Hepatic steatosis : metabolic consequences

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Chapter 9

Summary

In this thesis we focused on the causes and consequences of hepatic steatosis. Epidemiological studies in humans, as well as experimental studies in animal models, have shown an association between visceral obesity and dyslipidemia, insulin resistance and type 2 diabetes mellitus. The mechanism underlying this association remains unclear. Recently, attention has focused on the role of excessive accumulation of triglycerides (TG) in the liver (hepatic steatosis) in this association. Hepatic steatosis was considered a benign condition until it was discovered that a nonalcoholic fatty liver is associated with many cardiovascular risk factors. Subsequently, many studies have shown a strong association between hepatic TG content and hepatic insulin resistance. However, it remains unclear to what extent hepatic steatosis is actively or passively involved in the metabolic derangements of the glucose and lipid metabolism.

In Chapter 2 we summarize important principles of the pathophysiological involvement of the liver in disturbances in the glucose and lipid metabolism obtained in rodent models. We observed that in some models the strong association between hepatic TG content and hepatic insulin resistance does not hold. From this review we concluded that the liver is both actively and passively involved in the disturbances of the glucose and lipid metabolism.

The effect of insulin in normal livers with regard to the hepatic glucose output (HGO) has been studied extensively. In Chapter 3 we have compared the dose-dependent effects of insulin on HGO and VLDL production in the liver under hyperinsulinemic euglycemic conditions with different insulin concentrations. Interestingly, while the liver plays a central role in glucose and lipid metabolism, HGO and hepatic VLDL-TG production are differentially regulated by insulin. We found that hepatic glucose output is much more sensitive to insulin-mediated inhibition than hepatic VLDL-TG production.

CD36, or fatty acid translocase (FAT), is involved in the high affinity uptake of FA in the periphery. Mice lacking CD36 have considerably impaired FA uptake in muscle and in adipose tissue. These mice exhibit increased plasma FA and TG levels and show decreased plasma glucose levels. Furthermore these mice have an increased hepatic TG content and have severely insulin resistant livers. We showed in Chapter

4 that the increased plasma TG levels in CD36 deficiency were not due to a previously hypothesized enhancing effect on hepatic VLDL-TG production or an effect on intestinal lipid absorption. Instead, CD36 deficiency resulted in hypertriglyceridemia caused by decreased LPL-mediated hydrolysis of TG-rich lipoproteins resulting from FA-induced product inhibition.

In epidemiological studies insulin resistance is associated with chronic low-grade inflammation. This is reflected in associations between the degree of insulin sensitivity and plasma levels of several cytokines, such as tumor necrosis factor (TNF)α and interleukin(IL)-6. IL-10 is a potent anti-inflammatory cytokine, which is produced by T-cells, B-cells, monocytes and macrophages and plays a crucial role in the innate immune system. IL-10 potently inhibits the production of pro-inflammatory cytokines, including TNFα and IL-6. In Chapter 5 we established the direct consequences of IL-10 deficiency on hepatic and peripheral insulin sensitivity. Our data showed, that basal IL-10 production protects against hepatic steatosis during high fat feeding. However, endogenous IL-10 did not improve hepatic or whole-body insulin sensitivity during high fat feeding as assessed by the hyperinsulinemic euglycemic clamp technique.

The introduction of highly active antiviral therapy (HAART) has led to a significant reduction in the morbidity and mortality that was associated with HIV-infection. Unfortunately, these drugs are associated with severe adverse metabolic effects, such as the lipodystrophy syndrome. In this syndrome subcutaneous wasting of fat is observed (lipoatrophy) with or without accumulation of fat in the dorso-cervical region (“buffalo hump”) or in the abdomen (lipodystrophy). Hepatic steatosis is often observed in these patients. Several metabolic disturbances such as hyperlipidemia, hyperglycemia and insulin resistance are observed in subjects with the lipodystrophy syndrome. Few studies have shown a direct mechanism involved in the emergence of this syndrome. In Chapter 6 we conclusively elucidated the mechanism behind RTV-induced hypertriglyceridemia. RTV decreases plasma LPL activity, either by decreasing expression levels of LPL but most probably also via inhibition of the activity of the LPL enzyme that is present. With regard to the mechanism underlying lipodystrophy we found that the adipose tissue of RTV-treated mice takes up less FA derived from the plasma free FA pool and from VLDL-TG particles, compared to

untreated mice. In contrast to our expectations, although RTV induces an atherogenic lipoprotein profile, it protects against the development of atherosclerosis in the APOE*3-Leiden transgenic mice (Chapter 7).

In conclusion, the studies in this thesis show that hepatic steatosis is actively and passively involved in the metabolic disturbances in the glucose and lipid metabolism. The prevalence of hepatic steatosis in western countries is high and will certainly increase with the epidemics of obesity and diabetes. This will put an increasing number of subjects at risk for disturbances in the glucose and lipid metabolism and concomitantly for cardiovascular disease.