

## **The role of lipids and ROS in cardioprotective mechanism of chronic hypoxia**

Cardiovascular diseases, mainly ischemic heart disease is one of the most frequently cause of morbidity and mortality in developed countries. Therefore effective protection of the heart against ischemia and reperfusion injury is the crucial aim of experimental and clinical cardiology. One of the main streams of cardiovascular research is looking for possibilities of natural heart resistance augmentation. Adaptation to chronic hypoxia is one possibility how to protect the heart against ischemia-reperfusion injury. Chronic hypoxia increases resistance of the myocardium to acute deficiency of oxygen leading to ventricular arrhythmias, postischemic contractile dysfunction and necrotic changes in the tissue.

Recently, it has been shown that reactive oxygen species (ROS) play an important role in the cardioprotective mechanism of chronic hypoxia. It is known that oxidative stress has a harmful effect in acute ischemia-reperfusion however ROS generated during the adaptation to hypobaric intermittent chronic hypoxia play a role in the induction of cardioprotection. In this study, we demonstrated that adaptation of adult rats to chronic hypoxia increased the activity and protein abundance of manganese superoxide dismutase (MnSOD) in the mitochondrial fraction of left ventricular myocardium. The effect of chronic hypoxia on MnSOD activity and protein abundance of MnSOD in the mitochondrial fraction was prevented by antioxidant N-acetylcysteine (NAC) treatment. These results are in line with our recent observation that NAC attenuated the ROS-dependent cardioprotection induced by chronic hypoxia.

Lipids are important structural part of the cell membrane and are also important object of the ROS. Our finding of increased level of conjugated dienes in the myocardium of fish oil dietary group corresponds to the largest myocardial infarct size observed in these animals. On the other hand, the same fish oil group exhibited the lowest incidence and severity of ventricular arrhythmias.

We conclude that adaptation to chronic hypoxia increased oxidative stress, which is in line with induction of endogenous cardioprotection. Up-regulation and activation of mitochondrial MnSOD in close correlation with the reduction of myocardial infarct size suggest that this enzyme could potentially be involved in the mechanism of chronic hypoxia-induced tolerance against ischemia/reperfusion injury. Blunting of these effects by treatment with NAC supports the view that ROS-dependent signalling during hypoxic adaptation plays an important role in this form of cardioprotection. Both lipid diets as well as chronic hypoxia had systemic effects leading to distinct changes in the fatty acid profile in serum and heart lipids.