Uncoupling attenuates Complex I-derived superoxide production by accelerating electron flux and proton pumping within Complex I. However, under circumstances leading to hampered proton pumping pathway within Complex I, e.g. due to aberrant mutations of mtDNA encoding either ND2, ND4 or ND5 Complex I H+-pumping subunit, therapeutic strategy based simply on uncoupling would fail. Experimentally, hydrophobic amiloride EIPA mimicks the model of disabled H+-pumping. We show for the first time that EIPA is a real inhibitor of H+-pumping of mitochondrial Complex I. We searched for an agent that, unlike uncoupling, would be able to counteract oxidative stress associated with obstructed proton pumping of Complex I. Mitochondria-targeted ubiquinone MitoQ10 proved to be an effective antioxidant for this purpose when the rate of superoxide formation was high due to the electron flow retardation within Complex I. Because of its pro-oxidant properties, targeted delivery of MitoQ10 as a cure to the pathological tissue is necessary. Activation of mitochondrial phospholipase iPLA2 by mild oxidative stress can provide free fatty acid hydroperoxides as the cycling substrates for UCP2 that initiates mild uncoupling leading to the attenuation of reactive oxygen species (ROS) production, as a part of feedback regulatory loop of lipid peroxidation. Cells with lower oxidative phosphorylation content adapt less efficiently to the conditions of physiological normoxia. Glycolytic normoglycemic cells adapt to 5% oxygen by elevated state 4 respiration.