Interactions between hepatic glucose and fat metabolism in animal models of insulin resistance
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SUMMARY

Insulin resistance is a characteristic feature of the Metabolic Syndrome. It is defined as the inability of the body to respond adequately to physiological levels of circulatory insulin. The lack of adequate responses to this regulatory hormone results in severe alterations of hepatic and whole body glucose and fat metabolism. Decreased glucose disposal, increased hepatic glucose production and increased hepatic very-low density lipoprotein (VLDL) production results in increased plasma concentrations of glucose, insulin and triglycerides. Together with decreased plasma high density lipoprotein (HDL) levels and the presence of small, dense low density lipoprotein (LDL) particles, this phenotype is associated with an increased risk for the development of premature atherosclerosis. It has been estimated that up to 80% of diabetes-related mortality is due to cardiovascular diseases a result form an increased mortality rate in diabetes patients.

The liver plays a major role in glucose and fat metabolism. Glucose and fatty acids can be taken up, stored, oxidized and produced by the liver, processes that are, at least in part, under control of insulin. These processes are not adequately controlled under the insulin resistant conditions.

To study the development of disturbances in hepatic glucose and fat metabolism and their contribution to the progress of diabetes mellitus and the development of the characteristic plasma lipid profile, several animal models were used. These models included high-fat feeding in rats, the diabetic and obese ob/ob mouse model and the gene knockout Fabp1-/- mouse model. In addition, a chlorogenic acid derivative (S4048) was used to investigate the interactions between hepatic glucose and fat metabolism without the presence of insulin resistance. Hepatic metabolic fluxes were measured in these animals and were compared to hepatic expression levels of genes encoding enzymes involved in these pathways.

Chapter 1 gives an overview of the current understanding and knowledge of diabetes mellitus and insulin signaling in relation to hepatic glucose and fat metabolism.

Chapter 2 and 3 describe the effects of high-fat feeding on hepatic glucose and fat metabolism, respectively. High-fat feeding in rats results in insulin resistance due to decreased hepatic insulin signaling. More specifically, genes and proteins of the phosphatidylinositol 3-kinase (PI3K) pathway were, respectively, differentially expressed and not normally activated. This resulted in an inability of insulin to effectively suppress hepatic de novo glucose-6-phosphate (G6P) synthesis, hepatic glucose production and increase plasma glucose disposal (Chapter 2). In addition, high-fat feeding resulted in hepatic steatosis and an inability of insulin to suppress VLDL production (Chapter 3). These alterations due to high-fat feeding reflect characteristic adaptations of the liver as a response to a defective hepatic insulin signaling.

Two animal models in which the insulin resistant condition has a genetic basis are described in Chapter 4 and 5. The diabetic and obese ob/ob mouse model is leptin-deficient and has been studied for many years. Ob/ob mice are insulin resistant, develop whole body adiposity, accumulate hepatic fat resulting in a fatty liver and have defective hepatic insulin signaling at the level of gene expression and protein phosphorylation. Ob/ob mice have an increased production of fatty acids (de novo lipogenesis, DNL) but have a normal cholesterol synthesis rate. This was evident from hepatic expression levels of genes involved in DNL and cholesterol synthesis. DNL and/or cholesterol synthesis may influence hepatic VLDL production in a substrate-dependent way. VLDL production was, however, not affected in ob/ob mice suggesting that DNL is not a controlling factor in VLDL production. However,
limited availability of newly synthesized cholesterol may become rate-controlling for VLDL production in ob/ob mice.

The second animal model in which the insulin resistant has a genetic basis is the gene knockout Fabpi-/- mouse model (Chapter 5). In this model the gene encoding the intestinal fatty acid binding protein has been selectively knocked out. Fabpi-/- mice are insulin resistant but this condition is not caused by impaired hepatic expression of genes involved in insulin signaling. In contrast to the other animal models described in this thesis and to our expectations, VLDL production rates are decreased in Fabpi-/- mice. The precise mechanism involved in the development of the insulin resistant condition and the associated decreased VLDL production in these animals remains speculative.

The interaction between hepatic glucose and fat metabolism without the presence of insulin resistance are described in Chapter 6 and 7. Glucose-6-phosphatase (G6Pase) and glucokinase (GK) are two enzymes involved in control of hepatic glucose metabolism, specifically in controlling the rate and direction of hepatic glucose fluxes. G6Pase catalyses critical steps in both gluconeogenic and glycolytic pathways. Hepatic G6Pase activity in rats was blocked by infusion of a chlorogenic acid derivative S4048. This drug belongs to a class of compounds, which has been developed to block G6P translocase and thereby inhibiting hepatic glucose production. Blocking hepatic G6Pase activity resulted in decreased plasma glucose and insulin concentrations. Hepatic G6P and glycogen content were increased and result from a redirection of newly synthesized G6P towards glycogen (Chapter 6). Hepatic FA synthesis, but not cholesterol synthesis, was increased resulting in a fatty liver. Similar as observed in the ob/ob mouse model, increased fatty acid synthesis did not influence VLDL production, since this process was not altered upon blocking G6Pase activity (Chapter 7).

The studies described in this thesis delineate that changes in metabolic pathways can result in severe metabolic adaptations that can lead to or contribute to the development of insulin resistance. Hepatic steatosis results when fatty acid influx or production exceeds fatty acid oxidation or secretion as VLDL particles. Rats fed the high-fat diet, ob/ob mice and rats receiving the S4048 derivative all developed a fatty liver. An increase in fat calories and/or a genetic predisposition may result in hepatic adaptations to cope with the increase in fat load, which may lead to the development of the insulin resistant condition. This condition has serious consequences for hepatic VLDL metabolism and the associated atherogenic plasma lipid profile a risk factor for the development of cardiovascular diseases.