

ABSTRACT:

Cardiac energy metabolism is the one of the most complex system in the body. To sustain life, but also to respond quickly to any sudden changes (e.g. running, emotional stress), the heart has developed a unique ability and has become a metabolic “omnivore”. At physiological conditions, long chain fatty acids (LCFAs) present the major energetic source for the adult myocardium. However, the cardiac energy metabolism may be compromised during pathophysiological states. One of the most dangerous is, undoubtedly, ischaemia-reperfusion injury with its acute form, myocardial infarction. However, the adaptation to chronic hypoxia has been known for decades for its cardioprotective effect against I/R. Changes of cardiac energy metabolism induced by the adaptation have not been fully explored and the system conceals still too many secrets. This thesis has aimed to determine how adaptation to chronic hypoxia affects the cardiac metabolism of the rat LVs in the following set-ups:

1. The effect of chronic normobaric hypoxia (CNH; 3 weeks, 5500m) during a brief I/R protocol *in vitro* on the protein kinase B/hexokinase (Akt/HK) pathway, including the expression and phosphorylation of Akt, the expression and localization of HK, the expression of mitochondrial creatine kinase (mtCKS), and the level of Bcl-2 family proteins as well as the amount of activated adenosine monophosphate-dependent protein kinase (pAMPK α Thr¹⁷²).
2. The effect of CNH (3 weeks, 5500m) on the expression of major cardiac Akt isoforms, Akt1 and Akt2 with subsequent determination of HK enzyme activity in LVs of spontaneously hypertensive rat (SHR) and conplastic strain harbouring mitochondrial genome from Brown Norway strain, SHR-mtBN.
3. The effect of intermittent hypobaric hypoxia (IHH; 8h/day, 35 exposures, 7000m) on LV β -oxidation rates with respect to subcellular domains, on the expression of electron transport system (ETS) complexes (CI-CV), on respiratory rates, on glycolytic apparatus, NAD(H) pools, CK system, and finally, on mitochondrial susceptibility to Ca²⁺ overload.

The results have shown that:

1. Adaptation to CNH evoked an increase in HK1, HK2 expression and HK activity in ischaemia, concomitantly with pAkt Ser⁴⁷³. HK colocalization with mitochondria was not affected in CNH, whereas I/R cause HK disruption in N LVs. CNH prevented downregulation of mtCKS during I/R and decreased Bax/Bcl-2 ratio, suggesting a lower probability of apoptosis. Importantly, pAMPK α Thr¹⁷² levels were lower in CNH LVs during ischaemia, suggesting energetic advancement.
2. Adaptation to CNH upregulated Akt2 isoform in SHR-mtBN only. In contrast, no alterations of Akt1 expression in both strains neither Akt2 in CNH adapted SHR could be observed. Nevertheless, CNH upregulated the activity of HK in SHR-mtBN homogenates more profoundly than in SHR littermates. Mitochondrial HK activity was elevated in both strains similarly after CNH.
3. Adaptation to IHH decreased the β -oxidation rates in subsarcolemmal (SSM) and interfibrillar (IFM) mitochondria with concomitant reduction of CI+CII-stimulated respiration. The expression of CI and CIV was downregulated in IHH LVs. The activity of CI and citrate synthase, but not that of CII dropped after IHH. The downregulated CI expression and activity probably cause the elevated NADH/NAD⁺ ratio in IHH. Surprisingly, acyl-CoA oxidase (ACOX) as well as peroxisomal lactate dehydrogenase (LDHBx) were upregulated, suggesting that peroxisomes partially overtake FAs processing in IHH LV. The enzyme activity of glycolytic apparatus, phosphofructokinase (PFK) and LDH, were upregulated after

the adaptation. IHH evoked a complete remodelling of CK system with CKB upregulation and translocation to M-line of sarcomere. The susceptibility to mitochondrial permeability transition pore opening was improved after IHH.

These data support the view that cardiac energy system remodelling presents the basis of cardioprotection against I/R induced by the adaptation to chronic hypoxia. Our data, showing the improvement of carbohydrate metabolism with concomitant downregulation of FA metabolism, and CK system remodelling, may uncover the important aspects of the protective adaptation and thus contribute to the development of future treatment of myocardial I/R injury. Nevertheless, although the research may not lead to the kind of knowledge that can be expected to give immediate practical benefits, its importance in spite of its theoretical character is immense.