Endocrine and signalling role of adipose tissue: new perspectives on fat

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Abstract
White adipose tissue (WAT) is now recognized as a major endocrine and secretory organ, releasing a wide range of protein factors and signals termed adipokines – in addition to fatty acids and other lipid moieties. A paradigm shift came with the discovery of leptin, a pleiotropic hormone which is a critical signal to the hypothalamus in the control of appetite and energy balance. A number of adipokines, including adiponectin, tumour necrosis factor-alpha, interleukin (IL)-1β, IL-6, IL-8, IL-10, monocyte chemoattractant 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 mild inflammation, and the expression and release of inflammation-related adipokines generally rises as adipose tissue expands; a notable exception is adiponectin, with its anti-inflammatory action, the levels of which fall. WAT may be the main site of inflammation in obesity, increased circulating levels of inflammatory markers reflecting spillover from an ‘inflamed’ tissue, leading to the obesity-associated pathologies of type 2 diabetes and the metabolic syndrome. From the wide range of adipokines now identified, it is evident that WAT is highly integrated into overall physiological regulation, involving extensive crosstalk with other organs and multiple metabolic systems. Whether major changes in adipokine production in obesity, particularly of those factors linked to inflammation, are unique to this condition, or are a feature of all situations in which there are substantial increases in adipose mass (such as pregnancy, and pre-hibernatory and pre-migratory fattening) requires consideration.

Keywords adipocytes, adipokines, inflammation, obesity.

The adipose organ consists of two distinct tissues, namely brown (BAT) and white adipose tissue (WAT), and there is continuing debate on the extent to which there is inter-convertibility between them (Cinti 2001). BAT is specialized for heat production by non-shivering thermogenesis through the presence of the tissue-specific uncoupling protein-1 (UCP1) located in the inner mitochondrial membrane (Cannon & Nedergaard 2004). In brown fat, the lipid droplets (normally multiple within each brown adipocyte), are considered to serve primarily as a fuel for thermogenesis. In WAT, on the other hand, the stored triacylglycerols provide a long-term fuel reserve for the organism as a whole. Indeed, white fat is the main energy reservoir in mammals and birds, triacylglycerols providing storage at a high energy density, both because of the considerable caloric value of lipid (39.1 kJ g⁻¹ vs. 15.4–17.5 kJ g⁻¹ for carbohydrate) and because in
contrast to carbohydrate, triacylglycerols can be stored with little associated water.

Until relatively recently, the physiology of WAT centred on lipogenesis and lipolysis, and the regulation of these two opposing metabolic pathways. However, a revolution in our understanding of the biological role of white fat has occurred over the past decade; it is now recognized as a major endocrine and signalling tissue which interacts extensively with other organs in overall physiological and metabolic control. The present article considers some of the key developments in this area, focusing particularly on the adipokines and the role of white fat in inflammation and the inflammatory response.

Obesity and energy balance

The rapid escalation in the incidence of obesity, with its concomitant disorders, has been the major impetus behind much of the current work on WAT. Obesity is the most prevalent nutrition-related disorder in Westernized countries, and in the UK, for example, some 23% of adult males and 24% of adult females are now clinically obese (BMI > 30) (Rennie & Jebb 2005), while a further one-third of the population are overweight (BMI 25–29.9). The incidence of obesity has developed rapidly over the past two decades, with growing affluence (Fig. 1). In the early 1980s, just 6% of adult men and 8% of adult women in the UK were obese (Prentice & Jebb 1995). Obesity not only reduces life expectancy (by ~8 years), but there is also an increased risk of developing several major diseases; these diseases include type 2 diabetes, coronary heart disease and certain cancers. In the case of diabetes, the risk increases approximately 10-fold once a BMI of 30 is reached, and the more obese the greater the relative risk.

Paradoxically, white fat has been something of a ‘poor relation’ in energy balance and obesity research, most attention having been directed towards the perceived more complex neuroendocrine pathways involved in the hypothalamic control of food intake, together with the peripheral mechanisms of adaptive thermogenesis. The current focus on WAT reflects several factors: (1) obesity is defined by the expansion of the tissue, and should therefore be central to consideration of the disorder; (2) WAT is the primary site of the production of key hormones involved in energy balance, notably leptin; (3) proteins secreted from adipose tissue are increasingly considered to be directly linked to the pathologies associated with obesity, particularly insulin resistance and the metabolic syndrome.

Adipose tissue secretions: the adipokines

White adipocytes are now recognized to be major secretory cells (Frühbeck et al. 2001, Trayhurn & Beattie 2001, Rajala & Scherer 2003, Trayhurn & Wood 2004). Quantitatively, the most important secretion is fatty acids, of which there is a net release at periods of negative energy balance, particularly fasting and during acute cold exposure. In addition to fatty acids, several other lipid moieties are released by fat cells; these include prostanoids, which are synthesized by the tissue, and cholesterol and retinol, which are not synthesized but rather are stored and subsequently released (Trayhurn & Wood 2004). In addition, certain steroid hormone conversions can take place within white adipocytes, such as the activation of inert 11-dehydrocorticosterone (cortisone in humans) into active corticosterone (cortisol) catalysed by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (Masuzaki et al. 2001). The other major component of what can be defined as the ‘secretome’ of adipocytes (Trayhurn & Wood 2004) is a range of protein factors and signals. These secreted proteins, which we have recently argued should be referred to as ‘adipokines’ and not ‘adipocyto-

![Figure 1](image_url) The incidence of obesity (BMI, 30 or more) in the UK and its rise over the past 20 years.

The adipokines are highly diverse in terms of protein structure and of physiological function (Frühbeck et al. 2001, Trayhurn & Beattie 2001, Rajala & Scherer 2003, Trayhurn & Wood 2004), but many are linked to the immune system. They include classical cytokines [e.g. tumour necrosis factor-alpha (TNF-α), interleukin (IL)-6], growth factors [e.g. transforming growth factor-beta (TGF-β)] and proteins of the alternative complement pathway (adipsin); they also include proteins involved in the regulation of blood pressure (angiotensinogen), vascular haemostasis [e.g. plasminogen activator inhibitor-1 (PAI-1)], lipid metabolism (e.g. retinol binding protein, cholesterol ester transfer pro-
tein), glucose homeostasis (e.g. adiponectin) and angiogenesis (e.g. vascular endothelial growth factor).

The adipokine to have received most attention is leptin, a hormone that was discovered in 1994 as the product of the ob gene in the obese (ob/ob) mouse (Zhang et al. 1994). Leptin, which is a 16 000 mol. wt cytokine-like protein, is an essential signal from adipocytes to the hypothalamus in the control of food intake and energy balance. Indeed, without functional leptin severe obesity ensues – as in the ob/ob mouse (Zhang et al. 1994) and its human homologues (Montague et al. 1997, Strobel et al. 1998). Leptin is in practice a pleiotropic hormone, its functions extending far wider than appetite and energy balance to encompass a multiplicity of actions, including as a signal in reproduction and immunity (Harris 2000, Trayhurn & Beattie 2001). Although WAT is the main source of the hormone, there being a close correlation between body fat and the circulating leptin level (Considine et al. 1996, Ostlund et al. 1996), several other sites of synthesis have been identified. These include the placenta, stomach, bone (osteoblasts), mammary epithelium and cells of the hair follicles (Harris 2000, Rayner & Trayhurn 2001, Trayhurn & Beattie 2001). In each of these cases the target is likely to be local – a paracrine, rather than endocrine, action.

Much recent attention has focused on adiponectin, which appears to be produced exclusively by adipocytes; indeed, it is an abundant transcript in fat cells (Scherer et al. 1995, Maeda et al. 1996). This factor was discovered independently by several groups and consequently has been accorded different names, the most commonly used after adiponectin being acrp30 (Scherer et al. 1995, Maeda et al. 1996). In contrast to most adipokines, and leptin in particular, the expression and circulating levels of adiponectin fall in obesity (Arita et al. 1999, Hotta et al. 2000). A number of roles have been attributed to adiponectin, and these include the modulation of insulin sensitivity (Berg et al. 2001, Yamauchi et al. 2001). The hormone has also been implicated in vascular function and has an anti-inflammatory action (Ouchi et al. 1999, 2000, 2001).

Inflammation-related adipokines

A number of inflammation-related proteins are released by white adipocytes, in addition to adiponectin, and these include cytokines, chemokines and acute phase proteins (Rajala & Scherer 2003, Trayhurn & Wood 2004, Trayhurn 2005). Clear evidence for the expression and secretion of the following cytokines and chemokines has been documented: TNF-α, TGF-β, IL-β, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF). Acute phase proteins which are now clearly identified as adipokines are haptoglobin, serum amyloid-A and PAI-1. PAI-1 is also, of course, a key agent in vascular haemostasis (Skurk & Hauner 2004). In addition to these factors, several other inflammation-related adipokines are recognized, including leptin, the angiogenic protein vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) (Trayhurn & Wood 2004).

Nerve growth factor, which was the first of the family of neurotrophins to be discovered, is a recently described adipokine (Peeraully et al. 2004, Wang et al. 2005). Expression of the NGF gene has been observed in the major white fat depots of mice, as well as in human subcutaneous and omental adipose tissue, while studies on both murine and human adipocytes differentiated in culture have demonstrated that the protein is secreted from fat cells (Peeraully et al. 2004, Wang et al. 2005). The classical role of NGF is neurotrophic – as a critical factor in the growth and survival of sympathetic nerve endings (Levi-Montalcini et al. 1996) – and this is presumably part of its function in WAT (notwithstanding the limited sympathetic innervation of the tissue). However, it is also involved in immune and inflammatory responses, and in the case of white adipocytes expression and secretion of NGF are strongly stimulated by the pro-inflammatory cytokine TNF-α, in both murine and human fat cells (Peeraully et al. 2004, Wang et al. 2005). This suggests that NGF is an inflammatory response protein in adipocytes, a view supported by the subsequent observation that NGF secretion by 3T3-L1 cells is dramatically upregulated by prostaglandin PGD2 and by the J series prostaglandins, PGJ2 and Δ12-2 PGJ2 (Bulló et al. 2005).

Tumour necrosis factor-alpha has a pleiotropic effect on adipose tissue function, including the stimulation of lipolysis and apoptosis (Prins et al. 1997, Gasic et al. 1999, Ryden et al. 2004), as well as the regulation of adipokine expression. In recent studies examining the integrated effect of TNF-α on the expression pattern of inflammation-related adipokines in human white adipocytes, the most substantial responses occurred with IL-6, MCP-1, NGF and TNF-α itself, expression of each of which was strongly upregulated by the cytokine (Wang et al. 2005).

Inflammation and obesity

One of the major recent developments in obesity research is the emergence of the concept that the disorder is characterized by chronic mild inflammation (Yudkin et al. 1999, Festa et al. 2001, Engström et al. 2003). The basis for this view is that the circulating level of several cytokines and acute phase proteins associated with inflammation is increased in the obese; these inflammatory markers include C-reactive protein,
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haptoglobin, TNF-α and its soluble receptors, IL-6 and IL-18 (Yudkin et al. 1999, Festa et al. 2001, Bulló et al. 2003, Engström et al. 2003). Following from these observations is the growing view that the inflammatory state plays a causal role in the development of type 2 diabetes and the metabolic syndrome (which includes atherosclerosis, hypertension and hyperlipidaemia) associated with obesity. In this context, the reduction in adiponectin in the obese (Arita et al. 1999, Hotta et al. 2000) is of particular interest in view of the anti-inflammatory effect of this adipokine (Ouchi et al. 1999, 2000).

Given that adipocytes secrete a number of cytokines and acute phase proteins, the question arises as to the extent to which the expanded WAT mass contributes, either directly or indirectly, to the increased production and circulating levels of inflammation-related factors in obesity. In several cases, and perhaps most clearly with PAI-1, the evidence points to the tissue being an important direct contributor, while in others, such as C-reactive protein, there is an indirect role. C-reactive protein is synthesized mainly in the liver and it is evident that in obesity hepatic production and release is stimulated by IL-6 secreted from adipocytes (Yudkin et al. 2000, Yudkin 2003).

Close links between adipocytes and immune cells are increasingly apparent, and preadipocytes have been reported to act as ‘macrophage-like’ cells (Cousin et al. 1999). The inflammatory state of adipose tissue in obesity has been highlighted by recent reports demonstrating that there is extensive infiltration of the tissue by macrophages in the obese (Weisberg et al. 2003, Xu et al. 2003). The arrival of macrophages en masse is likely to lead to a considerable amplification of the inflammatory state in white fat, and TNF-α may play a pivotal role in this infiltration. Two key chemokines, MCP-1 and MIF, which are important in relation to attracting and preventing the exodus, respectively, of macrophages into a tissue are released by adipocytes (Hirokawa et al. 1997, Gerhardt et al. 2001, Sartipy & Loskutoff 2003, Skurk et al. 2005), and expression and secretion of MCP-1 is strongly upregulated by TNF-α (Gerhardt et al. 2001, Wang et al. 2005).

An important issue is why adipose tissue should mount a strong inflammatory response as fat mass expands in obesity. One possibility is that WAT is providing inflammatory mediators for a site, or sites, elsewhere in the body, whether because of inflammation in another specific locus or more systemically. However, we have recently argued the parsimonious view that WAT is itself in a state of inflammation as a reflection of local events within the tissue, with raised circulating levels of inflammatory markers reflecting spillover (Trayhurn & Wood 2004). We have further suggested that the inflammation may be a response to relative hypoxia in clusters of adipocytes distant from the capillary network as WAT mass expands, in advance of angiogenesis. Indeed, the proportion of cardiac output that goes to adipose tissue is decreased in obesity, and the obese do not show the post-prandial increase in blood flow which occurs in lean individuals (Karpe et al. 2002).

Activation of a transcription factor, hypoxia inducible factor-1 (HIF-1), through the stimulation of the expression of the HIF-1α subunit – the molecular sensor of hypoxia (Semenza 2001, Wenger 2002, Höpfl et al. 2004) – may be the mechanism through which low oxygen tension links to inflammation (Trayhurn & Wood 2004). The target genes for HIF-1 include VEGF and leptin, and expression of both of these has been shown to be stimulated in 3T3-L1 adipocytes in response to hypoxia (Lolmede et al. 2003).

Inflammation and adipose tissue in ‘physiological fattening’

Given the inflammatory events that take place in WAT in obesity, it is appropriate to consider whether the production of inflammation-related adipokines (linked to hypoxia) is also altered in the tissue during physiologically programmed increases in body fat. Examples would include late pregnancy where there may be extensive fat deposition, and in the considerable fattening that occurs in hibernating and migratory species prior to hibernation and migration, respectively. In certain species of ground squirrel, for example, body weight can double over a 3–4-month period between the spring arousal and the entrance into hibernation in late summer, most of the increase in weight being due to adipose tissue.

In this regard, it is of interest to note that the serum concentration of haptoglobin is increased in the hibernation season in bears (Mominoki et al. 1996), as is that of leptin (Hissa et al. 1998). The expression of another acute phase reactant, α2-macroglobulin, has also been shown to increase in hibernating ground squirrels, although similar changes are not evident with other acute phase proteins (Srere et al. 1995), and it is unclear whether WAT is a direct site of synthesis of the protein.

Adipose tissue and the cold

As emphasized above, much of the recent focus on the function of WAT is in the context of obesity. Interest in the mechanisms of adaptation to the cold has, of course, been principally concerned with events within BAT, but it is likely that there are extensive physiological changes in white fat as well. The total substrate flux through an animal, particularly small rodents, increases substan-
tially in a cold environment, with for example, the total energy intake of a mouse being approximately three times higher when acclimated at 4 °C than at the thermoneutral temperature of 32 °C (Trayhurn 1995). Acutely, cold exposure leads to a depletion of WAT mass to provide fuel for thermoregulatory heat production, whether in brown fat (via UCP1) or through shivering thermogenesis in skeletal muscle. This stimulation of lipolysis is driven by an increase in sympathetic activity in WAT, as indicated by measurements of noradrenaline turnover on cold exposure of rodents (Garofalo et al. 1996), paralleling the changes that occur during fasting (Migliorini et al. 1997).

There have been few reports on the effects of either acute or chronic cold exposure on adipokine production, but substantial changes would be predicted, not least because of the sympathetic activation in WAT. One of the earliest studies on leptin showed that acute exposure of mice to the cold induced a major suppression of ob gene expression in WAT (Trayhurn et al. 1995), and circulating levels of the hormone fall (Hardie et al. 1996). These changes, which are readily reversible on transfer to a warm environment, led to the proposition that there is a key role for the sympathetic nervous system in the regulation of leptin production; the sympathetic system provides a negative feedback loop to adipocytes, operating (at least in rodents) through the β3-adrenoceptor subtype (Giacobino 1996, Trayhurn et al. 1996, 1998). Although leptin expression is suppressed in WAT, as well as in brown fat, on acute cold exposure of rodents, little effect has been noted in the case of adiponectin and resistin expression, and circulating adiponectin levels are unchanged (Puerta et al. 2002).

More extensive studies need to be undertaken on the effects of cold exposure on WAT function, including chronic cold adaptation, with respect to other adipokines, particularly those associated with inflammation.

**Newly emergent adipokines**

The number and range of adipocyte secretory proteins is continuing to expand rapidly. In January 2005 alone, three major new adipokines were reported – apelin, visfatin and zinc-z2-glycoprotein (ZAG) – production of each of which was originally described in other tissues. Apelin was first identified as the endogenous ligand of the orphan G protein-coupled receptor, APJ (Tatemoto et al. 1998), and has now been found to be secreted from adipocytes (Boucher et al. 2005). It is synthesized as a 77 amino acid preprotein, which is cleaved to a 55 amino acid product and then to further products, the biologically active form apparently being apelin-36 (Tatemoto et al. 1998). Apelin expression and circulating levels are increased in hyperinsulinaemia-associated obesities, including in humans, and in cell culture its expression rises after adipocyte differentiation. Production of apelin is stimulated by insulin and it is suggested that this factor is a potential link with obesity-related changes in insulin sensitivity (Boucher et al. 2005).

Visfatin is especially intriguing in that this adipokine is highly enriched in visceral fat, in both animals and humans, and its circulating levels are also increased in obesity (Fukuhara et al. 2005). It was previously identified as pre-B cell colony-enhancing factor (PBEF), a 52 000 mol. wt cytokine expressed in lymphocytes, and importantly it appears to be an insulin mimetic, both binding to and activating the insulin receptor (Fukuhara et al. 2005). Such an action is not only surprising in itself, but also in relation to the augmented expression in visceral adipose tissue given the particular association between this fat depot and the metabolic syndrome.

Zinc-z2-glycoprotein, the third novel adipokine, is a 43 000 mol. wt glycoprotein which is synthesized by certain malignant tumours and which has been used as a marker for cancer. The protein stimulates lipid loss in cachexia, and this occurs through the activation of lipolysis (Hirai et al. 1998, Todorov et al. 1998, Sanchez et al. 1999) via β3-adrenoceptors (Russell et al. 2002). ZAG has recently been shown to be directly synthesized by white (and brown) adipocytes, there being a powerful upregulation at both the gene expression and protein levels in mice bearing the MAC16 tumour (a model for cachexia) (Bing et al. 2004). ZAG mRNA was increased 10-fold in the WAT of tumour-bearing mice, while the level of leptin mRNA was reduced some 30-fold (Bing et al. 2004). In studies using human SGBS (Simpson–Golabi–Behmel syndrome) adipocytes, ZAG has now been shown to be released from fat cells, indicating that it is an adipokine (Bao et al. 2005).

Expression of ZAG in human adipocytes is stimulated by the PPAR-γ agonist rosiglitazone and suppressed by TNF-z, and this is similar to adiponectin (Bao et al. 2005). It has been proposed that ZAG may play a local role in modulating lipolysis in WAT, the selective increase in tumour-bearing animals being responsible, at least in part, for fat depletion in cancer cachexia (Bing et al. 2004). Intriguingly, overexpression of ZAG is also reported to lead to an increase in adiponectin mRNA level in 3T3-L1 adipocytes, consistent with a linkage between these two adipokines (Gohda et al. 2003).

**Perspective**

From the wide range of protein signals and factors now identified, it is evident that WAT is a secretory
organ of considerable complexity which is highly integrated into the general homeostatic mechanisms of mammals (Fruhbeck et al. 2001, Trayhurn & Beattie 2001, Rajala & Scherer 2003, Trayhurn & Wood 2004). A corollary to the diversity of the adipokines is that WAT communicates extensively with other organs and is involved in multiple metabolic systems (Fig. 2). Co-culture studies, for example, have indicated that adipocytes directly signal to other tissues, such as the adrenal cortex and skeletal muscle (Dietze et al. 2002, Ehrhart-Bornstein et al. 2003), and there is a critical conversation between white adipocytes and the brain through leptin and the sympathetic system (Rayner & Trayhurn 2001). Extensive crosstalk between preadipocytes and adipocytes is likely, and between these cells and macrophages as part of the inflammatory response.

The emergence of the adipocyte as a key endocrine and secretory cell has been a major development, not only in the sphere of energy balance and obesity, but more generally – with growing impact in areas such as inflammation and ageing. The adipocyte is not, however, alone in its unexpected range of secreted factors; cells such as chondrocytes also release a wide range of protein signals, including many again linked to inflammation (De Ceuninck et al. 2004). Even skeletal muscle is now recognized to release large quantities of IL-6 on exercise, raising the possibility that there may be a family of ‘myokines’ (Pedersen et al. 2001, 2004), paralleling the recent evolution of the adipokines.

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