Signalling role of adipose tissue: adipokines and inflammation in obesity

P. Trayhurn and I.S. Wood

Obesity Biology Unit, Liverpool Centre for Nutritional Genomics, School of Clinical Sciences, University of Liverpool, Duncan Building, Liverpool L69 3GA, U.K.

Abstract

White adipose tissue (WAT) is a major endocrine and secretory organ, which releases a wide range of protein signals and factors termed adipokines. A number of adipokines, including leptin, adiponectin, tumour necrosis factor α, IL-1β (interleukin 1β), IL-6, monocyte chemotactic protein-1, macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, plasminogen activator inhibitor 1 and haptoglobin, are linked to inflammation and the inflammatory response. Obesity is characterized by a state of chronic mild inflammation, with raised circulating levels of inflammatory markers and the expression and release of inflammation-related adipokines generally rises as adipose tissue expands (adiponectin, which has anti-inflammatory action is an exception). The elevated production of inflammation-related adipokines is increasingly considered to be important in the development of diseases linked to obesity, particularly Type II diabetes and the metabolic syndrome. WAT is involved in extensive cross-talk with other organs and multiple metabolic systems through the various adipokines.

Introduction

White adipose tissue (WAT) has become the subject of considerable activity in recent years and is now a ‘hot spot’ in biomedical research. Much of the basis for this lies in the apparently inexorable rise in the incidence of obesity and its associated disorders, obesity being defined by an expansion of adipose tissue mass. In the U.K., for example, by 2002 some 23% men and 25% women were classed as obese on the basis of a body mass index (BMI) ≥ 30 [1], while in the U.S.A. the incidence of obesity is even higher, approaching one-third of all adults [2]. What has been termed ‘the obesity epidemic’ has developed rapidly over the past two decades, the incidence in the U.K. rising 3-fold in 20 years, from just 6% of men and 8% of women in the early 1980s [3].

The rise in obesity is of considerable public health importance, the disorder being associated with a reduction in life expectancy (of ~8 years) and with an increased risk of several major diseases, particularly Type II diabetes, coronary heart disease and certain cancers (such as breast and colon). In the case of diabetes, being obese increases the risk of developing the disease by 10-fold (or more), once a BMI of 30 is reached and the more obese the greater the relative risk. The consequence of the recent surge in obesity is that the current 1.8 million diagnosed diabetics in the U.K. is expected to rise to over 3 million within the next 5–10 years.

Until recently, the storage and release of fatty acids (and allied processes) were viewed as the only significant functions of WAT, although thermal insulation and a mechanical role for the tissue were recognized. Consequently, the main focus in metabolic studies on the tissue was lipogenesis and lipolysis and the regulation of these two pathways.

Secretory function of adipose tissue

WAT is a major secretory organ responsible for the release of fatty acids, particularly during fasting. Fatty acids are not, however, the only lipid moieties secreted by the tissue; cholesterol, retinol, prostanoids and steroid hormones are also released (see [4,5]). In contrast with certain prostanoids, cholesterol and retinol are not synthesized by WAT, but rather are taken up and stored within the tissue. Steroid hormone conversions can take place in white adipocytes, such as the activation of 11-dehydrocorticosterone (cortisone in humans) into active corticosterone (cortisol) catalysed by 11β-hydroxysteroid dehydrogenase type 1 [6].

It has long been recognized that the enzyme lipoprotein lipase is released from adipocytes to elicite the breakdown of circulating triacylglycerols to fatty acids, which are subsequently stored within fat cells following uptake and re-esterification. In the late 1980s, a further secreted protein from adipocytes was identified, namely the complement-related factor adipsin [7,8]. This was initially thought to be a signal relating to energy balance, but this was subsequently found not to be the case. In the early 1990s, a major step forward in the recognition of the secretory role of WAT occurred with the discovery that the pro-inflammatory cytokine TNFα (tumour necrosis factor α) is synthesized and released by adipocytes [9]. TNFα expression increases in obesity and it was proposed that this cytokine plays an important role in the induction of insulin resistance [10,11]. Subsequently, TNFα has been shown to have extensive metabolic effects in adipose
tissue, including the stimulation of lipolysis and of apoptosis [12,13].

The critical change in perspective on the physiological role of WAT occurred in 1994 with the identification of the hormone leptin [14]. This followed the characterization of the Ob gene, which in mutated form is responsible for the obesity of the ob/ob (obese–hyperglycaemic) mouse [14]. Leptin provides a key endocrine signal to the hypothalamus in the regulation of appetite and energy balance (see [4,15,16]). Pivotal, from the perspective of WAT, the identification of leptin led to the recognition that the tissue is an endocrine organ with adipocytes being major endocrine cells. Although leptin has subsequently been shown to be synthesized in a number of other sites, including the stomach, hair follicles, ovaries and placenta, quantitatively WAT is the key locus for the production of the hormone [4,16].

Adipokines

Following adipin, TNFα and leptin, there has been a rapidly growing recognition that adipocytes secrete a wide range of protein factors [4,5,17,18]. These secreted proteins, which now amount to more than 50 different molecular entities, are generally referred to as ‘adipokines’ (a term preferable to the earlier designation of ‘adipocytokines’). The totality of adipokines, which we have termed the ‘adipokinome’, together with the lipid moieties released constitute the ‘secretome’ of fat cells [5].

The adipokines appear to be involved in a wide range of physiological processes; these include haemostasis [e.g. PAI-1 (plasminogen activator inhibitor 1)], lipid metabolism (e.g. cholesteryl ester transfer protein and apolipoprotein E), blood pressure regulation (angiotensinogen), insulin sensitivity (e.g. adiponectin, resistin and visfatin) and angiogenesis [e.g. VEGF (vascular endothelial growth factor)] [4,5,17,18]. It is not easy to perceive functional unity between the various adipokines, but many are linked to immunity and inflammation with parallels having been drawn between adipocytes and immune cells. Indeed, preadipocytes are reported to be able to act like macrophages [19,20].

Adipokines and inflammation

The list of adipokines linked specifically to the immune system and inflammation is growing rapidly. In addition to adipin and leptin (which is cytokine-like), the list includes a number of cytokines (IL-1β (interleukin 1β), IL-6, IL-10, and TGFβ (transforming growth factor-β)), chemokines (IL-8 and MCP-1 (monocyte chemotactic protein-1), MIF/β (macrophage migration inhibitory factor β)), acute phase proteins [PAI-1, haptoglobin and SAA (serum amyloid A)] and angiogenic factors (VEGF) [5,18] (Figure 1). The major adipocyte hormone adiponectin has an anti-inflammatory action [21], in addition to its role in modulating insulin sensitivity, as well as several other metabolic processes [22,23].

The expression, production and release of a number of inflammation-related adipokines is increased in adipose tissue with obesity, including TNFα, IL-6, PAI-1, haptoglobin and leptin (see [5]). The major exception to this pattern of increased production is adiponectin, the expression and circulating levels of which decline in obesity [24]; given the anti-inflammatory action of the hormone [21], this exacerbates the degree to which adipose tissue is in a state of ‘inflammation’ in the obese. Inflammation in WAT is also powerfully augmented through the infiltration of macrophages as tissue mass expands [25,26].

Inflammation in obesity

One of the key developments in obesity research over the past 4 years is the recognition that the disorder is characterized by chronic mild inflammation [27–29]. The main basis for this view is that there is an increased circulating level of several inflammatory markers in the obese; these markers include CRP (C-reactive protein), TNFα, IL-6, IL-18, MIF, haptoglobin, SAA and PAI-1 [5,18,30]. In some cases, such as CRP and IL-18, a fall in the circulating level occurs on weight reduction [31,32].

Given the observation that WAT expresses and secretes a number of inflammation-related proteins, it is probable that it is a major source of the increase in inflammatory markers in obesity. However, documenting the quantitative importance of adipose tissue to the circulating levels is difficult. Nevertheless, there is strong evidence that the tissue is quantitatively the most important source of the raised PAI-1 levels in the obese [33]. In the case of some markers, however, this is not the case. CRP appears not to be produced in significant amounts, if at all, by the tissue [5] and it is proposed that IL-6 released from adipocytes stimulates hepatic synthesis of CRP in obesity [30,34]. Similarly, we have recently found that although IL-18 is expressed by fat cells and that expression is strongly stimulated by TNFα, adipocytes in culture do not appear to release significant amounts of this cytokine and are therefore unlikely to be an important source of the circulating protein (and particularly

Figure 1 | Adipokines linked to inflammation and the inflammatory response

NGF, nerve growth factor.

Causes and consequences of inflammation in obesity

It has increasingly been considered that the inflammatory state of obesity and particularly the production of inflammatory adipokines, is important aetiologically in the development of the diseases associated with a high BMI [30,35]. Thus Type II diabetes and atherosclerosis, as well as the other components of the metabolic syndrome, have been causally linked to inflammation. This accords with the growing recognition of the importance of inflammation as a component of a wide range of diseases, including those associated with aging such as the dementias [36]. However, much work needs to be done on unravelling the mechanistic basis for the link between specific inflammatory adipokines and the metabolic syndrome.

Little attention has been paid to the question of why obesity should be accompanied by inflammation. We have argued the parsimonious view that WAT is the main site of direct inflammation in obesity, raised circulating levels of inflammatory markers largely reflecting spill over from the tissue rather than systemic inflammation [5]. If this is indeed the case, then why should adipose tissue show a growing inflammatory response as obesity develops? We have recently proposed that hypoxia may be the critical factor, the underlying proposition being that WAT mass expands clusters of adipocytes distant from the vasculature may become relatively hypoxic [5]. It is suggested that the initiation of hypoxia leads to the stimulation of the release of inflammatory cytokines, chemokines and angiogenic factors, the function of which is to increase blood flow and stimulate vascularization [5]. This has parallels with wound healing and the situation in solid tumours [37].

In considering this proposition it is important to note that WAT is not highly vascularised (in particular compared with brown fat), that the proportion of blood flow going to the tissue is decreased in obesity and that the obese do not exhibit the post-prandial increase in blood flow to the tissue that occurs in lean subjects [38,39]. The transcription factor HIF-1 (hypoxia-inducible factor-1) plays a critical role in the transduction of the metabolic response to hypoxia [37,40,41]. Indeed, it is regarded as the ‘molecular sensor of low oxygen tension’. HIF-1 is composed of α and β subunits, the β-subunit being expressed constitutively. HIF-1 is activated in hypoxia by the stimulation of the expression of the HIF-1α subunit to form the functional transcription factor [37,40,41]. HIF-1α and HIF-1 are expressed in adipocytes and hypoxia in cell culture leads to increased levels [42]. The expression of a number of genes in other tissues is sensitive to low oxygen tension, including those encoding glycolytic enzymes and the facilitative glucose transporter, GLUT1, as well as PAI-1 and VEGF [37]. Expression of two specific adipokines, leptin and VEGF, has been shown to be induced by hypoxia in adipocytes in culture [42].

Coda

It is now evident that adipocytes are key endocrine cells, releasing a large number of protein signals and factors. This indicates that WAT is tightly integrated into overall metabolic control, adipocytes being involved in extensive cross-talk with other cell types. This interaction includes other cells within the tissue, such as macrophages, as well as other organs. A potent example of the cross-talk is the two-way communication between adipocytes and the hypothalamus – through leptin and the sympathetic nervous system [4,16].

Adipocytes are not alone in having an unexpectedly large number of secretory proteins. This is now also recognized with chondrocytes [43], for example, and also perhaps of myocytes. Following the observation that on severe exercise, skeletal muscle releases large quantities of IL-6 (which stimulates lipolysis in WAT) [44], the concept of ‘myokines’ as secreted proteins from myocytes has been introduced [45]. Finally, there is the important question of whether inflammation and the release of inflammatory adipokines occurs uniquely in obesity, or whether it is characteristic of any situation where there is a marked increase in adipose tissue mass. Such physiologically programmed changes in body fat include late pregnancy and prehibernatory and premigratory fattening. In principal, universality would be expected.

Our work is funded by grants from the Biotechnology and Biological Sciences Research Council, the European Union (OB-Age: QLK6-CT-2002-02288) and the Royal Liverpool and Broadgreen University Hospitals NHS Trust. We are grateful to our colleagues for their help and support.

Received 11 July 2005