COMPENSATION OF DEFICIENT FATTY ACID OXIDATION IN LONG CHAIN ACYL-CoA DEHDYROGENASE KNOCKOUT MICE

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Background: Mitochondrial fatty acid β-oxidation (FAO) is the prime pathway for the degradation of fatty acids. FAO is essential to maintain energy homeostasis in liver, muscle and heart and is of particular importance during fasting. FAO is catalyzed by a series of enzymes, for most of which inherited defects have been described. The main pathological consequences associated with FAO defects are hypoketotic hypoglycemia, and skeletal- and cardio-myopathy. Mouse models are useful to study the pathologic mechanisms and potential therapeutic approaches. In this study, we used long chain acyl-CoA dehydrogenase (LCAD) knockout (KO) mice to study hepatic and cardiac metabolism.
Methods: Hepatic glucose metabolism in fasted LCAD KO mice and wildtype controls was assessed by infusing stable isotopes, followed by mass isotopomer distribution analysis. Blood, plasma and organs were collected and used for metabolite and enzyme measurements, and gene expression analysis. Cardiac function was evaluated using cinematographic magnetic resonance imaging. Myocardial lipid content was assessed using localized proton magnetic resonance spectroscopy. Cardiac energy metabolism was measured using isolated working heart perfusions.
Results: Fasted LCAD KO mice have secondary carnitine deficiency and mild hypoketotic hypoglycemia. Carnitine administration does not prevent hypoglycemia. Our stable isotope infusion study shows that the hypoglycemia is caused by an increase of glucose metabolic clearance rate and a small decrease of endogenous glucose production. Importantly, gluconeogenesis rate was not affected, despite decreased hepatic glucose-6-phosphate levels. Plasma lactate, pyruvate and alanine levels were decreased indicating changes in tissue pyruvate metabolism.
Left ventricular ejection fraction was not impaired in LCAD KO mice despite cardiac hypertrophy and lipid accumulation. The cardiac hypertrophy is non progressive and expression markers for heart failure are not increased. Moreover in ex vivo working heart perfusions, LCAD KO hearts functioned normally during 30 minutes of low workload, but also during a 30 minute period of increased workload and pacing. Remarkably, palmitate oxidation was increased in LCAD KO hearts, with a parallel decrease in glucose oxidation rates.
Conclusions: Liver and heart can compensate for a significant defect in FAO as demonstrated in the LCAD KO. Although whole body glucose use is increased in this mouse model, LCAD KO hearts respond by increasing FAO rate. Failure of these compensatory mechanisms may be crucial in the pathogenesis of FAO defects.