The accumulation of assembly intermediates of the mitochondrial complex I matrix arm is reduced by limiting glucose uptake in a neuronal-like model of MELAS syndrome

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Résumé en anglais	Ketogenic diet (KD) which combined carbohydrate restriction and the addition of ketone bodies has emerged as an alternative metabolic intervention used as an anticonvulsant therapy or to treat different types of neurological or mitochondrial disorders including MELAS syndrome. MELAS syndrome is a severe mitochondrial disease mainly due to the m.3243A > G mitochondrial DNA mutation. The broad success of KD is due to multiple beneficial mechanisms with distinct effects of very low carbohydrates and ketones. To evaluate the metabolic part of carbohydrate restriction, transmitochondrial neuronal-like cybrid cells carrying the m.3243A > G mutation, shown to be associated with a severe complex I deficiency was exposed during 3 weeks to glucose restriction. Mitochondrial enzyme defects were combined with an accumulation of complex I (CI) matrix intermediates in the untreated mutant cells, leading to a drastic reduction in CI driven respiration. The severe reduction of CI was also paralleled in post-mortem brain tissue of a MELAS patient carrying high mutant load. Importantly, lowering significantly glucose concentration in cell culture improved CI assembly with a significant reduction of matrix assembly intermediates and respiration capacities were restored in a sequential manner. In addition, OXPHOS protein expression and mitochondrial DNA copy number were significantly increased in mutant cells exposed to glucose restriction. The accumulation of CI matrix intermediates appeared as a hallmark of MELAS pathophysiology highlighting a critical pathophysiological mechanism involving CI disassembly, which can be alleviated by lowering glucose fuelling and the induction of mitochondrial biogenesis, emphasizing the usefulness of metabolic interventions in MELAS syndrome.
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