart lipids, the expression of PKC δ and ε, on markers of oxidative stress and antioxidant enzyme activity in the myocardium. We also studied the role of reactive oxygen species (ROS) in the cardioprotective effect of IHA hypoxia using the antioxidant N-acetylcysteine (NAC).

Methods: Adult male Wistar rats were exposed to IHA hypoxia in hyperbaric chamber, altitude 7000 m, 8 hours per day, 5 days a week, 25 exposures. Animals were fed by standard diet and diet enriched with 10% fat (saturated - SFA and MUFA mononemnasycené), 10% corn oil (n-6 polyunsaturated MK PUFA) and 10% fish oil (n-3 PUFA) in the diet experiment. NAC was administered subcutaneously at a dose of 100 mg/kg daily before exposure to hypoxia.

Results: Adaptation to IHA hypoxia decreased concentration of diphosphatidylglycerol (inner mitochondrial membrane phospholipid) reduced the proportion of n-6 PUFA in favor of n-3 PUFA and increased unsaturation index in the left (LV) and right (RV) myocardium chamber. IHA hypoxia reduced myocardial infarct size, increased the level of ROS and increased expression of PKC δ. NAC antioxidant treatment eliminate these effects. The ratio of n-6/n-3 PUFA in serum and heart lipids correlated with this ratio in the diet administered. The arachidonic acid (20: 4n-6) and linoleic (18: 2n-6) in triglycerides and phospholipids of heart was replaced by docosahexaenoic acid (22: 6n-3) in diets with fish oil. N-3 diet increased levels of lipid peroxidation products (conjugated diene) in the heart. Furthermore IHA adaptation reduced the ratio of n-6 / n-3 PUFA in serum lipids, and in the LV myocardium in all dietary groups and stimulated catalase activity in PUFAs diets. Feeding with diets with different composition of MK affect both the myocardial infarct (IM) size and also the number and severity of I/R arrhythmias. Regarding normoxic controls, after the n-6 diet was smaller IM size as compared with the n-3 diet. IHA hypoxia reduced IM size in animals with SFA and n-3 diet, but did not have additional effect on the IM size in the n-6 diets. Conversely, n-3 diet had a beneficial effect on I/R arrhythmia, which decreased in normoxic controls and it is practically eliminated after adaptation to IHA hypoxia. PKC δ expression was negatively correlated with the IM size in normoxic groups and also after adaptation to chronic hypoxia.

Conclusion: Our results suggest that the protective effect of adaptation to IHA hypoxia may contribute to a reduction in the proportion of aerobic in favor of anaerobic metabolism, increasing the proportion of protective n-3 PUFAs in serum and membrane phospholipids. We confirmed that the protective mechanism is as important signaling molecules applied ROS and PKC δ. Diet with different composition of FA affects the IM size by mechanism, in which also plays a significant role PKC δ. Diet enriched with fish oil has clearly the largest anti-arrhythmic effect.