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Title of project: The Impact of Medium Chain Fatty Acids in the Regulation of the Appetite Modulating Hormone, Liver Expressed Antimicrobial Peptide 2 (LEAP2)

ABSTRACT

The high prevalence of obesity worldwide is associated with increased morbidity and mortality in addition to tremendous socio-economic costs. In order to develop anti-obesity pharmaco-therapeutics, the understanding of the complex interaction between nutrient intake, whole-body metabolism and appetite regulation require deeper knowledge.

Both human and rodent studies have demonstrated that medium chain fatty acids (MCFA) reduce food intake. However, the mechanisms behind the anorexigenic effect of MCFA has not yet been described. Liver expressed antimicrobial peptide 2 (LEAP2) is an endogenous antagonist of the ghrelin receptor that is predominantly expressed in the liver. However, the role of LEAP2 in metabolism was only recently recognized and the nutrients and metabolites that are involved in the expression pattern of LEAP2 remain poorly understood. Our preliminary findings show that MCFA upregulates LEAP2 mRNA expression in hepatocytes. Therefore, we hypothesize that MCFAs regulates LEAP2 mRNA levels in mice and on a protein level in both rodents and human. Furthermore, we hypothesize that the anorexigenic effect of MCFA is mediated by release of LEAP2 from the liver that acts on the GHSR-receptor in the hypothalamus.

This PhD project will investigate if MCFAs are consistently associated with increased levels of LEAP2 in three translational sub-projects. Firstly, we will identify if MCFA regulates liver expression and plasma levels of LEAP2, both *ex vivo* and *in vivo* mouse studies. Furthermore, we will reveal if the regulation of LEAP2 by MCFA is translational to humans by conducting a human clinical study. Secondly, we will determine if the satiety effect of MCFA is related to LEAP2 by use of two Knock Out (KO) mouse models, including ghrelin receptor KO mice and LEAP2-KO mice. Lastly, we will investigate how the molecular signalling mechanisms of MCFA affect LEAP2 expression by use of MCFA-receptor agonists and antagonists, as well as KO of MCFA receptor on hepatocytes. This PhD project is highly relevant for the understanding of liver-induced bodyweight regulation, which may point to novel avenues for anti-obesity treatment.