Hepatic fatty acid oxidation and glycine conjugation are down-regulated in mice with mitochondrial complex I deficiency

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Introduction: The oxidative phosphorylation (OXPHOS) process in mitochondria produces the bulk of ATP in many eukaryotic cells. It is especially active in organs with high energy needs, like the central nervous system and muscles. Unsurprisingly, disorders in this process often lead to neuromuscular degenerative diseases like Leigh syndrome, which is often associated with complex I deficiency. The biochemical perturbations linked to complex I deficiency have been studied exhaustively in muscle and brain samples of model animals, while the liver has received little attention despite its active role in metabolism. Since the liver plays an important role in mitochondrial fatty acid oxidation and phase 2 biotransformation (esp. glycine conjugation), the aim of this study was to investigate the effect of complex I impairment on these pathways.

Methodology: Metabolites were extracted from NDUFS4 knockout mice liver samples (which is a model of complex I deficiency and Leigh syndrome). The concentration of selected acylcarnitine and acylglycines were analysed with LC-MS/MS and compared to control mice. Total RNA was extracted from the same frozen liver aliquots. NGS RNA-sequencing was used to investigate the expression of target genes.

Results: The expression of key enzymes in the β-oxidation pathway was significantly lower in the NDUFS4 knockout mice liver, which include acyl-CoA synthetase (ACS) and carnitine paltmitoyltransferase (CPT) 2. Glycine-N-acyltransferase (GLYAT) expression was also markedly lower. Octanoylcarnitine, octanoylglycine, hexanoylglycine and butyrylglycine concentrations were significantly lower in the NDUFS4 knockout mice liver.

Discussion & conclusion: The first step in β-oxidation and glycine conjugation entail activation of fatty- and other organic acids by ACS. Lower expression of ACS genes in both pathways as well as CPT2 and GLYAT, resulted in lower levels of acylcarnitines and acylglycines; which suggest downregulated fatty acid oxidation and glycine conjugation in complex I deficient mice.

Keywords: mitochondrial disorder, NDUFS4 knockout, glycine conjugation, metabolomics, fatty acid oxidation, transcriptomics.