Regional differences in protein production by human adipose tissue
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Abstract
Human adipose tissue has an important protein secretory function. Cytokines, hormones, pro-
hormones and enzymes are secreted from fat cells and act in an endocrine or paracrine fashion. The
production of several of these proteins is affected by obesity; normally there is an increase in the
obese state. Protein production is, as a metabolic activity, subject to regional variations. In par-
cular, the production of leptin, angiotensinogen, interleukin-6 and plasmin activator inhibitor-1
differs between subcutaneous and visceral adipose tissue sites, but no regional differences have been
reported in the production of tumour necrosis factor α. It is possible that regional variations in
protein production by adipose tissue are of importance in some of the endocrine and metabolic
disturbances seen in various forms of obesity, such as visceral and upper-body obesity.

Introduction
It is well known that human adipose tissue is a heterogeneous metabolic organ [1]. Increased re-
lease of fatty acids from visceral fat has important effects on the liver and can explain many metabolic
abnormalities in subjects with upper-body obesity [1]. An important secretory function of adipose
tissue has been demonstrated recently; fat cells produce and secrete a number of cytokines, pro-
hormones, hormones and enzymes, which act in a paracrine or endocrine fashion [2]. The pro-
duction of most (but not all) of these proteins is increased in the adipose tissue of obese subjects,
and it is possible that increased endocrine/
paracrine activity of adipose tissue is involved in many complications of obesity, such as insulin resistance, disturbed energy homoeostasis, coagulation abnormalities and hypertension [2]. It is also possible that protein production, as a metabolic activity, varies between the human fat depots, and that such differences are of physiological and clinical importance. In this review I will discuss some aspects of the regional differences in protein production by human adipose tissue. The review will focus on leptin, tumour necrosis factor α (TNFα), plasmin activator inhibitor-1 (PAI-1), acylation-stimulating protein (ASP), interleukin-6 (IL-6) and angiotensinogen, since the regional production of these proteins is best characterized at present. The major findings are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Protein</th>
<th>Difference in subcutaneous as compared with visceral adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Increased mRNA levels and increased protein secretion</td>
</tr>
<tr>
<td>PAI-I</td>
<td>Controversial; increased as well as decreased mRNA levels and protein secretion have been reported</td>
</tr>
<tr>
<td>TNFα</td>
<td>No difference in three out of four reports.</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Increased mRNA levels</td>
</tr>
<tr>
<td>ASP</td>
<td>Increased mRNA levels of the precursor adipsin</td>
</tr>
<tr>
<td>IL-6</td>
<td>Decreased protein secretion</td>
</tr>
</tbody>
</table>

**Leptin**

The most solid data with regard to regional differences in protein production by adipose tissue are those on leptin. It was first described by Masuzaki et al. in 1995 [3], and then independently confirmed [4], that leptin mRNA levels were higher in subcutaneous than in visceral adipose tissue. Likewise, the rate of leptin release is higher from subcutaneous than from visceral adipose tissue [5]. The latter finding has been confirmed by an independent investigation [6]. The regional differences in leptin production are independent of body weight and also of variations in fat-cell size between the subcutaneous and visceral fat depots [5]. Interestingly, only subcutaneous leptin production is correlated with circulating leptin levels [5].

**PAI-1**

It is more controversial as to whether or not there are regional variations in the production of PAI-1 by adipose tissue. Two reports have found increased mRNA levels in, and PAI-1 release from, visceral fat tissue [4,7]. In these studies, non-obese subjects were investigated and PAI-1 secretion was measured after a long incubation under tissue culture conditions. In a recent study on obese subjects, using freshly isolated tissue, higher mRNA levels and more rapid PAI-1 secretion were found for subcutaneous than for visceral adipose tissue [8]. Thus it is unclear to what extent PAI-1 production by fat cells is subject to site-specific variation. It is possible that methodological factors and the type of subjects investigated (lean/obese) influenced the reported data. Another importance source of PAI-1 is the vascular bed of adipose tissue. Endothelial cells produce large quantities of PAI-1, and visceral fat tissue is much more vascularized than the subcutaneous depot. Thus the contribution of endothelial PAI-1 must be considered when intact pieces of visceral adipose tissue are used for protein and mRNA studies of the enzyme.

**TNFα**

Several independent studies have reported on TNFα mRNA levels in visceral and subcutaneous adipose tissue. In three studies there was no regional variation in gene expression [4,8,9]. However, one group of investigators found increased TNFα mRNA levels in the subcutaneous depot [10]. It should be noted, however, that the latter investigators used a semi-quantitative method to determine TNFα mRNA levels. Rates of secretion of TNFα from adipose tissue were not found to be different between the subcutaneous and visceral sites [8]. Thus, when all published data on TNFα are considered together, it is reasonable to conclude that there are no important regional variations in the production of this cytokine by human adipose tissue.
**Angiotensinogen**

There have been two independent reports on angiotensinogen mRNA levels in different adipose regions. A much higher level was demonstrated in omental than in visceral adipose tissue in both studies [9,11]. Unfortunately, protein secretion was not measured in the two investigations. Such measurements are hampered by a lack of commercially available tools for the direct measurement of the human angiotensinogen protein.

**ASP**

Adipsin is produced by fat cells and secreted into the stroma compartment of adipose tissue, where it is converted into ASP [2]. It was demonstrated that adipsin mRNA levels were higher in omental than in subcutaneous adipose tissue, but no data were reported on ASP protein production [9].

**IL-6**

There is one report on IL-6 in different adipose regions. Protein secretion rates were found to be 2–3 times higher in visceral than in subcutaneous adipose tissue [12].

**Other proteins**

Adipose tissue produces several other proteins in addition to those mentioned above. These include adiponectin, adipo Q and soluble TNFα receptors. To the best of my knowledge there are no publications regarding the regional aspects of the production of these proteins.

**Conclusions and future directions**

It is very likely that the endocrine/paracrine function of human adipose tissue, as a metabolic function, is subject to regional variations. The most solid data are on leptin and TNFα. All published reports on leptin show that gene expression and protein secretion rate are much higher in the subcutaneous than in the visceral fat depot. On the other hand, TNFα gene expression and protein production do not appear to be under regional influence, as concluded in three out of four published reports.

It is less clear if IL-6, ASP and angiotensinogen production are subject to regional variation, since only single reports have been published for each of IL-6 and ASP, and only mRNA was measured for angiotensinogen. The role of regionality in adipose tissue production of PAI-1 is confusing at present, as contradictory results have been published.

Fat distribution is markedly influenced by gender and obesity. So far there have been no reports on the interaction between gender and regional variations in the adipose tissue production of proteins. Furthermore, only one report has studied the influence of obesity on regional aspects. Therefore it remains to be established if the same or different regional variations in the adipose tissue production of proteins exist between men and women, or between lean subjects and subjects with various forms of obesity, such as upper-body, peripheral or visceral obesity.

Another question that remains to be answered is the extent to which regional variations in protein production are due to primary or environmental factors in adipose tissue. It is possible that visceral and subcutaneous fat cells are genetically distinct cells. They may originate from different pools of precursor cells. Circulatory factors or events in the stroma surrounding fat cells could also play a role. In addition, there may be a combination of primary and secondary factors responsible for regional variations in protein production (and metabolic activity) of human fat cells. These questions can best be answered by investigation of pre-adipocytes, which can be induced to proliferate and differentiate under defined conditions. However, the fact that there is no general pattern in the regional differences (i.e. production of all proteins investigated is increased in one and the same adipose site) makes it likely that primary factors are involved, at least to some extent.

What is the significance of regional variations in the paracrine/endocrine function of human adipose tissue? Unfortunately, there are no laboratory animal models available at present in which to address this question, so one has to speculate.

With regard to leptin, it has been suggested that regional variations in leptin production are of importance in determining the final size of a particular fat depot [4,8]. If we assume that subcutaneous fat cells produce more leptin than other fat cells from the beginning of adipose tissue development, then signalling between the brain and adipose tissue would be strongest for this site. This assumption is indirectly supported by the observation that only leptin production by subcutaneous adipose tissue is related to circulating leptin levels [5]. Indeed, the subcutaneous fat depot is by far the major adipose region, constituting at least 80% of all adipose tissue in both lean and obese subjects.
Increased production of angiotensinogen and adipsin in visceral fat tissue could be of importance in the development of visceral obesity. Angiotensinogen is believed to promote the proliferation and differentiation of adipose tissue [13]. If high adipsin production is accompanied by increased ASP formation, then fat accumulation would be promoted, as ASP appears to be very important for the regulation of fatty acid turnover by human fat cells [14].

Once visceral obesity has developed, such as in many overweight men, angiotensinogen production at this site could be of importance for obesity-related hypertension, because of the role of angiotensinogen in blood-pressure control through the renin system [15]. The combined effects of enlarged visceral fat mass and a regional increase in the production of angiotensinogen could be a driving force in the hypertension that occurs among viscerally obese subjects.

Adipose IL-6 may play a role in endothelial function, since the hepatic acute-phase protein (C-reactive protein) is regulated by circulating IL-6 levels [16]. Indeed, a correlation between the adipose tissue level of IL-6 and the serum C-reactive protein concentration has been demonstrated in obese subjects [17]. It is possible that visceral adipose tissue is of importance in the development of atherosclerosis in viscerally obese subjects.

One way to study the relative role of visceral adipose tissue is to surgically remove parts of this adipose depot. It is possible to remove all parts of the greater omentum, which constitutes around 10% of visceral fat, without causing significant side-effects. There is preliminary evidence that removal of this fat depot has profound effects on weight regulation and metabolic profile in obese subjects [18].

In conclusion, the protein secretory capacity of adipose tissue, which forms the basis of an important endocrine and paracrine role for this tissue, has recently been discovered. Distinct regional variations in the production of some of the secreted proteins have been reported. Further studies will tell us more about the physiological and pathophysiological impact of site-specific variations in the endocrine and paracrine activities of human adipose tissue.

References

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