The addition of ketone bodies alleviates mitochondrial dysfunction by restoring complex I assembly in a MELAS cellular model

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Résumé en anglais	Ketogenic Diet used to treat refractory epilepsy for almost a century may represent a treatment option for mitochondrial disorders for which effective treatments are still lacking. Mitochondrial complex I deficiencies are involved in a broad spectrum of inherited diseases including Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes syndrome leading to recurrent cerebral insults resembling strokes and associated with a severe complex I deficiency caused by mitochondrial DNA (mtDNA) mutations. The analysis of MELAS neuronal cybrid cells carrying the almost homoplasmic m.3243A>G mutation revealed a metabolic switch towards glycolysis with the production of lactic acid, severe defects in respiratory chain activity and complex I disassembly with an accumulation of assembly intermediates. Metabolites, NADH/NAD ratio, mitochondrial enzyme activities, oxygen consumption and BN-PAGE analysis were evaluated in mutant compared to control cells. A severe complex I enzymatic deficiency was identified associated with a major complex I disassembly with an accumulation of assembly intermediates of 400kDa. We showed that Ketone Bodies (KB) exposure for 4weeks associated with glucose deprivation significantly restored complex I stability and activity, increased ATP synthesis and reduced the NADH/NAD+ ratio, a key component of mitochondrial metabolism. In addition, without changing the mutant load, mtDNA copy number was significantly increased with KB, indicating that the absolute amount of wild type mtDNA copy number was higher in treated mutant cells. Therefore KB may constitute an alternative and promising therapy for MELAS syndrome, and could be beneficial for other mitochondrial diseases caused by complex I deficiency.
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