MNRR1

The impact of mitochondrial nuclear retrograde regulator 1 (MNRR1) in ischemic preconditioning

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Projektbeschreibung

 Aims. This project aims at clarifying MNRR1 expression as the key player in the mechanisms of preconditioning and identification of the UPR branch(es) responsible for its activation. We plan to test the UPR modulators and MNRR1 expression in relevant preclinical models of shock and ischemia in order to create a basis for translation of our results into the clinical practice.

 Content. Preconditioning represents a phenomenon where transient exposure of cells to an initiating moderate event leads to protection against subsequent, potentially lethal stimuli. These events include, for example, short sublethal hypoxia, heat stress, oxidative stress and cellular stress in general. The mechanisms underlying this effect are still unclear. The fact that quite different events induce similar protective mechanisms suggests that there is a common pathway underlying this phenomenon. Mitochondria play an integral role in the restoration of aerobic metabolism, but simultaneously they are also primary targets for the damage caused by cellular stress. This damage is associated with reduction of ATP synthesis and induction of apoptosis, which are promoted by the loss of cytochrome c. However, the link between mitochondrial function and beneficial effects of precondition is still missing.

 Methods. We will use in this project two pre-clinical models of hypovolemic shock and liver ischemia. Optionally we also will analyse the samples from a model of cardiac arrest established at medical university of Vienna. For mechanistic purposes, we will examine primary culture of hepatocytes. All experiments will be conducted in rats. We will determine markers of ogan damage in blood (LDH, AST, ALT, cardiac Troponin and others), extracted tissues will be subjected to histological analysis. We will determine activation unfolded protein response (UPR), expression of mitochondrial nuclear retrograde regulator 1 (MNRR1), mitochondrial function. We will use real time PCR, western blot, high resolution respirometry and a number of other common biochemical methods.

 Expected results. We expect to identify the intracellular reactions responsible for beneficial effect of preconditioning mediated by UPR. We plan to estimate the contribution of systemic and local effects on the processes of preconditioning. We will establish a causal link between induction of specific branch of UPR, mitochondrial function and the expression of MNRR1. We anticipate finding a hint for clinical application of the obtained knowledge.

Projektpartner

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