High fat diet induced disturbances of energy metabolism

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Summary

The incidence of obesity and type 2 diabetes has taken epidemic proportions. In addition to genetic makeup, age and gender, factors such as overeating and dietary composition are known to affect the development of both pathologies. In the first part of **Chapter 1**, the determinants of the development of obesity and insulin resistance as well as a number of widely used experimental rodent models are introduced. In the second part of **Chapter 1**, a short overview is presented on the two techniques that are most used in this thesis; the hyperinsulinemic-euglycemic clamp analysis and indirect calorimetry.

In **Chapter 2** we studied the time dependent alterations in hepatic lipid composition as well as the development of systemic inflammation as a function of time and diet. Using two high fat diets, we were able to study the effect of dietary composition on both hepatic lipid composition as well as the development of systemic inflammation. We found that, in spite of the differences in dietary composition, the overall changes in hepatic lipid composition and markers of systemic inflammation were largely similar. In addition, we could identify three successive temporal phases of hepatic and systemic adaptation during the development of high fat diet induced obesity and insulin resistance. These phases were characterized as an acute phase inflammatory phase, an intermediate phase and eventually a late phase, characterized by hepatic lipid accumulation, hyperleptinemia, insulin resistance and obesity. Interestingly, although the changes in hepatic lipid composition as well as markers of systemic inflammation was largely similar, the extend to which insulin resistance was induced was different between the high fat diets.

In **Chapter 3** and **Chapter 4** we focused on the effects of dietary fatty acid composition on oxidative metabolism, obesity and insulin resistance in more detail. It is commonly known that fatty acid chain length as well as the degree of saturation of fatty acids affects nutrient partitioning and, therefore, changes in their potency to induce obesity and insulin resistance. Long chain saturated fatty acids (LCSFA) such as palmitic acid (C16:0) and stearic acid (C18:0) are regarded as "bad fat", due to their deleterious effects on metabolism. In **Chapter 3** the effect of fatty acid chain length was studied in detail. We used C57Bl/6 mice, an inbred strain which becomes very obese upon high fat feeding, and fed them a diet rich in medium chain triglycerides (MCT) or long chain triglycerides (LCT). As was expected, the LCT diet resulted in a more obese phenotype, due to the adverse effects of LCT on oxidative metabolism and food intake. Moreover, the LCT diet resulted in ectopic fat accumulation in the liver, which was associated with a severe degree of insulin resistance in this organ. In **Chapter 4**, we found similar results by adding stearic acid to a high fat diet. The addition of only minute amounts of stearic acid was sufficient to induce severe hepatic insulin resistance and diet induced obesity. Interestingly, stearic acid was demonstrated to exert its adverse effects independent of food intake, as no

differences were found between the control and stearic acid fed group. In conclusion, **Chapter 3** and **Chapter 4** demonstrate that a diet rich in LCSFA results in impaired nutrient partitioning and hepatic insulin resistance, probably due to an impairment in nutrient partitioning.

Chapter 5 describes the effects of the iminosugar AMP-DNM on energy partitioning and obesity. In this study we used leptin deficient ObOb mice, which are hyperphagic and become extremely obese and insulin resistant. By treating ObOb mice with AMP-DNM, we were able to partly prevent obesity by reducing food intake. The reduction in food intake was associated with higher rates of fatty acid oxidation and lower rates of carbohydrate oxidation, which is favourable in terms of energy balance. The higher rate of fatty acid oxidation may be the result of increased hepatic beta-oxidation, since hepatic triglyceride accumulation was lower, and genes involved in beta oxidation were expressed higher in livers of treated animals. Whether AMP-DNM has additional effects than reducing food intake is currently investigated.

In **Chapter 6** we focussed on the intra-individual variations in food intake and oxidative metabolism in C57Bl/6 mice fed a higher fat diet. Since food intake has been demonstrated in a large number of studies to be major determinant of the development of obesity, we assessed whether differences in food intake are accompanied by changes in oxidative metabolism. In **Chapter 6** we demonstrate that animals with a high food intake also had a higher degree of whole body energy expenditure. This higher degree of expenditure was associated with a higher rate of fatty acid oxidation than would be expected based on food intake, suggesting an uncoupling of fatty acid oxidation from ATP production. This was confirmed on the mitochondrial level, where the degree of coupling was tight for glycolitic substrates but not fatty acid substrates. We therefore concluded that the higher degree of mitochondrial uncoupling may provide a protective mechanism against the development of obesity which is associated with high levels of food intake, by functioning as a blow off valve for excess energy.

Chapter 7 starts with the discussion of the results found **in Chapter 2, 3, 4, 5, and 6**, in the context of the knowledge already available in literature. In **Chapter 7** all chapters are reviewed, individually and in relation to each other. In **Chapter 8**, suggestions and future perspectives are included which may aid in future studies of energy balance, and how the techniques and concepts of the current experiments may be improved.