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Secretory factors from human adipose tissue and their functional role

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Obesity is characterized by an expanded adipose tissue mass. Recent data suggest that adipose tissue is a multi-functional organ rather than simply a passive storage site for excess energy. It has been clearly demonstrated that human adipose tissue produces a variety of secretory factors that exert multiple effects at both the local and the systemic level. To date, >100 products, covering a broad range of protein families as well as many fatty acids and prostaglandins, have been reported to be secreted by adipose tissue. The source of these secreted factors is not only mature fat cells but also poorly-identified cells present in the stromal–vascular fraction including macrophages. Secreted factors of particular interest include many cytokines or chemokines, such as TNF-α, IL-6, IL-8, as well as plasminogen activator inhibitor-1, angiotensin-II, leptin, and adiponectin. In the obese state the expression and secretion of these factors is disturbed. With the exception of adiponectin, most circulating factors are elevated. From this perspective, obesity can be described as a pro-inflammatory condition. In addition, regional differences in adipose expression of many of these factors have been found. There is now growing evidence that many secretory factors play an important role in the pathophysiology of the metabolic and cardiovascular complications of obesity. The question arising from these observations is how the secretory pattern of adipose tissue can be modified by dietary and pharmacological measures to reduce the health risks of obesity.

Adipose tissue: Obesity: Cytokines: Complications: Secretory factors

Obesity has become the most common nutritional disorder and its prevalence is increasing rapidly in most parts of the world, particularly among younger age-groups (World Health Organization, 2000). Numerous epidemiological studies indicate that an increased body fat mass is associated with an increased risk of developing a variety of adverse health consequences and diseases. It is now well established that excess body fat induces a wide range of established cardiovascular risk factors, including insulin resistance, glucose intolerance, dyslipidaemia, elevated blood pressure, impaired fibrinolysis and endothelial dysfunction, also known as metabolic syndrome (Hauner, 2002).

This metabolic syndrome represents a highly atherogenic network. Individuals exhibiting this profile are at increased risk of suffering from cardiovascular complications such as myocardial infarction and stroke. Recent prospective studies have consistently shown that the presence of metabolic syndrome is associated with a two- to three-fold increased probability of developing cardiovascular complications (Lakka *et al.* 2002; Sattar *et al.* 2003).

Currently, little is known about the mechanisms that link obesity with the metabolic risk factors described earlier, as well as with the other complications of excess body fat. For many years the hypothesis that elevated release of fatty acids from enlarged fat stores may play a central role in the development of some metabolic disturbances such as dyslipidaemia, impaired glucose metabolism and insulin resistance has been extensively discussed (Boden, 1997). This situation has changed completely since the discovery of leptin 10 years ago. Leptin has been identified as a fat cell-derived protein of cytokine-like structure that signals the size of energy stores to the brain (Zhang *et al.* 1994).
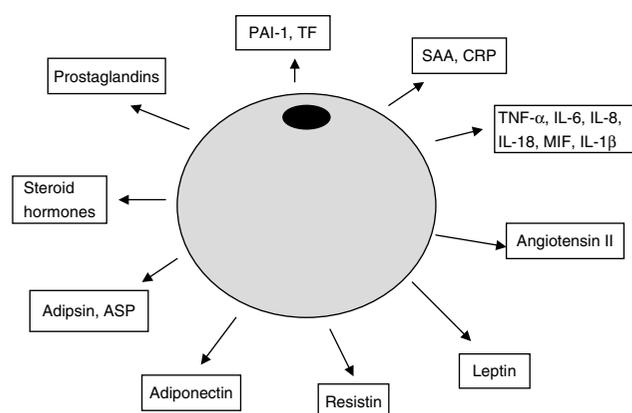
Fig. 1. Selected secretory products released by human adipose tissue. PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; SAA, serum amyloid A; CRP, C-reactive protein; MIF, migration inhibitory factor; ASP, acylation-stimulating protein.

In addition, leptin has been found to act as a satiety hormone by interfering with hypothalamic regulatory systems in the control of food intake. Several studies have consistently shown that circulating leptin levels are closely correlated with both body fat mass and fat cell size (Friedman & Halass, 1998).

It has subsequently been established that adipose tissue is far more than a lipid-storing organ that mobilizes fatty acids in case of increased energy demand or shortage of energy supply. More and more proteins have been found to be produced and released from adipose tissue. Today, it is evident that adipose tissue is a multifunctional organ maintaining an intensive cross talk with many other organs. Thus, adipose tissue is fully integrated in the complex network of energy homeostasis and body-weight regulation as well as nutrient partitioning.

To date, >100 factors have been identified to be produced and released by adipose tissue. These products belong to different types and families of molecules and may exert a variety of actions. Fig. 1 gives an overview of the most important and best studied secretory products. However, little is currently known about the physiological function of all the products released from adipose tissue. It is, therefore, the aim of the present review to summarize the present knowledge of the nature and function of some of the best-characterized factors, with special reference to the complications of obesity.

In order to give an integrated view of the comprehensive function of human adipose tissue it is important to address first the cellular composition of adipose tissue. This organ consists not only of mature adipocytes, large rounded cells with a signet-ring morphology, but also contains a so-called stromal cell fraction that still remains poorly defined. However, it is clear that most cells of this fraction have the potential to undergo differentiation into fat cells under appropriate conditions (Ailhaud & Hauner, 2004). In addition, adipose tissue also contains endothelial cells, sympathetic nerve fibres and macrophages, which may all contribute to adipose tissue function. However, because of the enormous size of fat cells, which have an impressive capacity to store triacylglycerols, this cell type comprises

Table 1. Cellular components (%) of human adipose tissue

Mature adipocytes	50–70
Stromal 'preadipocytes'	20–40
Endothelial cells	1–10
Macrophages	1–30
Other cell types	?

the majority of the tissue volume. Table 1 gives approximate estimates of the relative amounts of the various cell types present in adipose tissue. However, the cellular composition of adipose tissue can vary substantially according to anatomical location, body weight and other factors. Regional differences are most pronounced between omental and subcutaneous depots. Knowledge of the cellular composition of adipose tissue is essential, as all types may contribute to the secretory function of adipose tissue.

When the function of secretory products is considered it is important to distinguish between a local paracrine action and a possible systemic role of the products. Only a limited number of fat cell products are released into the bloodstream in substantial detectable amounts resulting in increased circulating levels in the obese state. The majority of factors may be acting only locally. Some factors may also have a dual action, both on surrounding cells and on remote organs. Another possibility could be that factors have a local action, but the subsequent change may induce secondary effects on other organs. Table 2 shows a list of secretory products from human adipose tissue, the circulating levels of which are either increased or decreased possibly because of an impaired secretion pattern in obese human subjects. In the following section some of the most important factors that may be relevant for the pathophysiology of obesity-associated complications are introduced in more detail.

Cytokines or chemokines

Hotamisligil *et al*. (1993) originally reported that adipose tissue from rodent models of obesity expresses high levels of TNF-α. They have also shown elevated serum concentrations of the cytokine and an association with impaired insulin action in these animals, as infusion of a soluble TNF-α antibody improves insulin sensitivity in the animals. Subsequent studies have revealed that human obesity is also associated with an increased adipose expression of TNF-α and its two receptor subtypes, indicating an up-regulation of the TNF system (Hotamisligil

Table 2. Serum concentrations of adipokines in obesity

IL-6	↑
IL-8	↑
IL-18	(↑)
TNF-α	(↑)
Angiotensin II	↑
Leptin	↑↑
PAI-1	↑↑
ASP	↑
Adiponectin	↓

(↑), Modestly elevated; ↑, elevated; ↑↑, highly elevated; ↓, decreased; PAI-1, plasminogen activator inhibitor-1; ASP, acylation-stimulating protein.

et al. 1995; Kern et al. 1995; Hube et al. 1999). The increased production of TNF-α by adipose tissue may have a variety of consequences, as demonstrated recently in a number of studies. Elevated levels of TNF-α in adipose tissue are associated with increased lipolysis, impaired insulin action on glucose transport, reduced expression of lipoprotein lipase, inhibition of fat cell recruitment and possibly induction of fat cell apoptosis (Hube & Hauner, 1999). It has been hypothesized that the main physiological purpose of increased TNF-α expression could be to limit adipose tissue expansion; the consequence being the induction of insulin resistance and subsequent disturbances in glucose and lipid metabolism. However, the question of whether elevated adipose expression of TNF-α contributes substantially to insulin resistance in man has not been resolved.

IL-6

IL-6 was originally described as a cytokine mainly produced by immune cells, but also by other cell types. Numerous studies have suggested that this cytokine is involved in the regulation of many metabolic and endocrine systems and may play a central role. Prospective studies have also indicated that elevated serum concentrations of IL-6 are predictive for the development of type 2 diabetes mellitus and CVD (Ridker et al. 2000; Spranger et al. 2003b). Several research groups have recently reported that IL-6 is also a product of adipose tissue. Fried et al. (1998) have shown that omental adipose tissue secretes substantially more IL-6 than subcutaneous abdominal adipose tissue. In addition, the secretion of IL-6 from isolated fat cells is much lower than that from whole adipose tissue, indicating that cells other than adipocytes are the major source of this cytokine in adipose tissue. Clinical data also suggest that a positive association exists between body fat mass and circulating IL-6. Mohamed-Ali et al. (1997) have reported that the elevated concentrations found in obese subjects are partly a result of the release of IL-6 from adipose tissue. It has recently been demonstrated by immunohistochemistry (Päth et al. 2001) that IL-6 is produced by cultured adipocytes. In addition, the IL-6 receptor system is expressed in adipose tissue. However, it is unclear whether IL-6 exerts an important local action in adipose tissue; only a weak inhibitory action on adipose differentiation of precursor cells has been observed (Päth et al. 2001). IL-6 may play a central role in the pathophysiology of CVD, as this adipokine has been shown to stimulate the production of fibrinogen and C-reactive protein by liver, decrease HDL-cholesterol, induce increased aggregability of thrombocytes and induce the expression of adhesion molecules by endothelial cells (Woods et al. 2000). Taken together, such data suggest that adipose production and release of IL-6 could directly promote atherosclerosis in obese subjects.

Renin–angiotensin system

Recent studies have reported that human adipose tissue expresses all components of the renin–angiotensin system

(Karlsson et al. 1998). It is also interesting to note that the expression of angiotensinogen is higher in adipose tissue from obese subjects compared with lean subjects (van Harmelen et al. 2000b), and plasma angiotensinogen levels are positively correlated with BMI (Umemura et al. 1997). In addition, adipose cells from the omental depot produce more angiotensinogen than fat cells from the subcutaneous depots (van Harmelen et al. 2000a). Knock-out of the angiotensinogen gene results in a lowering of blood pressure (Massiera et al. 2001). However, angiotensin II produced in adipose tissue may have other functions in addition to its role in local blood pressure regulation. It has been shown that angiotensin II stimulates the production of prostacyclin, a potent promoter of adipose differentiation, in preadipocyte cell lines (Darimont et al. 1994). In man, however, angiotensin II has been demonstrated to act as an inhibitor of adipose tissue differentiation, whereas the presence of a selective angiotensin II type 1 receptor antagonist induces fat cell formation (Janke et al. 2002). Data from studies in endothelial cell models have shown that angiotensin II acts as a mediator of a chronic sub-acute inflammatory state. In a recent study to determine whether angiotensin II promotes similar effects in adipose tissue (Skurk et al. 2001), it was found that angiotensin II is a potent inducer of plasminogen activator inhibitor-1 (PAI-1) production in human fat cells. This effect is completely abolished by blockade of the angiotensin II type 1 receptor. In another study (Skurk et al. 2004) the addition of angiotensin II at low near-physiological concentrations also stimulates the expression of IL-6 and IL-8, while the peptide has no effect on TNF-α and transforming growth factor β expression. This activity is mediated by the classical NFκB pathway. It has also been observed that angiotensin II promotes the expression of leptin via a mitogen-activated protein kinase-dependent pathway (T Skurk, K Röhrig, WF Blum and H Hauner, unpublished results). These results suggest that adipose tissue-derived angiotensin II may be an important mediator of adipokine expression, thereby contributing to the chronic inflammation characteristic of obesity.

Plasminogen activator inhibitor-1

Adipose expression of PAI-1 was first demonstrated in the epididymal fat pads of rodents (Sawdey & Loskutoff, 1991). Subsequent studies have shown that PAI-1 is also expressed in human adipose tissue, including both pre-adipose and fully-developed fat cells. It has also been observed that the production rates are higher in omental fat cells than in subcutaneous fat cells, although the reasons for this difference are as yet unknown (Alessi et al. 1997; Eriksson et al. 1998; Gottschling-Zeller et al. 2000). However, a plausible explanation for this phenomenon could be that PAI-1 expression is promoted by cytokines and angiotensin II, both of which are expressed at higher rates in omental adipose tissue. The most-potent stimulator of PAI-1 expression in adipose tissue is transforming growth factor β, which is also locally produced. TNF-α is another cytokine that has been shown to stimulate PAI-1 production (Alessi et al. 1997; Birgel et al. 2000; Gottschling-Zeller et al. 2000).

It is also interesting to note that circulating levels of PAI-1 are closely associated with BMI, and in particular with an abdominal type of body fat distribution (Skurk & Hauner, 2004). Recent data suggest that increased levels of PAI-1 are not only linked to thrombosis but also to insulin resistance. PAI-1-deficient mice are characterized by increased insulin sensitivity and improved glucose tolerance on a high-fat diet compared with wild-type mice. In addition, the transgenic animals show an increased RMR and express higher levels of PPARγ and adiponectin mRNA (Ma *et al*. 2004). Thus, these data suggest that PAI-1 could be directly involved in the pathophysiology of obesity-linked insulin resistance.

Adiponectin

Adiponectin is a 30 kDa adipose-specific secretory protein that has only recently been discovered. The molecule consists of an NH_2-terminal collagen-like domain and a carboxy-terminal head domain with structural similarities with complement factor C1q (Berg *et al*. 2002). The protein is abundantly expressed in adipose tissue but, in contrast to the other adipokines, expression and circulating levels are decreased with increasing BMI. Adiponectin levels are negatively correlated with insulin resistance and type 2 diabetes (Weyer *et al*. 2001), and weight loss results in an increase in circulating levels, indicating that the decrease in adiponectin production in obesity is reversible (Yang *et al*. 2001). Interestingly, baseline plasma levels of adiponectin in healthy individuals are an independent risk factor for the development of type 2 diabetes (Spranger *et al*. 2003*a*). Other clinical data suggest that low adiponectin concentrations are also associated with the development of the metabolic syndrome and atherosclerosis. Experimental studies have indicated that adiponectin decreases glucose production in the liver (Berg *et al*. 2001). In accordance with these data, other studies have shown that adiponectin expression in adipose tissue is improved by thiazolidine-diones and decreased by TNF-α (Berg *et al*. 2002). Thus, adiponectin is now being recognized as a secretory protein with intriguing properties that make it a possible new therapeutic tool for type 2 diabetes and atherosclerosis.

Co-culture of fat cells with other cell types

To obtain a better insight into the cross talk between adipose tissue and other organs the development of co-culture systems may serve as a useful tool. Using a co-culture system developed recently to study the interaction between human myocytes and fat cells (Dietze *et al*. 2002), it has been shown that the presence of fat cells results in an impairment of the insulin-signalling cascade at the level of akt (a serine threonine protein kinase) serine phosphoryla-tion in muscle. Simultaneous exposure of muscle cells to a thiazolidindione prevented this blockade, indicating a glitazone-sensitive mechanism.

In a second co-culture model that combines human fat cells and human adrenocortical cells (NCI-H295R) the con-ditioned medium from fat-cell cultures has been observed to stimulate steroidogenesis, with a predominant positive effect on mineralocorticoid secretion (Ehrhart-Bornstein *et al*. 2003). Aldosterone production is stimulated ≥7-fold by the fat cell-conditioned medium. None of the known adipokines account for the effect. The mineralocorticoid-stimulating activity is heat-sensitive and can be detected in a fraction with a molecular weight >50 kDa that represents 60% of the total activity. This as yet unidentified factor could represent another adipokine that may be responsible for the development of hypertension with increasing body fat mass.

Role of local macrophages in the secretory function of adipose tissue

It has been demonstrated (Bornstein *et al*. 2000) that omental adipose tissue contains a higher proportion of CD68-positive cells (a marker of macrophages) than sub-cutaneous adipose tissue from the same donors. Two recent studies (Weisberg *et al*. 2003; Xu *et al*. 2003) have provided convincing evidence that obesity is associated with an accumulation of macrophages in adipose tissue. One of these studies (Weisberg *et al*. 2003) has shown that 30% of the 100 proteins most highly correlated with body fat in adipose tissue are characteristic of macrophages. There is also a positive correlation between the percentage of cells expressing the macrophage marker CD68 and both adipocyte size and BMI in human subcutaneous adipose tissue samples. Expression analysis of macrophage and non-macrophage cell populations isolated from adipose tissue further suggests that macrophages are responsible for almost all adipose tissue TNF-α expression and major amounts of other inflammatory markers. Thus, these and other data (Fain *et al*. 2004) strongly suggest that macrophages resident in adipose tissue accumulate in obesity and participate in the chronic inflammatory process.

Based on this observation and from the perspective of potential future interventions the question may arise as to how macrophage accumulation is triggered in adipose tissue. It has been hypothesized that both monocyte chemoattrac-tant protein 1 and macrophage inflammatory protein 1α may be involved in this process (Wellen & Hotamisligil, 2003), but other workers (C Herder, T Skurk, S Müller-Scholze, P Rating, W Koenig, B Thorand, B Haastert, B Holle, T Jllig, W Rathmann, J Seissler, H-E Wichmann, H Hauner and H Kolb, unpublished results) have been unable to find an association between circulating concen-trations of either chemokine and BMI. It has recently been reported (Skurk *et al*. 2005) that macrophage migration inhibitory factor may be another candidate in this context, as the adipose expression and secretion of this chemokine shows a close correlation with BMI, and migration inhibi-tory factor has been proposed to be involved in macrophage infiltration. However, a completely different possibility is that adipocyte precursor cells can transform into macrophage-like cells (Cousin *et al*. 1999).

Cellular origin of secretory products from adipose tissue

The discovery and preliminary evidence that macrophages contribute substantially to the secretory function of adipose

Table 3. Cellular origin of adipokines secreted from human adipose tissue

Factor	Fat cells	Stromal cells	Macrophages
IL-6	+	+	++
TNF-α	+	+	++
PAI-1	+	+	?
MCP-1	(+)	+	++
MIP-1α	(+)	+	++
MIF	+	+	++

(+), Data not yet completely clear; +, clear evidence; ++, very strong expression; MCP-1, monocyte chemoattractant protein 1; MIP-1α, macrophage inflammatory protein 1α; MIF, migration inhibitory factor; PAI-1, plasminogen activator inhibitor-1.

Table 4. Changes in serum concentrations and adipose expression of adipokines after weight loss

Adipokine	Serum concentration	Adipose expression
TNF-α	↓	↓
IL-6	↓	↓
IL-8	↓	↑
Leptin	↓	↓
Angiotensinogen	↓	↓
PAI-1	↓	↓↑*
Adiponectin	↑	↑

↑, Elevated; ↓, decreased; PAI-1, plasminogen activator inhibitor-1.
*Depot-specific differences.

tissue also raises the question of whether other cell types are potentially responsible for the pro-inflammatory activity associated with obesity. Such cellular sources include adipocytes and stromal mesenchymal cells as well as macrophages. However, very little information is currently available about the relative contributions of these cellular components to the pattern of adipokine secretion. Nevertheless, it is becoming more and more evident that the mesenchymal cells are also an important site of cytokine production and release. Table 3 summarizes some recent data on the cellular origin of factors released from adipose tissue.

Can the secretory function of adipose tissue be modified?

In view of the growing evidence for a functional role of adipose secretion the question of whether it is possible to alter this function may gain growing attention. In principle two intervention strategies may appear reasonable: dietary intervention, including weight reduction or specific diets; pharmacological intervention. The treatment of choice is weight loss by dietary measures, as this approach has repeatedly been shown to be associated with restoration of normal secretion of the adipokines under investigation. The improvement in the secretory pattern is usually proportional to the extent of weight reduction. Little is known as to whether this improvement is associated with, or even causes, the improvement in metabolic disturbances. It is currently also unclear whether these changes are the result of stable weight loss or energy restriction, as most measurements were done immediately after completing a weight-loss programme. Table 4 summarizes some of the most important findings.

In addition to dietary treatment there is also growing evidence that frequently-used drugs with anti-inflammatory activity, such as thiazolidinediones, metformin and angiotensin II type 1 receptor antagonists, may directly influence the secretory function of human adipose tissue. One example of such effects is the down-regulation of adipose PAI-1 production by drugs such as troglitazone, metformin or candesartan (Skurk & Hauner, 2004). Even statins have been found to restore IL-6 secretion in human adipose cells (van Harmelen *et al.* 2003). The most effective agents in this respect are the thiazolidinediones, which have been reported to normalize most of the abnormalities in adipokine secretion described so far.

Summary

In summary, recent studies overwhelmingly indicate that adipose tissue is a rather active organ that secretes a variety of factors into the local environment as well as into the circulation, thus maintaining a complex communication with other organs. There is also growing evidence that adipose tissue is integrated in a complex network that serves to optimize fuel partitioning and availability. Obesity is now considered to be a state of impaired secretory function. In particular, an elevated release of inflammatory proteins is observed, possibly as a result of invading and accumulating macrophages. The key question to be answered is whether and how these secretory products are related to the pathophysiology of the metabolic and cardiovascular complications of obesity. There is at least circumstantial evidence that an impaired secretion of various adipokines from adipose tissue in the obese state is involved in the manifestation of such complications. Thus, from a medical point of view, it is extremely important to understand whether the dysfunction of adipocytes can be restored by dietary intervention or by drugs.

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