

ABSTRACT

Cardiovascular diseases, particularly acute myocardial infarction, are the leading causes of death in developed countries including the Czech Republic. One of the ways to increase cardiac resistance against acute ischemia/reperfusion (I/R) injury is adaptation to chronic hypoxia. However, changes at the molecular level associated with this adaptation have still not been fully explored. It is obvious that the myocardial function depends on maintaining membrane integrity and cellular homeostasis of cardiomyocytes. From this perspective, phospholipases A₂ (PLA₂) are the key enzymes that take part in the remodeling and repairing of the cell membranes. Moreover, PLA₂ are also involved in generation of lipid signaling molecules – free long chain fatty acids (FA) and 2-lysophospholipids. In myocardium, members of three major PLA₂ classes are present: cytosolic PLA₂ (cPLA₂), calcium-independent PLA₂ (iPLA₂) and secretoric PLA₂ (sPLA₂).

This thesis aimed to determine the following in the left ventricular myocardium of adult male Wistar rats:

- 1) The effect of intermittent hypobaric hypoxia (IHH; 8 hours/day, 5 days/week, 5 weeks, ~ 7000 m) on the expression of total cPLA₂α and its phosphorylated form (p-cPLA₂α, Ser⁵⁰⁵), and further iPLA₂ and sPLA₂IIA, as well as signaling proteins activating cPLA₂α enzyme and its downstream targets.
- 2) The reactive oxygen species (ROS) involvement in IHH effect on PLA₂ expression and phospholipid FA remodeling by chronic administration of antioxidant tempol.
- 3) The effect of continuous (CNH; 3 weeks, 10 % O₂, ~ 5500 m) and intermittent (INH; 3 weeks, 23 hours/day, 10 % O₂, ~ 5500m) normobaric hypoxia on amounts of cPLA₂α, iPLA₂ and sPLA₂IIA and superoxide dismutase (SOD), and also marker of oxidative stress malondialdehyde (MDA).

The results showed that:

- 1) Adaptation to IHH increased the amount of total and phosphorylated cPLA₂α and, on the other hand, reduced the amounts of iPLA₂ and sPLA₂IIA. In parallel, under IHH conditions we detected elevated expression of signaling proteins involved in the activation of cPLA₂α (protein kinase Cα, p-PKCα; extracellular signal-regulated kinases 1/2, p-ERK1/2; p38 mitogen-activated protein kinases, p-p38) as well as downstream molecules of cPLA₂α (cyclooxygenase 2, COX-2; prostaglandin E₂, PGE₂), respectively. IHH induced activation of cPLA₂α and COX-2 *via* β₂-adrenoreceptors/G_i proteins mediated stimulation of the PKCα and/or ERK/p38 pathway which directly activates the cPLA₂α/COX-2/PGE₂ pathway.
- 2) Chronic tempol treatment prevented only IHH-induced cPLA₂α and p-cPLA₂α up-regulation. However, we did not observe participation of ROS in the IHH-induced down-regulation of iPLA₂ and sPLA₂IIA, and in phospholipid remodeling.
- 3) Adaptation to CNH increased the level of cPLA₂α, iPLA₂ and mitochondrial SOD (MnSOD) without affecting MDA concentration. Daily reoxygenation abolished cPLA₂α, iPLA₂ and MnSOD up-regulation, and increased MDA.

These data support the view that cPLA₂α participates in the development of a cardioprotective phenotype during adaptation to IHH and suggest that ROS are responsible for the activation of cPLA₂α under these conditions. Elucidation of the signaling pathways associated with cardioprotection induced by adaptation to chronic hypoxia might contribute to the development of future treatment of myocardial I/R injury, and thus have importance for clinical practice.

Keywords: heart, chronic hypoxia, cardioprotection, phospholipases A₂, cytosolic phospholipase A₂α, oxidative stress