Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells

Titre	Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells
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Résumé en anglais	Heme biosynthesis begins in the mitochondrion with the formation of delta-aminolevulinic acid (ALA). In acute intermittent porphyria, hereditary tyrosinemia type I and lead poisoning patients, ALA is accumulated in plasma and in organs, especially the liver. These diseases are also associated with neuromuscular dysfunction and increased incidence of hepatocellular carcinoma. Many studies suggest that this damage may originate from ALA-induced oxidative stress following its accumulation. Using the MnSOD as an oxidative stress marker, we showed here that ALA treatment of cultured cells induced ROS production, increasing with ALA concentration. The mitochondrial energetic function of ALA-treated HepG2 cells was further explored. Mitochondrial respiration and ATP content were reduced compared to control cells. For the 300 µM treatment, ALA induced a mitochondrial mass decrease and a mitochondrial network imbalance although neither necrosis nor apoptosis were observed. The up regulation of PGC-1, Tfam and ND5 genes was also found; these genes encode mitochondrial proteins involved in mitochondrial biogenesis activation and OXPHOS function. We propose that ALA may constitute an internal bioenergetic signal, which initiates a coordinated upregulation of respiratory genes, which ultimately drives mitochondrial metabolic adaptation within cells. The addition of an antioxidant, Manganese(III) tetrakis(1-methyl-4-pyridyl)porphyrin (MnTMPyP), resulted in improvement of maximal respiratory chain capacity with 300 µM ALA. Our results suggest that mitochondria, an ALA-production site, are more sensitive to pro-oxidant effect of ALA, and may be directly involved in pathophysiology of patients with inherited or acquired porphyria.
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