Adiponectin in glucose metabolism
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Summary
Obesity is a major risk factor for insulin resistance, diabetes and cardiovascular diseases. Over the past years adipose tissue has been recognized as the largest endocrine organ in the body, synthesizing and secreting several biologically active hormones, the adipocytokines, that participate in the regulation of glucose and lipid metabolism. Among those adipocytokines is adiponectin. Plasma adiponectin levels are reduced in insulin resistant subjects with obesity, type 2 diabetes mellitus and HIV-associated lipodystrophy. As adiponectin has insulino-mimetic properties, the reduction in adiponectin could play a role in the pathogenesis of the disturbances in glucose metabolism in these subjects.

The aim of this thesis was to examine some aspects on the regulation of adiponectin and to investigate its role in the disturbances in glucose and lipid metabolism in human subjects with an emphasis on patients with infections and HIV-lipodystrophy.

Chapter 1 is the general introduction to this thesis. An overview of glucose and lipid metabolism in healthy human subjects is given, followed by a summary of the methods we used in this thesis to measure glucose production, gluconeogenesis and lipolysis. The function of adipose tissue is described, emphasizing its role as an endocrine organ. Furthermore, some aspects on the regulation and role of adiponectin in the disturbances in glucose and lipid metabolism are briefly reviewed.

Insulin mediates its metabolic effects via 3 different signal transduction pathways: the phosphatidylinositol 3-kinase (PI3K) pathway, the Mitogen-activated protein kinase (MAPK) pathway and in synergy with amino acids the mammalian target of rapamycin (mTOR) pathway. In Chapter 2, we examined the influence of these different insulin signaling cascades on the production and secretion of adiponectin in 3T3-L1 adipocytes. In addition, we investigated whether autophago-lysosomal breakdown regulates adiponectin levels.

We found that insulin stimulated adiponectin synthesis and predominantly adiponectin secretion. The stimulation by insulin was PI3K dependent but mTOR and MAPK independent. Amino acids also stimulated adiponectin synthesis, largely by virtue of their role as substrates for adiponectin production. The stimulation by amino acids was independent of PI3K, MAPK and mTOR. Autophago-lysosomal breakdown did not regulate adiponectin levels. We concluded that the production of adiponectin is substrate driven and that insulin stimulates adiponectin production and secretion via the PI3K pathway.
In Chapter 3, we examined the short term, selective effects of insulin, glucose and its combination on plasma (HMW) adiponectin levels in healthy subjects. Plasma adiponectin levels were suppressed by insulin, whereas hyperglycemia prevented the suppressive effect of insulin. We concluded that in contrast to glucose, insulin could be involved in the down-regulation of plasma adiponectin in insulin resistant patients.

Sepsis and other acute infections are often associated with disturbances in glucose homeostasis. No data on peripheral and hepatic insulin sensitivity in early sepsis in humans exist. In Chapter 4, we studied glucose metabolism during hyperinsulinemic-euglycemic clamps with the use of stable isotopes in healthy volunteers after bacterial lipopolysaccharide (LPS) administration and in a control setting. We demonstrated that 2 hours after administration of LPS, peripheral and hepatic insulin sensitivity increased, which may contribute to hypoglycemia occurring early in sepsis. There was no difference in the change in total plasma adiponectin levels between the LPS and the control group. From these data it can be postulated that adiponectin is not involved in the etiology of the changes in insulin sensitivity during early sepsis.

Disturbances in glucose metabolism frequently complicate severe malaria. In Chapter 5, we investigated plasma adiponectin levels in 7 patients with cerebral malaria, 6 with uncomplicated malaria and 12 matched controls and correlated these levels to endogenous glucose production rates. Adiponectin levels were not different between the patients with malaria and the control group. However patients with cerebral malaria had significantly higher values of adiponectin than the patients with uncomplicated malaria. Glucose production and gluconeogenesis rates were positively correlated to plasma adiponectin in the patients, while these correlations were absent in the controls. As adiponectin is known to inhibit glucose production, stimulation of adiponectin secretion during infection could be intended to restrain the glucose production rate, which is increased during infection by the high levels of glucose counter-regulatory hormones and cytokines.

Patients with antiretroviral therapy-associated lipodystrophy are characterized by changes in body fat distribution as well as by derangements in lipid and glucose metabolism. In Chapter 6 and 7, in order to obtain more insight into the contribution of individual drug classes, NRTI in particular, and into the sequence of onset of metabolic disturbances, we investigated body composition and metabolism in detail in antiretroviral therapy-naive, HIV-1-infected patients starting antiretroviral treatment. We compared a NRTI-containing
regimen (lopinavir/ritonavir + zidovudine/lamivudine (LPV/r + AZT/3TC)) with a NRTI-sparing regimen (lopinavir/ritonavir+nevirapine (LPV/r + NVP)).

In Chapter 6, we showed that 3 months of treatment with a NRTI-containing, but not a NRTI-sparing regimen, resulted in a 25% decrease in insulin-mediated glucose disposal and a 22% increase in fasting lipolysis without affecting body composition or plasma adiponectin levels. Therefore, NRTI may directly affect glucose metabolism, the mechanism by which remains to be elucidated.

In Chapter 7, we demonstrated that the decrease in insulin-stimulated peripheral glucose disposal in patients on a NRTI-containing regimen was persistent after 24 months. This decrease was followed by a transient reduction in insulin suppression of lipolysis after 12 months. In the LPV/r + NVP arm, hepatic insulin sensitivity improved after 24 months. In the patients on a NRTI-containing regimen, limb fat was decreased after 24 months, whereas visceral fat was increased. Plasma adiponectin levels increased in both arms. We concluded that the early decrease in peripheral insulin sensitivity in patients on a NRTI-containing regimen is probably a direct effect of the medication since no changes in body fat distribution or plasma adiponectin occurred at that time point, although the fat distribution changes occurring later on may have contributed to the persistence of peripheral insulin resistance. The transient change in lipolysis may be caused by fat depot specific sensitivity for the inflammatory and pro-apoptotic effects of NRTI, with limb fat possibly being more sensitive than visceral fat, explaining the return of lipolysis rates to baseline with the reduction of limb fat and increase in visceral fat.

From the data of these 2 studies, we concluded that the disturbances in glucose and lipid metabolism are not preceded by a decrease in total plasma adiponectin levels in HIV-1 infected patients starting antiretroviral therapy (Chapter 6) and developing lipodystrophy (Chapter 7).

Considering the insulino-mimetic properties of adiponectin, up-regulation of plasma adiponectin could result in improved glucose and lipid metabolism in HIV-associated lipodystrophy. In Chapter 8, we studied the effects of a rosiglitazone-induced increase in adiponectin levels on insulin sensitivity by performing hyperinsulinemic-euglycemic clamps using stable isotopes at baseline and 16 weeks after starting treatment in HIV-lipodystrophic patients. Despite inducing a marked increase in plasma adiponectin levels, primarily of the active HMW form, rosiglitazone did not improve insulin sensitivity at the level of the liver or peripherally. This questions the importance of adiponectin in regulating glucose metabolism in HIV-lipodystrophy.
In *Chapter 9* we summarize and put into perspective (our) recent advances on the regulation of adiponectin and its role in lipid and glucose metabolism. We hypothesize that adiponectin plays an important physiological role during prolonged fasting in humans as well as during hibernation in animals. Whereas adiponectin could be involved in the pathogenesis of the disturbances in metabolism in patients with obesity or type 2 diabetes mellitus, this does not seem to be the case in patients with HIV-lipodystrophy.