MITOCHONDRIAL GENERATED NO$^{\bullet}$ PROTECTS AGAINST PERMEABILITY TRANSITION VIA FORMATION OF MEMBRANE PROTEIN S-NITROSOTHIOLS

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Nitric oxide (NO$^{\bullet}$) generated in mitochondria seems to regulate energy metabolism, O_2 consumption, and reactive oxygen species (ROS) formation by the organelle. Here we report that the NOS inhibitors (L-NAME, L-NNA and L-NMMA) administered either *in vitro* or *in vivo* induce Ca^{2+}-dependent mitochondrial permeability transition (MPT) in rat liver mitochondria via a mechanism independent on changes in the energy state of the organelle and associated with a significant decrease in the content of membrane protein S-nitrosothiol. In the experiments *in vitro*, the effect of NOS inhibitors was dose dependent in the concentration range of 1 to 50 μM and MPT was judged by the occurrence of a cyclosporine A sensitive mitochondrial membrane potential disruption followed by mitochondrial Ca^{2+} release and swelling. Furthermore, liver mitochondria isolated from L-NAME-treated (50 mg/kg i.p.) rats presented a higher susceptibility than control mitochondria to develop MPT. In addition to CsA, L-NAME-induced MPT was sensitive to Mg^{2+}, ATP, EGTA, *N*-ethylmaleimide, and to a lower degree to catalase or dithiothreitol. In contrast to L-NAME, its isomer D-NAME did not induce MPT. It was also observed that low amounts of SNAP (a NO$^{\bullet}$ donor) restored the content of membrane protein nitrosothiol after L-NAME treatment thus preventing MPT triggered either by Ca^{2+} alone or Ca^{2+} plus L-NAME, by a mechanism independent on changes in Ca^{2+} accumulation by the organelle. It is proposed that nitrosilation of critical membrane protein thiols protects against MPT and thus against mitochondrial damage and cell death.

Key words: Nitric Oxide, Mitochondrial Permeability Transition, S-nitrosothiols

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