

01 ACUTE ADMINISTRATION OF MAGNESIUM OROTATE AT REPERFUSION IMPROVES MITOCHONDRIAL RESPIRATION IN ISOLATED RAT HEARTS

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Acute administration of magnesium orotate (Mg-Or) at reperfusion has been previously shown to elicit significant protection in isolated rat hearts. Since recovery of mitochondrial function is mandatory for cardioprotection, the present study was aimed at characterising the effects of Mg-Or on mitochondrial respiration. Isolated male adult rat hearts (n=6/group) subjected to 30 min global ischaemia and 120 min reperfusion were randomised to receive: (i) no additional intervention (Ctrl); (ii) Mg-Or at 28 min of ischaemia (Mg-Or-28I) and (iii) Mg-Or at 3 min of reperfusion (Mg-Or-3R). Mitochondria were isolated at 15 min of reperfusion and oxygen consumption was measured at 37°C by polarographic oxymetry in the presence of NAD and FAD-linked substrates, respectively. Basal (state 2) and ADP-stimulated (state 3) respiratory rates were recorded and expressed as nanoatoms oxygen/min/mg mitochondrial protein and respiratory control ratio (RCR) was calculated. In mitochondria respiring on glutamate/malate a statistically significant increase in state 3 respiratory rates was observed in the Mg-Or-28I group but not in Mg-Or-3R when compared to the ischaemic Ctrl (514±29 and 386±17 vs 350±13, respectively, p<0.001). Subsequently, RCR increased from 6.2±0.38 in Ctrl group to 8±0.28 in Mg-Or-28I group (p<0.05). In the presence of complex II-dependent substrate (succinate+amytal) both administration protocols elicited an important increase in state 3 respiration (Mg-Or-28I: 488±25, Mg-Or-3R: 463±20 vs Ctrl: 355±15, respectively, p<0.001). In isolated rat hearts, magnesium 355+orotate elicited a protocol-dependent improvement of mitochondrial respiration at reperfusion that may contribute to its cardioprotective effect against reperfusion injury.

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02 MITOCHONDRIAL DNA DAMAGE, DYSFUNCTION AND ATHEROSCLEROSIS

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Rationale Atherosclerosis remains the leading cause of death in the western world. Mitochondrial DNA (mtDNA) damage has been associated with the disease, but it is unknown when the damage occurs relative to atherogenesis, and what the functional and clinical consequences are.

Methods To assess the role of mtDNA damage in atherosclerotic development, we studied its time course, by quantifying the abundance of oxidative adducts and the 4977 base pair "common" deletion. We further examined respiratory chain complex expression and function in apolipoprotein E null mice.

Results We identified that aortic tissues have oxidative lesions of mtDNA at the early stages of atherogenesis, while the common 4977 base pair deletion was increased in established plaque. Despite normal respiratory complex expression, isolated mitochondria showed reduced complex I activity, which correlated with advanced atherosclerosis.

Conclusions We confirm that mtDNA damage is present in the early stages of atherogenesis and may be contributive to disease. We also identified a respiratory chain defect which may compromise the

bioenergetic capacity of the cells, leading to increased plaque vulnerability.

03 VARICOSE AND NON-VARICOSE VEINS ARE ABLE TO ACTIVATE THE HYPOXIA-INDUCIBLE FACTOR PATHWAY WHEN EXPOSED TO HYPOXIA

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Introduction Hypoxia has been postulated to contribute to various venous pathology including varicose veins (VV) and vein graft thrombosis or stenosis. Hypoxia-inducible factors (HIF) are nuclear transcriptional factors regulating transcription of genes mediating oxygen homeostasis. This study aimed to investigate the in vitro effects of hypoxia on the HIF pathway in VV and non-varicose veins (NVV).

Methods Six VV and six NVV were used to prepare organ cultures which were exposed to normoxia, hypoxia (oxygen 1%), or hypoxia-mimicking dimethylxallyl glycine (DMOG) 1 mM for 16 h. The veins were analysed for HIF-1 α , HIF-2 α , and their target genes expression with Q-PCR and immunoblot.

Results Hypoxia and DMOG treatment was associated with a significant reduction of HIF-1 α mRNA expression in VV (0.48±0.11; p<0.05 and 0.24±0.07; p<0.001, respectively) and NVV (0.39±0.06; p<0.001 and 0.23±0.04; p<0.001, respectively) compared to normoxia. No significant HIF-2 α mRNA expression change was measured in both veins in hypoxia or DMOG compared to normoxia. Increased HIF-1 α and HIF-2 α protein expression was observed in VV and NVV in hypoxia or DMOG compared to normoxia. Significant increases of HIF target genes (CA9, BNIP-3, GLUT-1, PHD-2 and PHD-3) mRNA expression were measured in VV and NVV in hypoxia or DMOG compared to normoxia. The upregulation of HIF target genes was also reflected at protein level.

Conclusion Exposure of VV and NVV to hypoxia or DMOG was associated with upregulation of HIF-1 α and HIF-2 α protein, and HIF target genes. Our data suggest that the HIF pathway may play a role in hypoxia related venous pathology.

04 THE REGULATION OF MITOCHONDRIAL ENERGY METABOLISM BY L-CARNITINE LOWERING AGENTS IN ISCHAEMIA-REPERFUSION INJURY

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Mitochondrial L-carnitine system plays an important role in energy metabolism of the cardiac cells. Administration of both mildronate and sodium pivalate decreases myocardial concentration of L-carnitine. However, mildronate induces cardioprotective effect, while administration of sodium pivalate results in ventricular dysfunction. The present study was performed to clarify the molecular mechanisms behind the opposite effects of both L-carnitine lowering agents. Mildronate (100 mg/kg) or sodium pivalate (500 mg/kg) were administered to Wistar rats for 14 days to reduce the L-carnitine content in heart tissues to comparable level. In heart tissues, L-carnitine content, activities of carnitine palmitoyltransferase I (CPT I) and carnitine acetyltransferase (CrAT) as well as mitochondrial respiration were measured. In addition, the isolated rat heart ischaemia-reperfusion experiments were performed to analyse the cardioprotective effects of both treatments. The L-carnitine

Heart

01 Acute administration of magnesium orotate at reperfusion improves mitochondrial respiration in isolated rat hearts

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