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General discussion
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Perspective

Obesity is a major risk factor for insulin resistance, diabetes and cardiovascular diseases. Traditionally, adipose tissue is known to be an organ that passively stores excess of energy as fat. However, in recent years, adipose tissue has been shown to synthesize and secrete a variety of biologically active molecules that influence systemic metabolism, including TNF- α , IL-6, resistin, leptin and adiponectin ¹. Of those adipocytokines, adiponectin appears to be the most interesting hormone by its insulin-sensitizing effects and its potent role in the pathogenesis of disturbances in glucose metabolism.

Adiponectin was originally identified in 1995. In order to identify novel adipocyte-specific proteins, mRNA induced during adipocyte differentiation of 3T3-L1 fibroblasts was randomly sequenced. As the mRNA expression of adiponectin was induced over 100-fold during adipocyte differentiation, this new adipocytokine was discovered. Adiponectin was shown to be produced and secreted predominantly by differentiated adipocytes. In addition, it was shown that adiponectin is a relatively abundant serum protein, accounting for up to 0.05% of total serum protein ².

Structure

Adiponectin consists of a N-terminal collagenous domain, a variable domain and a C-terminal globular domain. The globular domain bears a striking similarity to a family of hibernation-specific serum proteins ²⁻⁵. In plasma, adiponectin circulates in several different size entities. Post-translational modification by hydroxylation and glycosylation of the collagenous domain of adiponectin produces multiple isoforms, which assemble into trimeric (low-molecular-weight) forms. Via disulfide bond formation at the cysteine-36 residue in the variable domain, hexameric (medium-molecular-weight) and high-molecular-weight (HMW) complexes are formed ⁶. The HMW oligomer has been implicated as the most active form, responsible for the insulin-sensitizing effects of adiponectin in the liver and skeletal muscle. In contrast with its peripheral effects, the central (i.e. in the central nervous system (CNS)) actions of adiponectin appear to be mediated predominantly by its hexameric and trimeric isoforms ^{7, 8}.

Adiponectin exerts its metabolic effects via binding to 2 receptors, adipoR1 and adipoR2. Although both adiponectin receptors are ubiquitously expressed, adipoR1 is primarily expressed in skeletal muscle, whereas adipoR2 is most abundantly expressed in the liver ⁹.

Metabolic effects of adiponectin in rodents

In healthy rodents, peripheral administration or overexpression of adiponectin ameliorates glucose metabolism by enhancing peripheral glucose uptake and suppressing hepatic

glucose output¹⁰⁻¹⁴. Moreover, in lipoatrophic and obese animals administration of adiponectin reverses insulin resistance^{12, 14, 15}. These effects occur via activation of AMP-activated protein kinase (AMPK) in muscle cells, adipocytes as well as in hepatocytes. Via sequential activation of peroxisome proliferator-activated receptor α (PPAR α), AMPK stimulates free fatty acid (FFA) oxidation and consequently causes a reduction in triglycerides content in muscle and liver^{14, 16, 17}. Adiponectin has also been described to redistribute adipose tissue in a metabolic advantageous way: it decreases the amount of visceral fat, whereas it increases the amount of subcutaneous fat^{13, 18, 19}. This change in body fat distribution attributes to improved insulin sensitivity. Overexpression of adiponectin in mice also increases the amount of interscapular fat, which is known to be brown fat, involved in thermogenesis¹¹. Peripheral administration of adiponectin in Agouti yellow obese mice upregulates mRNA expression of uncoupling proteins (UCP) in brown fat, white fat and skeletal muscle, resulting in a rise in thermogenesis and energy expenditure¹⁸. However, in contrast to this study, overexpression of adiponectin in ob/ob mice resulted in a reduction in energy expenditure¹⁹. These data suggest within-species differences in the effects of adiponectin, at least in regulation of energy expenditure.

Besides direct effects in the periphery, adiponectin also acts centrally to regulate metabolism. In mice, intracerebroventricular administration of the hexameric form of adiponectin activates AMPK in the hypothalamus. This results in increased food intake and decreased energy expenditure⁸.

The data on glucose metabolism in adiponectin knock-out mice are in accordance with the improvements in glucose metabolism after adiponectin administration or overexpression in healthy rodents. After a high fat/ sucrose diet, adiponectin knock-out mice exhibit severe insulin resistance. Adiponectin treatment reverses the impairment in insulin sensitivity²⁰. Furthermore, adiponectin receptor knock-out mice (adipoR1 or adipoR2) show a decrease in insulin sensitivity as well²¹.

Adiponectin levels in human subjects

Obesity and type 2 diabetes mellitus

As adiponectin is mainly synthesized and released by white adipose tissue, it may be expected that its expression in adipocytes would increase in obesity. However, plasma levels of adiponectin are lower in obese subjects compared to non-obese subjects²². In patients with type 2 diabetes mellitus, plasma adiponectin concentrations, primarily the HMW form, are lower compared to BMI-matched, non-diabetic subjects^{23, 24}. Furthermore, insulin resistant patients were shown to have a decrease in adiponectin mRNA expression in subcutaneous and in visceral fat^{25, 26}. The low total and HMW plasma adiponectin

levels were closely correlated to the degree of insulin resistance^{24, 27-29}. Prospective studies showed that a decrease in total plasma adiponectin precedes the development of hyperglycemia and type 2 diabetes mellitus^{30, 31}, suggesting a pathophysiological role for adiponectin in the development of insulin resistance rather than just being a marker of insulin resistance.

HIV-lipodystrophy

HIV-infected patients on antiretroviral therapy frequently develop metabolic disturbances and changes in body fat distribution or lipodystrophy³². The metabolic disturbances include dyslipidemia and alterations in glucose metabolism, ranging from insulin resistance at the level of peripheral glucose disposal, hepatic glucose production and lipolysis to overt diabetes mellitus type 2³³⁻³⁵. The pathogenesis of these perturbations is likely multifactorial: both protease inhibitors and nucleoside reverse transcriptase inhibitors may play a major role (*Chapter 6 and 7*)³⁶⁻⁴⁰.

Plasma adiponectin levels are reduced in HIV-lipodystrophic patients compared to HIV-positive patients without lipodystrophy and compared to healthy subjects⁴¹. In addition, adiponectin mRNA expression in subcutaneous adipose tissue of HIV-lipodystrophic patients is lower compared to in HIV-infected patients without lipodystrophy⁴². The low plasma adiponectin levels correlate with the degree of insulin resistance⁴¹. In contrast to patients with type 2 diabetes mellitus, 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*), suggesting that the role of adiponectin in relation to the onset of insulin resistance is different in HIV-uninfected individuals with type 2 diabetes mellitus and HIV-infected patients with lipodystrophy, respectively.

Infections other than HIV

Hypoglycemia is seen as an infrequent feature of early sepsis^{43, 44}. Sepsis can be mimicked in healthy human subjects via intravenous administration of Gram-negative bacterial lipopolysaccharide (LPS). In healthy human volunteers, it was demonstrated that administration of LPS, compared to a control setting, resulted in an increase in peripheral and hepatic insulin sensitivity after several hours, 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 (*Chapter 4*).

A prolonged duration of sepsis however is associated with a reversible state of insulin resistance, leading to hyperglycemia^{28, 45-48}. In healthy volunteers, the induction of

insulin resistance, measured by the Homeostatic Model Assessment (HOMA)-index, 24 hours after LPS administration, was not associated with a change in total or HMW plasma adiponectin²⁸. These data together suggest that adiponectin is not involved in the disturbances in glucose metabolism during sepsis.

Hypoglycemia is also a common complication of severe falciparum malaria, occurring in 8–30% of individuals affected with this disease, particularly in those with cerebral malaria⁴⁹. Total plasma adiponectin levels were not different between malaria patients and healthy controls. However, in patients with cerebral malaria, plasma adiponectin levels are higher compared to patients with uncomplicated malaria. In addition, patients infected with *Plasmodium falciparum* who have higher glucose production rates, also have higher plasma adiponectin levels. As adiponectin inhibits glucose production in rodents, stimulation of adiponectin secretion 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. As hypoglycemia was not seen in these malaria patients, a possible pathophysiological role of adiponectin in the development of hypoglycemia can not be excluded (*Chapter 5*).

156 Regulation of adiponectin

Several studies have examined the role of the glucose counter-regulatory hormones and cytokines in the regulation of adiponectin production and secretion in vitro. In 3T3-L1 adipocytes and rodents, cortisol and β -adrenergic stimulation were both shown to decrease mRNA expression as well as total plasma adiponectin levels⁵⁰⁻⁵⁴. Of the cytokines, TNF- α and IL-6 inhibited adiponectin expression and secretion in 3T3-L1 adipocytes and human subcutaneous fat^{52, 55, 56}.

Since hyperinsulinemia and hyperglycemia are characteristic biochemical features of insulin resistant patients, insulin as well as glucose could potentially be responsible for the down-regulation of adiponectin. The effects of insulin have been investigated extensively. Most, but not all studies⁵² have reported an increase in adiponectin production and secretion in 3T3-L1 adipocytes in response to insulin (*Chapter 2*)^{53, 57-59}. The insulin-stimulated increase in adiponectin production and secretion is mediated by the phosphatidylinositol 3-kinase (PI3K)-dependent signaling pathway, since selective inhibition of this pathway prevented the effect of insulin (*Chapter 2*)^{59, 60}. Two other important insulin signaling cascades, the Mitogen-activated protein kinase (MAPK) pathway and the mammalian target of rapamycin (mTOR) pathway did not have a major influence on adiponectin production or secretion (*Chapter 2*)⁵⁹.

However, in contrast to these studies in 3T3-L1 adipocytes, insulin decreases plasma adiponectin levels in humans. Hyperinsulinemic-euglycemic clamp studies in lean subjects reduced total plasma adiponectin levels by 10-20% (*Chapter 3*)⁶¹⁻⁶³. The ratio of HMW to total adiponectin was not affected by insulin in these subjects (*Chapter 3*).

The differences between the influence of insulin on adiponectin in 3T3-L1 adipocytes compared to human subjects remain to be elucidated. The most likely explanation is the major difference between artificial isolated cell systems in which only a few factors are controlled and human in-vivo studies. One of those differences could be inter-organ effects. It can be hypothesized that insulin affects adiponectin production or secretion indirectly in humans, e.g. via the CNS. In addition, insulin could increase the clearance of adiponectin. These possibilities have not been explored.

The regulation of adiponectin by glucose has been examined less thoroughly. One study has reported on the effects of hyperglycemia on adiponectin expression and plasma concentrations in rats. Hyperglycemia resulted in enhanced adiponectin expression in visceral fat, whereas plasma levels remained constant⁶⁴. In lean humans, hyperglycemia prevented the suppressive effect of insulin (*Chapter 3*). The latter data are contrary to expectation and suggest that the characteristic biochemical feature of insulin resistant patients, hyperinsulinemia plus hyperglycemia is not the most obvious explanation for the low adiponectin levels in type 2 diabetes mellitus.

The same holds true for another characteristic feature of type 2 diabetes mellitus: high FFA levels. The acute impact of FFA on plasma adiponectin levels in healthy humans has been investigated by short term modulation of FFA via administration of pharmacological inhibitors of lipolysis (acipimox) or the fat emulsion intralipid. Neither of these 2 interventions affected plasma adiponectin levels, indicating that adiponectin is not acutely regulated by FFA⁶⁵⁻⁶⁷. Furthermore, plasma (HMW) adiponectin concentrations were not altered postprandially in response to a normal⁶⁸ or a high-fat meal⁶⁹⁻⁷¹ in healthy human subjects.

These observations do not support a role for adiponectin in the acute (minutes-hours) regulation of glucose metabolism in humans.

Up-regulation of adiponectin in humans

In view of the insulin-sensitizing properties of (HMW) adiponectin and its low levels in insulin resistant states, it can be hypothesized that up-regulation of plasma adiponectin could result in improved metabolism. As adiponectin has not (yet) been administered to human subjects, at this stage plasma (HMW) adiponectin can only be increased in an indirect manner. The most potent enhancers of adiponectin are the peroxisome

proliferator-activated receptor- γ (PPAR- γ) agonists. PPAR- γ agonists markedly increase adiponectin levels, predominantly the HMW form¹³. In patients with type 2 diabetes mellitus, treatment with PPAR- γ agonists results in an increase in insulin sensitivity both at the level of the liver as well as peripherally^{72,73}. The improvements in insulin sensitivity were associated with an increase in total plasma adiponectin levels. More recently, it was shown that in diabetic patients this association could be further strengthened by taking the HMW to total adiponectin ratio into account^{13,73}. Although the exact mechanisms of the insulin sensitizing effects of PPAR- γ agonists remain to be elucidated, these data suggest that an increase in adiponectin, in particular of the HMW form, could play a role in improving disturbances in metabolism in diabetic patients. One can however not rule out that this may only represent an association in time rather than a causal relationship.

The effects of PPAR- γ agonists have also been investigated in patients with HIV-lipodystrophy⁷⁴⁻⁷⁹. However, the majority of these reports focused on the influence of PPAR- γ agonists on body composition and therefore did not examine glucose homeostasis in detail. One study reported an increase in the HMW form of adiponectin, which was associated with a significant improvement in hepatic insulin sensitivity⁸⁰. However in this study, hepatic insulin sensitivity was determined by the HOMA-index, which can not distinguish accurately between insulin sensitivity at the level of the liver and peripherally. Recently, by performing hyperinsulinemic-euglycemic clamps with the use of stable isotopes, it was shown that the PPAR- γ agonist rosiglitazone did not improve insulin sensitivity at the level of either peripheral glucose disposal, hepatic glucose production or lipolysis in HIV-lipodystrophy, although it did induce a marked increase in plasma (HMW) adiponectin (*Chapter 8*), stressing, as mentioned earlier, that insulin resistance in type 2 diabetes mellitus and in HIV-associated lipodystrophy are probably different pathophysiological entities. Extrapolation of data on this issue from one disease to the other is therefore not warranted.

Pathophysiological role of adiponectin

Plasma levels of (HMW) adiponectin are reduced in insulin resistant subjects with obesity, type 2 diabetes and HIV-associated lipodystrophy^{23,24,41}. In HIV-lipodystrophic patients, the disturbances in glucose and lipid metabolism are not preceded by a decrease in plasma adiponectin (*Chapter 6 and 7*). Moreover, a rosiglitazone-induced increase in plasma (HMW) adiponectin did not improve peripheral or hepatic insulin sensitivity (*Chapter 8*). These data question the importance of adiponectin in regulating metabolism in HIV-lipodystrophy.

In contrast, in obese and diabetic patients the reduction in (HMW) adiponectin could be involved in the pathogenesis and/ or perseverance of the disturbances in glucose metabolism. Firstly, because the decrease in total plasma adiponectin levels precedes the development of insulin resistance^{30, 31} and secondly because up-regulation of adiponectin by PPAR- γ agonists results in an improvement of insulin sensitivity in these patients^{13, 73}.

Plasma (HMW) adiponectin concentrations did not change in human models of endotoxemia, neither during the early hypoglycemic state, nor during a prolonged duration associated with a state of insulin resistance. From these data it can be postulated that adiponectin is not involved in the etiology of the changes in insulin sensitivity during sepsis (*Chapter 4*)²⁸.

In patients infected with malaria, plasma adiponectin levels were positively associated to glucose production rates. It can be hypothesized that adiponectin secretion is stimulated during malaria to limit the high glucose production rates, induced by cytokines and glucose counter-regulatory hormones.

Physiological role of adiponectin

When observing metabolism from an evolutionary point of view, it is not reasonable to believe that adiponectin is developed in order to protect us from diseases associated with high caloric food intake and a sedentary lifestyle. It can be hypothesized that the other way around may be more likely and that adiponectin originated as a starvation signal during prolonged fasting in humans as well as during hibernation in animals^{13, 21, 81}. During starvation with limited fat reserves, an increase in adiponectin could serve as a systemic sign that the adipocyte size is being reduced and that metabolic adaptations directed at survival are needed. By favoring FFA oxidation over glucose oxidation in the periphery, HMW adiponectin would save the required supply of glucose to the CNS. Moreover, the hexameric and trimeric isoforms of adiponectin could stimulate food intake and decrease energy expenditure via central effects. During hibernation in animals, adiponectin could enhance the amount of brown fat to increase thermogenesis. In addition, via redistribution of fat from the liver and skeletal muscle towards subcutaneous adipose tissue, adiponectin could play a role in the preservation of body temperature by heat insulation.

Besides these metabolic properties of adiponectin, aimed at survival during prolonged fasting, the hypothesis of adiponectin as a starvation signal is supported by several other observations. Firstly, human adiponectin has a relatively long half-life of approximately 14 hours⁷¹ in comparison with other hormones, which suggests that adaptation to acute metabolic challenges is not the primary function of adiponectin. In accordance with this,

under normal physiological conditions, the acute regulation of adiponectin is relatively modest. Although a small decrease is seen in response to high insulin levels (*Chapter 3*)⁶¹⁻⁶³, adiponectin does not change markedly in response to a meal⁶⁸⁻⁷¹ or FFA⁶⁵⁻⁶⁷.

Therefore it might be expected that adiponectin is responsible for more chronic adaptive responses, e.g. during prolonged starvation. Indeed, in human subjects short term fasting did not change adiponectin concentrations⁸²⁻⁸⁴, while on the contrary prolonged caloric restriction, when accompanied by marked weight loss, resulted in higher plasma (HMW) adiponectin⁸⁵⁻⁸⁹. Moreover, in patients with cardiac cachexia⁹⁰ and anorexia nervosa plasma (HMW) adiponectin concentrations are increased, whereas weight recovery reversed the concentrations to levels comparable to controls^{91, 92}. Finally, the supposed role of adiponectin as a starvation signal is supported by the fact that the globular domain of adiponectin bears a striking resemblance with hibernation-specific serum proteins²⁻⁵.

Interestingly, similar to adiponectin, the adipocytokine leptin was initially seen as an anti-obesity hormone as well, whereas with increasing knowledge, it became evident that leptin also (mainly?) serves as a mediator of the adaptation to fasting and that this role may be the primary function for which the molecule evolved^{93, 94}.

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Although several observations imply that adiponectin functions as a starvation signal during prolonged fasting, some study results indicate that adiponectin has an additional role in the adjustments to disturbances of glucose metabolism in human subjects as well. The positive correlation between plasma adiponectin levels and glucose production rates in patients infected with *Plasmodium falciparum* could represent a stimulatory effect on the secretion of adiponectin to limit glucose production rates during malaria (*Chapter 5*). The prevention of the insulin-induced suppression of adiponectin by hyperglycemia could also function as a compensatory mechanism to restrain glucose levels (*Chapter 3*). Future studies should clarify the role of adiponectin in disturbances of metabolism in humans.

Conclusion

In conclusion, the physiological role of adiponectin could be that of a starvation signal during prolonged fasting in humans as well as during hibernation in animals. The increased adiponectin levels in these situations may have a protective role in maintaining energy homeostasis.

In HIV-lipodystrophic patients the endocrine function of adipose tissue is disturbed due to visceral obesity, peripheral lipoatrophy or its combination. The low adiponectin levels in these subjects most likely reflect dysfunction of adipose tissue rather than a

pathophysiological mechanism underlying the insulin resistance observed in these patients.

In contrast, in patients with obesity or type 2 diabetes mellitus, adiponectin could be involved in the pathogenesis and/ or perseverance of the disturbances in metabolism in these patients. Firstly, because the decrease in total plasma adiponectin levels precedes the development of insulin resistance. Secondly, because up-regulation of adiponectin by PPAR- γ agonists results in an improvement of insulin sensitivity in these patients. This suggests that adiponectin has a different role in relation to the onset of insulin resistance in HIV-uninfected subjects with type 2 diabetes mellitus and HIV-infected patients with lipodystrophy, respectively.

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