

suggest that activation of p38^{MAPK}-regulated signaling cascade leads to increased expression of Ucp2 in cardiomyocytes as seen on protein as well as mRNA level offering a protective mechanism against CPT-related apoptosis.

This research is supported by grants GACR 303/08/0658 and MSM 6198959216.

doi:10.1016/j.bbabo.2008.05.250

S10.25 Effect of targeted quinones on ROS production and lipid peroxidation in mitochondria: Mitochondrial DNA polymerase mutant mice exhibit high sensitivity

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Oxidative damage of mitochondrial compartments contribute to a range of degenerative diseases. Here protective effect of quinones and their derivatives on mitochondrial proteins and lipids under oxidative stress was analysed. The most effective quinone analogues appear to be conjugates of lipophilic cations ("Skulachev cations", by D. Green) with ubiquinone (Murphy et al., 2007) or plastoquinone (Skulachev et al., 2008, in press), so called "mitochondrially targeted antioxidants" (MTAO). MTAO effectively inhibit lipid peroxidation and protect membrane cardiolipin from oxidation. Using dihydroethidium and Amplex Red as a probes for ROS detection, we found that MTAO effectively suppress ROS production from different sites of the mitochondrial respiratory chain. In succinate-energised mitochondria there is a lag-period for the MTAO effect, but not in pyruvate/malate-energised mitochondria. When mitochondria isolated from the heart of a mouse strain mutated on mitochondrial DNA polymerase PolgA (Trifunovic et al., 2004) were used, we found that the mitochondria of PolgA mice did not produce more ROS than wild type, but the inhibitory effect of MTAO was stronger and more pronounced. Taken together, these data provided evidence that MTAO could be useful for treatment of genetic disorders, manifested degenerative diseases and aging complications.

doi:10.1016/j.bbabo.2008.05.251

S10.26 Nerolidol disturbs mitochondrial bioenergetics but delays the permeability transition pore due a membrane antioxidant protective effect

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Nerolidol is a naturally occurring sesquiterpenol found in the essential oils of many types of plants and flowers. The aim of this study

was to assess the impact of a racemic mixture of nerolidol on the oxidative phosphorylation of mitochondria isolated from rat liver. We examined the effect of nerolidol on respiratory indexes, membrane potential and opening of the mitochondrial permeability transition pore, all the assays were performed with 0.5 mg mitochondrial protein/mL. Our results showed a complex array of effects on liver mitochondrial bioenergetics. With nerolidol (1.2 µM) we observed an increase in state 4 respiration rate (170 ± 5.4% of control), a depression in state 3 (64 ± 9.7% of control) and a decreased uncoupled respiration rate (53 ± 10.1% of control). Mitochondrial membrane potential was decreased (1.2 µM; 27 ± 6.4% of control) by nerolidol in a concentration manner. ATP synthase was not significantly affected in the concentration range of study (0–1.2 µM). Nerolidol seems to increase the mitochondrial ability to accumulate calcium by decreasing the susceptibility of mitochondria to the opening of the transition pore. Nerolidol (0.2 µM) protect against *tert*-buthylhydroperoxide mitochondrial membrane lipid peroxidation, however H₂O₂ produced by mitochondria with blocked respiratory complexes was increased by nerolidol. From our data it is concluded that concentrations of nerolidol lower than 0.4 µM don't affect mitochondrial bioenergetics and could probably used to prevent the deleterious effect of some oxidative events occurring in mitochondria.

doi:10.1016/j.bbabo.2008.05.252

S10.27 Deletion of mitochondrial uncoupling protein 2 gene enhances ischemic brain damage by suppressing cell cycle gene and anti-oxidative gene

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Mitochondrial uncoupling proteins (UCPs) are inner mitochondrial membrane proteins that dissipate the mitochondrial proton gradient by transporting H⁺ across the inner membrane, thereby stabilizing the inner mitochondrial membrane potential ($\Delta\Psi_m$) and reducing the formation of ROS (Nicholls 1977; Stuart et al., 2001). Previous studies have shown that UCP2 protects neurons against oxidative stress and cerebral stroke (Bechmann et al., 2002; Mattiasson et al., 2003). However, a recent study reported opposite effects of UCP2 by showing that ablation of UCP2 reduced stroke infarct area in the brain (de Bilbao et al., 2004). The objectives of this study are to clarify the effects of UCP2 on ischemic brain damage and to explore whether deletion of UCP2 gene alters expression profile of other genes after transient cerebral ischemia. Middle cerebral artery occlusion (MCAO) of 1 h duration was induced in UCP2 knockout (UCP-KO) and wild type mice. Animals were sacrificed 24 h after reperfusion. The infarct volume was depicted using the TTC staining. The integrity of the circle of Willis of UCP2-KO and wild type mice was examined by carbon black injection. Transcript levels of 84 genes in the cortical ischemic penumbra area were detected using a Mouse Stress Toxicity PCR array (Super Array). The results were normalized against housekeeping genes Hprt1 and beta actin. The results showed that deletion of UCP2 gene significantly increased infarct size and there was no obvious vascular abnormalities observed. The SuperArray study demonstrated that knocking out UCP2 gene significantly suppressed DNA repair gene cyclin G1 (van Lookeren Campagne and Gill 1998), antioxidative gene GSTM1 (McBride et al., 2005) and neuroprotective gene MDM2 (Saito et al., 2005). These results were further verified by immunohistochemistry. It is concluded that knocking out of UCP2 gene exacerbates neuronal death after cerebral ischemia and reperfusion and that deletion of UCP2 gene suppresses genes associated with cell survival.

doi:10.1016/j.bbabo.2008.05.253