N^G-NITRO-L-ARGININE METHYL ESTER INDUCES MEMBRANE PERMEABILITY TRANSITION IN RAT LIVER MITOCHONDRIA

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Mitochondrial permeability transition (MPT) is a non-selective inner membrane permeabilization that is involved in necrotic and apoptotic cell death in a variety of pathological situations. Strong evidences suggest that MPT is the consequence of oxidative damage to mitochondrial membrane proteins resulting in the formation of a proteinaceous pore, which causes in mitochondrial swelling, outer membrane rupture and leakage of pro-apoptogenic mitochondrial molecules. N^G-nitro-L-arginine methyl ester (L-NAME), a non-selective inhibitor of nitric oxide synthase, has been used in patients and experimental models to evaluate multiple effects of $NO^{\bullet}$ availability on the vascular system. Adverse side effects of this compound have not been described yet. Here, we report that L-NAME *in vitro* induced MPT in a dose-dependent manner (0.1 – 50 μM) in Ca^{2+}-loaded rat liver mitochondria. Furthermore, liver mitochondria isolated from *in vivo* L-NAME-treated (50 mg/kg) rats also presented a higher susceptibility to develop MPT when compared to control mitochondria. L-NAME-induced MPT was sensitive to cyclosporin A (inhibitor of cyclophilin), ATP (adenine nucleotide carrier ligant), EGTA (calcium quelator), *N*-ethylmaleimide (thiol reagent), and Mg^{2+}, but insensitive to catalase and dithiothreitol (disulfide reducing agent). These results indicate that L-NAME leads to MPT at low concentrations through mechanisms dependent on Ca^{2+}-induced alterations of membrane thiol group reactivity.

Key words: Permeability transition; L-NAME; calcium.

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