Fatty acid oxidation in health and disease
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Perspectives

The aim of this thesis was to understand the specific role of FAO enzymes in (patho)physiology. We first focused on the auxiliary enoyl-CoA isomerases for which no human deficiencies have been described so far. We studied a mouse model (Eci1 KO) in order to identify a potential presentation of enoyl-CoA deficiency in humans. Although this approach seems indirect, the lack of human patients makes the use of a mouse model inevitable at this stage. Recent developments in human genetics however enabled the rapid and cheap sequencing of the complete exome or genome of patients. This approach is now very successful in identifying the molecular cause in many inborn errors. We expect that these so-called next generation sequencing techniques will identify patients with defects in auxiliary enzymes, who display mild or unexpected phenotypes.

Mouse models are also very helpful in studying the pathophysiology of inborn errors. Several mouse models for FAO disorders were characterized and investigated. Many symptoms of FAO defects are also observed in FAO deficient mice, notably hypoketotic hypoglycemia and cardiac hypertrophy. Skeletal muscle pathology is not observed. Therefore, we continued to explore new models such as the LCAD$^{-/-}$; VLCAD$^{+/-}$ mouse. However, initial characterization of the LCAD$^{-/-}$; VLCAD$^{+/-}$ mouse revealed no indications for fasting-induced rhabdomyolysis. Therefore, we will proceed by exercising these mice to induce a muscle phenotype. Another possibility to investigate rhabdomyolysis is to generate an inducible knockout mouse model, for example for the MTP gene. MTP is the most interesting gene, because the MTP KO mouse has a very severe phenotype (Ibdah et al., 2001). A muscle-specific KO can be generated using a transgenic mouse line expressing Cre recombinase under the control of the human alpha-skeletal actin promoter. In general, the use of new and improved FAO deficient mouse models will further contribute to our knowledge of the (patho)physiology of FAO.

From the perspective of therapy, new mouse models like the LCAD$^{-/-}$; VLCAD$^{+/-}$ mouse are necessary to critically evaluate existing and new therapeutic opportunities. The most common disease presentation in FAO deficiencies is hypoketotic hypoglycemia, which is often provoked by fasting in combination with an illness. This clinical feature can lead to coma or even sudden death, but can be easily prevented by the avoidance of fasting or intravenous glucose administration. There is however, still a lack of therapeutic approaches to prevent or causally treat cardiomyopathy and myopathy except for dietary long-chain triglyceride (LCT) restriction and medium-chain triglyceride (MCT) supplementation. Interestingly, VLCADD patients improved by the treatment with anaplerotic odd-chain triglyceride (triheptanoin) (Roe et al., 2002). In addition, other studies using D- and L-3-hydroxybutyrate and bezafibrate as therapeutic agents have shown improvement of the (cardio)myopathy and rhabdomyolysis in patients with (long) chain FAO disorders (Bastin et al., 2011; Bonnefont et al., 2010; Van Hove et al., 2003). However, these treatments need to be investigated in a larger cohort of patients.

In our work we hypothesized that the pathogenesis of a FAO deficiency is related to the accumulation of toxic lipid intermediates and/or a decreased metabolic flexibility for energy generation. Unexpectedly, we have also found chronic activation of mTOR in tissues of the LCAD$^{-/-}$ mouse upon fasting (unpublished observations). This suggests that some of the pathogenic processes might be related to chronic mTOR activation and that inhibition of mTOR using rapamycin might be a novel therapy for FAO disorders. Future experiments will address the effect of rapamycin on fasting-induced hypoglycemia and cardiac hypertrophy.
References


