Adipose Tissue and Adipokines—Energy Regulation from the Human Perspective

Abstract

There has been a rapid rise in the incidence of obesity, primarily as a result of changes in lifestyle (diet and activity levels). Obesity has provided considerable impetus for the investigation of the fundamental mechanisms involved in the regulation of energy balance. Important developments include the identification of novel factors involved in the control of appetite, such as ghrelin, orexin A, and the endogenous cannabinoids, and the emergence of the concept of “nonexercise activity thermogenesis” (NEAT) provided new perspectives on energy expenditure. Studies on white adipose tissue have led to the recognition that it is an important endocrine organ, communicating with the brain and peripheral tissues through the secretion of leptin and other adipokines. There is a rapidly expanding list of protein factors released by white adipose tissue, including the key hormone, adiponectin. Of particular note is the range of cytokines, chemokines, and other inflammation–related proteins secreted by white fat as tissue mass rises; indeed, obesity is characterized by chronic mild inflammation. The adipokines provide an extensive network of communication both within adipose tissue and with other organs, and some are implicated directly in the pathologies associated with obesity, particularly the metabolic syndrome. Although the focus remains very much on obesity in humans, the disorder and its sequelae are also a growing concern in companion animals.
companion animals. However, in contrast to humans, an objective definition of obesity is lacking in cats and dogs, and the assessment is usually made on the basis of the “body condition score” (4). This, of course, involves a subjective element, unlike BMI, and the cut-off points for normal weight, overweight, and obesity are somewhat arbitrary with no clear reference to the amount of body fat or the threshold for the risk of type 2 diabetes and other associated diseases. As a consequence, estimates of the incidence of obesity in companion animals vary widely; in dogs, for example, these range from between 10 and 40% of the population (4–7).

We emphasize, however, that the human classification of obesity based on BMI is not without complications. Body builders, for example, have a high BMI in relation to body fat because of their large muscle mass, whereas the threshold for obesity of a BMI of 30 kg/m², based primarily on Europeans and North Americans, is now recognized as inappropriate for some other population groups, such as those in South East Asia, where a lower cut-off value is increasingly employed. This is a reflection of the fact that for a given BMI, these populations are likely to have more abdominal fat and are therefore more likely to exhibit the deleterious metabolic consequences that accompany “central obesity” (8).

**Regulation of energy balance**

The growing concern with obesity has been the main impetus behind much recent research on the regulation of energy balance, reflecting the fact that it has been axiomatic that the disorder is fundamentally a problem of energy balance. Put simply, obesity can develop only when energy intake is in excess of energy expenditure, with the differences in input and output buffered primarily by changes in fat stores. There is an underlying genetic predisposition to obesity, with distinct differences between breeds of dog, for example, in the tendency to become obese. Genetic changes do not provide an explanation, however, for the present surge in the incidence of obesity in human populations (or in cats and dogs). The rise in obesity is, in practice, a consequence of changes in lifestyle (diet and the levels of physical activity) in both humans and companion animals.

At a mechanistic level, major developments have occurred recently in the control of energy balance through the identification of novel factors involved in appetite, such as ghrelin, orexin A, and the endogenous cannabinoid system (9–12). Similarly, important developments in our understanding of energy expenditure have come through the emergence of the concept of “nonexercise activity thermogenesis” (NEAT) (13), together with the discovery of new mitochondrial uncoupling proteins (UCP), primarily UCP2 and UCP3 (12). However, these novel uncoupling proteins are no longer thought to provide an immediate locus for adaptive thermogenesis in tissues outwith brown fat (14).

The primary buffering of energy intake and expenditure is through fatty acid deposition (as triacylglycerols) and release in white fat, an organ that until recently was considered a “poor relation” in energy balance and obesity research. However, this has changed radically over the past few years with the tissue becoming a focus of intense research activity. There are several reasons for this change in position: 1) obesity is defined by the expansion of the tissue, which therefore has to be central in the consideration of the disorder; 2) white adipose tissue (WAT) is the primary site of the production of key hormones involved in energy balance, notably leptin; 3) the tissue secretes a number of factors involved in a range of metabolic and physiological
processes; some of these factors are implicated in the pathologies associated with obesity, particularly insulin resistance and the metabolic syndrome (15,16).

**White adipose tissue**

The apparent simplicity of both white adipocytes and of WAT itself, histologically and metabolically, is the key reason why the organ has been relatively ignored until recently. With triacylglycerols constituting up to 85% of tissue weight, it is not surprising that WAT was regarded as essentially limited in function to lipid synthesis and breakdown. The simplicity is, however, illusory. At the cellular level, there is considerable heterogeneity, with mature adipocytes accounting for no more than half of the total cell content of white fat, the tissue containing fibroblasts, endothelial cells, preadipocytes, and macrophages, for example (17–19). Complexity is also evident at the level of the basic process of glucose transport into white adipocytes; of the 14 members of the facilitative glucose transporter (GLUT) gene family (gene name SLC2A), as many as 8, GLUT1, GLUT3, GLUT4, GLUT5, GLUT8, GLUT10, GLUT12, and HMIT, are expressed in white adipocytes (20; Yao, Wood, and Trayhurn, unpublished observations). Thus, the process of sugar uptake into white adipocytes is thought to involve a range of different transport proteins, each with its own distinct kinetic characteristics, and at least one (GLUT4) displaying insulin sensitivity.

WAT is a major secretory organ, particularly through the release of fatty acids during fasting. The tissue also releases other lipid moieties, such as cholesterol, retinol, steroid hormones, and prostaglandins (21). 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 to corticosterone catalyzed by 11β-hydroxysteroid dehydrogenase type 1 (22). The enzyme lipoprotein lipase is released from adipocytes for the breakdown of circulating triacylglycerols to fatty acids, which are subsequently stored within fat cells. In the late 1980s, a further secreted protein from adipocytes was identified, namely, adipin, a complement–related factor (23,24). Adipin was initially thought to be a direct signal in energy balance, but this was subsequently found not to be the case.

A major step forward in the recognition of the secretory role of WAT occurred in the early 1990s with the discovery that the proinflammatory cytokine tumor necrosis factor–α (TNF–α) is synthesized and released by adipocytes (25). TNF–α expression increases in obesity, and this cytokine plays an important role in the induction of insulin resistance (26,27). TNF–α was shown to have extensive metabolic effects in adipose tissue, including the stimulation of lipolysis and apoptosis (28,29).

The pivotal change in perspective on the role of WAT as a secretory organ came with the identification of the hormone leptin in 1994 (30). This followed the search for the Ob gene, a mutation in which is responsible for the obesity of the ob/ob mouse (30). Leptin, a 16,000 MW cytokine–like protein, is a critical hormonal signal from adipocytes in the regulation of appetite and energy balance (21,31,32), interacting with several hypothalamic orexigenic and anorexigenic pathways. Thus, the neuropeptide Y, melanin–concentrating hormone, orexin A, agouti–related peptide, and cannabinoid systems have each been reported to be inhibited by leptin (33–37). In contrast, the key anorexigenic systems of pro–opiomelanocortin/melanocortin, cocaine– and amphetamine–regulated transcript, and corticotrophin–releasing hormone are
upregulated by the hormone (33, 34, 37, 38). These multiple effects of leptin result in a powerful suppression of food intake.

In addition to inhibiting intake, leptin plays a role in the regulation of energy expenditure; a potent example of this comes from overfeeding studies on normal and ob/ob mice. In one study, lean mice fed a “cafeteria diet” overate by ~70% in energy terms with no additional energy deposition; this is a powerful illustration of the much debated phenomenon of diet–induced thermogenesis (39, 40). Serendipitously, in this particular study, the energy intake of the lean mice fed the cafeteria diet was the same as that of ob/ob mice fed a standard laboratory diet. However, the rate of energy deposition of the obese was 3 times that of the lean (39). Thus, the ob/ob mutants lacking functional leptin had a greatly reduced capacity for diet–induced thermogenesis.

**Adipokines**

The identification of leptin led to the recognition that white fat is an important endocrine organ. Indeed, it is now evident that white adipocytes secrete a multiplicity of protein signals and factors (Fig. 1), termed *adipokines* (15, 16, 21, 41). The diversity of the adipokines is considerable, in terms of both protein structure and function. The adipokines encompass classical cytokines (e.g., TNF-α, IL-6), chemokines [e.g., monocyte chemoattractant protein–1 (MCP–1)], proteins of the alternative complement system (e.g., adipsin), and proteins involved in vascular hemostasis [e.g., plasminogen activator inhibitor–1 (PAI–1)], the regulation of blood pressure (angiotensinogen), lipid metabolism (e.g., cholesteryl ester transfer protein, retinol binding protein), glucose homeostasis (e.g., adiponectin), and angiogenesis [e.g., vascular endothelial growth factor (VEGF)].

![FIGURE 1](https://example.com/figure1.png)

**FIGURE 1**

Major adipokines secreted from white adipose tissue. The figure shows some of the key adipokines, particularly those linked to inflammation. TGF–β, transforming growth factor–β; ZAG, zinc–α2–glycoprotein.

From the wide range of adipokines identified over the past few years, it is apparent that white fat is a secretory organ of considerable complexity that is closely integrated into overall physiological and metabolic control (15, 16, 21, 41). A corollary to the secretion of such a wide
range of protein signals and factors is that WAT communicates extensively with other organs. Co-culture studies indicated, for example, that adipocytes signal directly to other tissues such as the adrenal cortex (42), and there is a distinct cross-talk between white adipocytes and the brain through leptin and the sympathetic nervous system (32). Indeed, the sympathetic system plays an important role in the regulation of leptin production in white adipocytes (32), whereas leptin stimulates the sympathetic activity in several organs, including the kidneys and brown adipose tissue (43).

A number of adipokines are linked to inflammation and the immune response (Fig. 1), and parallels have been drawn between adipocytes and immune cells. Indeed, preadipocytes are reported to be able to act like macrophages (44,45). The inflammation-related adipokines include cytokines, chemokines, and acute phase proteins (15,16,46). Clear evidence for the expression and secretion of the following cytokines and chemokines has been documented: TNF-α, transforming growth factor-β, IL-1β, IL-6, IL-8, IL-10, MCP-1, and macrophage migration inhibitory factor. Acute phase proteins that have been clearly identified as adipokines are haptoglobin, serum amyloid-A, and plasminogen activator inhibitor-1 (PAI-1). PAI-1 is also, of course, a key agent in vascular hemostasis (47).

In addition to these factors, several other inflammation-related adipokines are recognized, including leptin, the angiogenic protein VEGF, and the first of the family of neurotrophins to be discovered, namely, nerve growth factor (NGF) (16,48,49). Importantly, the major adipocyte hormone adiponectin has an anti-inflammatory action (50) in addition to its role in insulin sensitivity and several other metabolic processes (51,52).

**Inflammation in obesity**

The expression and release of a number of inflammation-related adipokines, including IL-6, TNFα, PAI-1, haptoglobin, and leptin (16), are increased in adipose tissue with obesity. There is, however, an important exception to this general pattern of increased production; the expression and circulating levels of adiponectin decline in obesity (53). Because adiponectin has an anti-inflammatory action (59), this exacerbates the extent to which adipose tissue is in a state of “inflammation” in the obese. Inflammation in WAT is now thought to be powerfully augmented in obesity through the infiltration of macrophages as tissue mass expands (18,19).

Inflammation is one of the most important developing areas in obesity biology; the obese state was recognized recently as characterized by chronic low-grade inflammation (54–57). The main basis for this view is that the circulating levels of several markers of inflammation, such as IL-6, IL-18, C-reactive protein, PAI-1, and haptoglobin, are elevated in obesity and are reduced with weight loss (54,56,58,59). Given that WAT secretes a wide range of inflammation-related adipokines, it is probable that the tissue is the source of at least some of the elevated plasma levels of these factors in the obese.

It is increasingly thought that the mild inflammatory state of obesity, and particularly the production of inflammatory adipokines, is important in the development of the diseases associated with a high BMI (60). In particular, insulin resistance, type 2 diabetes, and atherosclerosis, as well as other components of the metabolic syndrome, were causally linked to inflammation. This parallels the growing recognition of the importance of inflammation as an element in a wide range of diseases, including those associated with aging such as the dementias.
However, much work must be done to unravel the mechanistic basis for the link between specific inflammatory adipokines and the metabolic syndrome.

The reason why obesity should be accompanied by inflammation has received little attention. We recently argued the parsimonious view that given the increased production of inflammation-related adipokines in WAT, the tissue is the main site of direct inflammation in obesity, and raised circulating levels of inflammatory markers reflect spillover from fat rather than serve as an indication of systemic inflammation (16). We argued further that this occurs as a response to hypoxia, proposing that as WAT mass expands in obesity, pockets of adipocytes distant from the vasculature become relatively low in oxygen (16). Hypoxia then leads to the stimulation of the production and release of inflammatory cytokines, chemokines, and angiogenic factors to stimulate blood flow and increase vascularization (16). This general proposal has parallels with the metabolic responses in wound healing and to the events within solid tumors (62), and involves the recruitment of the transcription factor hypoxia inducible factor–1, which is regarded as the molecular sensor of low oxygen tension (63, 64).

**Perspectives**

The continuing increase in the incidence of obesity and its associated disorders in affluent populations will provide an ongoing focus for investigation of the fundamental mechanisms of energy regulation. The radical change in how white fat is viewed has led to adipose tissue biology becoming a “hot” area of biomedical research. White adipocytes are key endocrine and secretory cells that release a wide range of regulatory factors. There is extensive cross-talk between white adipocytes and other cells and tissues through both endocrine and paracrine signaling. The local communication between adipocytes and macrophages within WAT is critical in the inflammatory response exhibited in the tissue in obesity, and perhaps other situations in which body fat increases, particularly because of the link between inflammation and the metabolic syndrome.

The cross-talk within WAT is likely to include preadipocytes as well as macrophages and mature adipocytes, and this will be central to the local regulation of adipogenesis.

The endocrine link between WAT and the hypothalamus through leptin is a critical component of the regulation of appetite and energy balance. There has been much interest in whether other adipokines also act centrally as signals in energy balance, with possible candidates including IL-6. However, there is recent evidence that adiponectin, a major adipocyte-derived hormone, plays a direct role in the regulation of energy balance. This pleiotropic adipokine reduces body weight and, intriguingly, appears to do so without affecting appetite, the central action involving stimulation of energy expenditure (65). The effect on expenditure may occur through the melanocortin system and involve, at least in part, an activation of brown adipose tissue thermogenesis (65).

Given the public health concern with obesity, most studies have inevitably focused directly on humans or laboratory rodents as models. Many of the concepts that have been established in these species are likely, however, to be applicable to companion animals. With a view to exploring the link between inflammation and obesity–associated diseases in dogs, we recently began exploring the extent to which canine adipose tissue synthesizes inflammatory adipokines. The early results indicate that the major canine WAT depots are able to express the genes encoding a range of adipokines, including adiponectin, leptin, IL–6, PAI–1, haptoglobin, NGF, and TNFα (66). Furthermore, expression takes place in the adipocytes themselves, as demonstrated
through fractionation of freshly isolated tissue and after differentiation of fibroblastic preadipocytes into mature adipocytes in primary culture (66). Thus, canine WAT appears similar to the human and rodent tissue in its ability to produce major inflammatory adipokines.

The similarities between the metabolic syndrome in dogs and humans (67), together with the availability of the canine genome sequence (68), suggest that rapid progress can be made in exploring the links among WAT, adipokines, inflammation, and metabolic disease in companion animals.

Footnotes

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5 Abbreviations used: MCP–1, monocyte chemoattractant protein–1; NEAT, nonexercise activity thermogenesis; NGF, nerve growth factor; PAI–1, plasminogen activator inhibitor–1; TNFα, tumor necrosis factor–α; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

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