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Plenary Lecture

The biology of obesity

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Obesity is a multidisciplinary area, the 'biology' of which encompasses: (1) the fundamental mechanisms of energy balance and its regulation; (2) the biological basis for the development of obesity; (3) adipose tissue function; (4) the biological description of the obese state; (5) the pathological consequences of obesity; (6) the physiological basis for treatment strategies. At a mechanistic level, important developments in recent years include the identification of novel neuroendocrine factors in the control of appetite (such as cocaine- and amphetamine-regulated transcript, the orexins, the endocannabinoids) and the discovery of new peripheral signals (such as leptin, ghrelin). Despite the identification of additional uncoupling proteins (UCP2, UCP3), mitochondrial uncoupling in brown adipose tissue through UCP1 remains the only major mechanism for adaptive thermogenesis. White adipose tissue (WAT) has now moved centre stage in energy balance and obesity research, and there are three main reasons: (1) it is the organ which defines obesity; (2) it is the source of a critical endocrine signal in the control of body weight; (3) it secretes a range of diverse protein factors, termed adipokines, some of which are directly implicated in the pathologies associated with obesity. WAT is now recognised as a key endocrine organ, communicating both with the brain and peripheral tissues through the adipokines. Obesity is characterised by mild inflammation, and WAT may be the main locus of the inflammatory state, producing cytokines, chemokines, acute-phase proteins and angiogenic factors. It has been suggested that inflammation in obesity is principally an adaptive response to hypoxia in clusters of adipocytes within the expanding adipose mass.

Adipokines: Appetite: Energy balance: Inflammation: Obesity: White adipose tissue

Obesity is now very much a multidisciplinary field, encompassing public health, social, cultural, behavioural and political dimensions, in addition to the strictly biological. In the UK the political dimension is symbolised by a recent enquiry and report on obesity from the House of Commons Health Committee (2004). While in some respects the fact that obesity is now on the political agenda may be welcomed, it is appropriate to be cautious, given the risk that it will become viewed as an issue that is remedied primarily through Government action, thereby minimising the role and responsibilities of the individual in terms of lifestyle decisions, i.e. diet and physical activity.

Given the present multidisciplinary nature of obesity, it is appropriate to consider the particular contribution that biologists and medical scientists have to make to a field that has been until recently very much our own. The question is perhaps best answered by defining the landscape covered by the 'biology of obesity'; this landscape encompasses the following:

the fundamental mechanisms of energy balance and its regulation (genes, appetite, energy expenditure, endocrine factors);
the biological basis for the development of obesity (again genes, appetite, energy expenditure);

Abbreviations: NGF, nerve growth factor; WAT, white adipose tissue.

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adipose tissue function;
the biological description of the obese state (particularly physiological adaptations);
the pathological consequences of obesity (mechanistic basis of associated disorders);
the physiological basis of treatment strategies (nutritional, behavioural, pharmacological).

In addition to genomics, the field requires the application of transcriptomics, proteomics and metabolomics, as well as more classical physiological approaches. In the present overview some selected aspects of the biology of obesity are considered.

Energy balance

It has long been axiomatic that obesity is fundamentally a problem of energy balance. Put simply, obesity can only develop when energy intake is in excess of energy expenditure, differences in input and output being buffered primarily by changes in the fat stores. Understanding the basis of how the balance between intake and expenditure is regulated has been a longstanding challenge in fundamental biology. The simplicity of the energy balance equation has led to an inappropriate focus on obesity as being either a problem of food intake control or of energy expenditure; in practice, a rather more holistic and integrative approach is required.

There are two immutable 'Laws of Obesity': (1) that for obesity to develop intake must be in excess of expenditure; (2) obese subjects have a higher energy expenditure, and therefore a higher average energy intake, than lean subjects. The first is a reflection of the Laws of Thermodynamics, while the second is the result of energy expenditure studies carried out from the late 1970s (Prentice *et al*. 1986, 1996; Bandini *et al*. 1990). These studies demonstrate that obese subjects have a higher 24 h energy expenditure than lean subjects, indicating that their habitual intake is greater when they are weight stable or in energy balance (Prentice *et al*. 1986, 1996). The higher expenditure reflects, of course, the additional energy costs associated with a greater body mass.

The difficulty in undertaking in man long-term energy balance studies with the required degree of precision has been a key reason for the extensive focus on animal models, and on laboratory rodents in particular. A number of such models are available, including those in which obesity is induced by dietary manipulation (e.g. high-fat diet), endocrinologically (e.g. by administration of corticosteroids or neuropeptide Y), surgically (lesions of the ventromedial hypothalamus), chemically (e.g. gold thioglucose administration) or through transgenics (e.g. uncoupling protein 1, 11β-hydroxysteroid dehydrogenase-1 and melanocortin-4 receptor knockouts; Lowell *et al*. 1993; Huszar *et al*. 1997; Masuzaki *et al*. 2001). In addition, several spontaneous mutations that lead to frank obesity have long been recognised (single gene mutants such as *ob/ob* and *db/db* mice), as well as physiologically-programmed fattening during the normal life cycle (e.g. pregnancy, and seasonal obesity in hibernators and migratory birds; see Trayhurn, 1984).

One of the most interesting approaches is that recently reported using genome-wide RNA interference analysis of the fat regulatory genes in the worm *Caenorhabditis elegans* (Ashrafi *et al*. 2003). In this study the estimated 16 737 worm genes were systematically suppressed using RNA interference, and 417 of these inactivations were found to result in alterations in body fat. Of these inactivations, 305 reduce body fat while 112 lead to increases (Ashrafi *et al*. 2003). Although a number of the genes identified were predictable on the basis of mammalian studies, some were not. For example, inactivation of glyceraldehyde 3-phosphate dehydrogenase, the dopamine receptor or a K^+ channel was found to result in a reduction in body fat. In contrast, inactivation of the glutamate receptor or a chemoreceptor leads to increased fat. This type of approach has the potential to widen the possible systems involved in body fat regulation and to identify novel candidate genes in studies on the genetic basis of obesity. However, it does not follow that the homologue to a *C. elegans* gene will necessarily exert the same influence physiologically on body fat in man.

Appetite and energy expenditure

There have been a number of major developments in recent years in the understanding of the central hypothalamic control of food intake. New orexigenic systems have been identified, adding to those such as neuropeptide Y that have been recognised for some time. Thus, the orexins (orexin A induces acute hyperphagia, while orexin B has little effect on intake) and the endogenous cannabinoids (e.g. anandamide) are both recent additions to the orexigenic pathways (Sakurai *et al*. 1998; Arch, 2000; Berry & Mechoulam, 2002; Rodgers *et al*. 2002; Harrold & Williams, 2003). On the other hand, novel anorexigenic factors have been identified, such as cocaine- and amphetamine-regulated transcript (Kristensen *et al*. 1998; Thim *et al*. 1998).

Several peripheral signals are recognised in the regulation of food intake, with much recent focus on ghrelin and peptide YY. Ghrelin, a twenty-eight amino acid polypeptide discovered in 1999, is released principally from the stomach and the upper small intestine (Kojima *et al*. 1999; Nakazato *et al*. 2001). It is an unusual peripheral signal in that it stimulates, rather than inhibits, food intake, with chronic administration leading to obesity (Kojima & Kangawa, 2002; Wang *et al*. 2002). Peptide YY (3–36) is released from the gastrointestinal tract in response to a meal, and opposes neuropeptide Y action by competing with neuropeptide Y as an antagonist to the Y2 receptor (Batterham *et al*. 2002; Batterham & Bloom, 2003).

The best-characterised peripheral signal is leptin, which is secreted principally from the white adipose tissue (WAT) depots (although it is also synthesised in other tissues such as the placenta and cells of the hair follicle; Trayhurn *et al*. 1999; Harris, 2000; Rayner & Trayhurn, 2001). This cytokine-like hormone interacts with several orexigenic and anorexigenic pathways in the hypothalamus (Fig. 1). Thus, the neuropeptide Y, melanin-concentrating hormone, orexin A, agouti-related peptide and cannabinoid systems have each been reported to be inhibited by leptin (Schwartz *et al*. 1996; Meister, 2000; Di Marzo *et al*. 2001;

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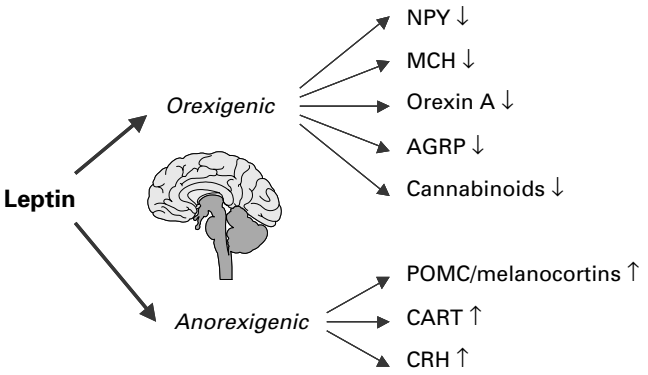

Fig. 1. Schematic view of the integrative effect of leptin on appetite through the regulation of hypothalamic neuroendocrine factors. NPY, neuropeptide Y; MCH, melanin-concentrating hormone; AGRP, agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotrophin-releasing hormone.

Wilding, 2002; Zhu *et al*. 2002). On the other hand, the anorexigenic systems of pro-opiomelanocortin/melanocortin, cocaine- and amphetamine-regulated transcript and corticotrophin-releasing hormone are up regulated by the hormone (Schwartz *et al*. 1996; Kristensen *et al*. 1998; Meister, 2000; Wilding, 2002). These combined effects of leptin lead to a powerful suppression of food intake. Indeed, in genetically-obese *ob/ob* mice, which have a mutation in the leptin gene such that the functional hormone is not synthesised, administration of recombinant leptin can reduce food intake by up to three-quarters (Mercer *et al*. 1996).

One of the continuing issues in the biology of obesity has been the extent to which changes, or adaptations, in energy expenditure (variations in energetic efficiency) are central to the development of the disorder. This issue led to one of the dominant themes of obesity research between the mid 1970s and early 1990s, i.e. the functional importance of thermogenesis. Despite a large number of studies being conducted, little compelling evidence has emerged on the general importance of thermogenesis in energy balance and the development of obesity in man. However, the late Michael Stock, in his masterful Wasserman Prize Lecture in 1999 (Stock, 1999), proposed that the protein content of the diet is the key, thermogenesis being exhibited when the protein level is low.

Animal studies have provided much more clear-cut results, which are encapsulated by two different types of study. Pair-feeding young *ob/ob* mice to the *ad libitum* food intake of lean siblings results in a rate of energy deposition in the obese mice that is more than two times that of the lean mice, with a corresponding increase in gross efficiency (Thurlby & Trayhurn, 1979). Such a difference can only result from the *ob/ob* mice having a lower energy expenditure, which has been attributed primarily to a reduction in brown adipose tissue thermogenesis (Trayhurn, 1984; Himms-Hagen, 1989). In contrast, the classic studies of Rothwell and Stock (Rothwell & Stock, 1979, 1981; Rothwell *et al*. 1982) in which overfeeding was induced by the provision of a variable and palatable 'cafeteria diet', have demonstrated that much of the extra intake, certainly of younger rats, is not deposited but rather is dissipated as diet-induced thermogenesis.

A potent example of the phenomenom of diet-induced thermogenesis, which also demonstrates differences between genotypes, is exhibited by a study of overfeeding conducted on lean and *ob/ob* mice. Lean mice fed a cafeteria diet overate by approximately 70% in energy terms, there being no additional energy deposition, which is a powerful illustration of diet-induced thermogenesis (Trayhurn *et al*. 1982). Serendipitously, in this particular study the energy intake of the lean mice fed the cafeteria diet was found to be the same as that of *ob/ob* mice fed a standard laboratory diet. However, the rate of energy deposition of the obese mice was shown to be three times that of the lean mice (Trayhurn *et al*. 1982). In other words, the *ob/ob* mice lacking functional leptin have a greatly reduced capacity for diet-induced thermogenesis (Fig. 2). This finding, in turn, is a clear demonstration of the importance of leptin in energy expenditure, as well as its confirmed role in the central regulation of appetite.

Despite much effort having been committed to identifying putative metabolic systems for adaptive thermogenesis, there is little evidence for the quantitative importance of any process other than the uncoupling of oxidative phosphorylation through uncoupling protein-1 in brown adipose tissue mitochondria (Cannon & Nedergaard, 2004; Rousset *et al*. 2004). Initial expectations that the new uncoupling proteins, uncoupling proteins 2 and 3 and brain mitochondrial carrier protein (uncoupling protein 5), might provide a mechanism for thermogenesis in organs outwith brown fat have been disappointed (Ricquier & Bouillaud, 2000; Rousset *et al*. 2004). The function of these proteins now seems to be more concerned with fatty acid utilisation, or protection from reactive oxygen species, than with thermogenesis *per se* (Dulloo & Samec, 2001; Rousset *et al*. 2004).

White adipose tissue

The primary buffering of energy intake and expenditure is through triacylglycerol deposition and release in WAT, an organ that until recently has been something of a 'Cinderella' in energy balance and obesity research. However, over the past few years WAT has moved centre stage, for which there are three primary reasons. First, obesity is defined by the expansion of white fat mass, and it is therefore unsurprising that the tissue should be of major interest to those researchers concerned with the disease (researchers concerned with colon cancer, for example, would find it eccentric not to focus on events in the colon). Second, adipose tissue is now recognised as a source of endocrine signals, particularly leptin, in the regulation of energy balance (Frühbeck *et al*. 2001; Rayner & Trayhurn, 2001). Third, the tissue secretes a number of factors involved in a range of metabolic and physiological processes, some of these factors having been implicated in the pathologies associated with obesity (Frühbeck *et al*. 2001; Trayhurn & Beattie, 2001; Rajala & Scherer, 2003; Trayhurn & Wood, 2004).

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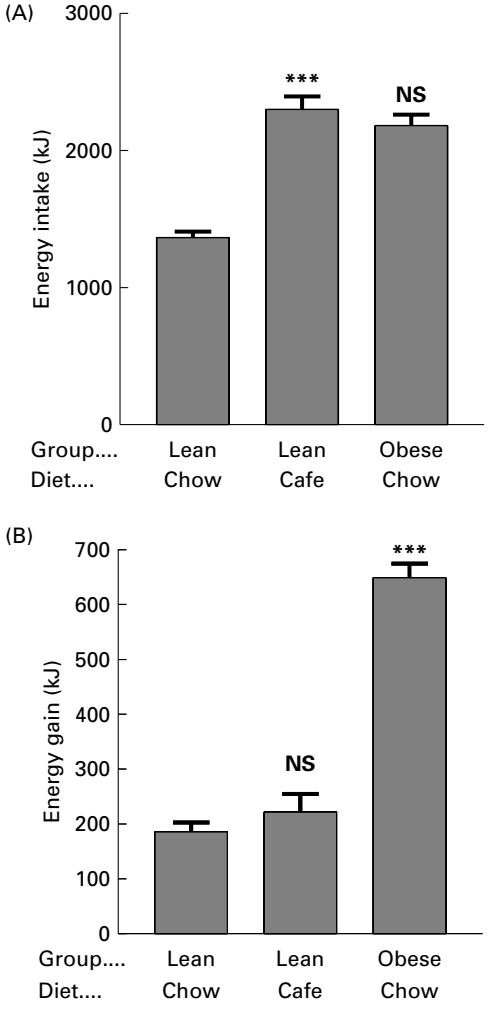

Fig. 2. Diet-induced thermogenesis in lean mice and its attenuation in *ob/ob* mutants lacking functional leptin. Lean and *ob/ob* mice were fed *ad libitum* either a standard laboratory diet (chow group) or given access to a 'cafeteria' diet (cafe group), and (A) energy intake and (B) energy gain was measured. Values are means with their standard errors represented by vertical bars. (A) Mean value was significantly different from that for the lean chow group: $^{***}P < 0{\cdot}001$. Mean value for obese chow group was not significantly different from that for the lean cafe group. (B) Mean value was significantly different from that for the lean café group: $^{***}P < 0{\cdot}001$. Mean value for lean cafe group was not significantly different from that for the lean chow group. (Adapted from Trayhurn *et al.* 1982.)

The apparent simplicity of WAT, and of white adipocytes in particular, both histologically and metabolically, is perhaps the central reason why the organ has been relatively ignored until recently. With triacylglycerols constituting ≥85% of the tissue weight, there being only a 'thin skim' of cytoplasm between the fat droplet and the plasma membrane, it is unsurprising that the tissue has been regarded as essentially limited in function to lipid synthesis and breakdown. The simplicity is, however, illusory. A direct illustration of this misconception comes from the number of glucose transporters that adipocytes express. There are some fourteen members of the facilitative glucose transporter gene family (gene name SLC2A), and white adipocytes appear to express as many as eight members: GLUT1, GLUT3, GLUT4, GLUT5, GLUT8, GLUT10, GLUT12, H^+-coupled *myo*-inositol transporter (Wood *et al*. 2003; Wood & Trayhurn, 2003; S Yao, IS Wood and P Trayhurn, unpublished results). Thus, even the basic process of sugar uptake into white adipocytes appears to involve a range of different transport proteins, each of which has its own distinct kinetic characteristics, with at least one (GLUT4) being insulin sensitive.

Secretory role of white adipose tissue: adipokines

Quantitatively, the most important secretory product of white adipocytes is fatty acids. The tissue also releases other lipid moieties, such as cholesterol, retinol, steroid hormones and prostaglandins (see Trayhurn & Beattie, 2001). These substances are, however, not synthesised *de novo* within fat cells, although certain steroid transformations can take place. It was the discovery of the cytokine-like hormone leptin in 1994 that led to the recognition that WAT is an important, indeed critical, endocrine organ (Zhang *et al*. 1994). Although the release of some other proteins, including adipsin, lipoprotein lipase and TNF-α (Cook *et al*. 1987; Hotamisligil *et al*. 1993) had been described, the broader secretory role of adipocytes was not recognised.

It is now evident, however, that white adipocytes secrete a multiplicity of protein signals and factors, now generally termed adipokines (Frühbeck *et al*. 2001; Trayhurn & Beattie, 2001; Rajala & Scherer, 2003; Trayhurn & Wood, 2004). The diversity of the adipokines, both in terms of protein structure and of function, is considerable. The group includes classical cytokines (e.g. TNF-α, IL-6), growth factors (e.g. transforming growth factor-β), proteins of the alternative complement system (e.g. adipsin, acylation-stimulating protein) and proteins involved in vascular haemostasis (e.g. plasminogen activator inhibitor-1, tissue factor), 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), as well as acute-phase and stress responses (e.g. haptoglobin, metallothionein).

From the wide range of protein signals and factors already identified it is evident that WAT is a secretory organ of considerable complexity that is highly integrated into the overall physiological and metabolic control systems of mammals (Frühbeck *et al*. 2001; Trayhurn & Beattie, 2001; Rajala & Scherer, 2003; Trayhurn & Wood, 2004). A corollary to the secretion of such a wide range of adipokines is that WAT communicates extensively with other organs. Co-culture studies have indicated, for example, that adipocytes directly signal to other tissues such as skeletal muscle and the adrenal cortex (Dietze *et al*. 2002; Ehrhart-Bornstein *et al*. 2003). There is also, in particular, a distinct cross talk between white adipocytes and the brain through leptin and the sympathetic nervous system (Rayner & Trayhurn, 2001).

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Novel factors recently identified as being produced by white adipocytes include zinc-α2 glycoprotein (Bing *et al*. 2004). This 43 000-molecular weight glycoprotein is synthesised by certain malignant tumours and has been used as a marker for cancer (Diez-Itza *et al*. 1993; Hale *et al*. 2001). Recent studies indicate that it stimulates lipid loss in cachexia, which occurs through the activation of lipolysis (Hirai *et al*. 1998; Todorov *et al*. 1998; Sanchez *et al*. 1999). Indeed, zinc-α2 glycoprotein appears to act like a β3-adrenoceptor agonist, which is surprising given its structure (Russell *et al*. 2002). The protein has now been shown to be synthesised by white (and brown) adipocytes, there being a powerful up-regulation at both the gene expression and protein levels in mice bearing the MAC16 tumour (a model for cancer cachexia); zinc-α2 glycoprotein mRNA has been found to be increased tenfold in the WAT of tumour-bearing mice, while the level of leptin mRNA is reduced thirtyfold (Bing *et al*. 2004). It has been proposed that zinc-α2 glycoprotein 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. Recent studies (Y Bao, C Bing and P Trayhurn, unpublished results) now indicate that zinc-α2 glycoprotein is secreted from human adipocytes in culture, indicating that it is a genuine adipokine.

A further recently-identified adipokine is nerve growth factor (NGF), which is likely to be a key component of the communication between adipocytes and sympathetic neurones. This target-derived neurotrophin is expressed in each of the major WAT depots in mice, with expression being primarily in the mature adipocytes, as well as in human fat depots (Peeraully *et al*. 2004). NGF is secreted from 3T3-L1 adipocytes in cell culture, and a number of factors have been shown to modulate both NGF gene expression and protein secretion *in vitro* (Peeraully *et al*. 2004). The sympathetic agonists noradrenaline, isoprenaline and a selective β3-adrenoreceptor agonist have only a small inhibitory effect; thus, in contrast to brown adipose tissue, the sympathetic nervous system is not an important regulator of NGF production in white adipocytes. Insulin, dexamethasone and rosiglitazone (a PPARγ agonist), together with IL-6, are also inhibitory. The inhibitory effect is especially marked with dexamethasone and rosiglitazone, and this may relate to their anti-inflammatory action.

A powerful effector of NGF expression and secretion is the pro-inflammatory cytokine TNF-α, which is strongly stimulatory. Treatment with TNF-α increases NGF mRNA levels in 3T3-L1 adipocytes by ninefold, while the release of NGF into the medium rises thirty- to fortyfold (Peeraully *et al*. 2004). Such a potent effect suggests that NGF is involved in inflammation in white adipocytes, which is consistent with findings from studies on other tissues that the factor is not only a target-derived neurotrophin, but is also involved in immune and inflammatory responses (Levi-Montalcini *et al*. 1996; Vega *et al*. 2003).

Inflammation

NGF is one of a number of inflammation-related proteins released by white adipocytes (Fig 3). These factors include the cytokines TNF-α, IL-β, IL-6, IL-8 and IL-10, and the acute-phase proteins haptoglobin, serum amyloid-A and plasminogen activator inhibitor-1; plasminogen activator inhibitor-1 is also, of course, a key agent in vascular haemostasis (Rajala & Scherer, 2003; Trayhurn & Wood, 2004).

In recent studies examining the global effect of TNF-α on the expression pattern of inflammation-related and other adipokines in human white adipocytes (using microarrays and real-time PCR; M-S Do, B Wang and P Trayhurn; unpublished results) the most dramatic response has been shown to occur with monocyte chemoattractant protein-1 and NGF, with the expression of both being strongly up regulated in response to the cytokine. The marked stimulation of monocyte chemoattractant protein-1 production by TNF-α in white adipocytes, which has been shown in 3T3-L1 cells (Sartipy & Loskutoff, 2003), is consistent with the recent reports that macrophages infiltrate WAT in obesity and are part of the inflammatory cascade within the expanded tissue mass (Weisberg *et al*. 2003; Xu *et al*. 2003). It is, however, important to note that macrophages are unlikely to initiate inflammation in white fat, but rather to amplify a response that has already been established.

The issue of inflammation is one of the most important developing areas in obesity biology. Indeed, obesity, as well as diabetes, is now recognised to be associated with chronic low-grade inflammation (Yudkin *et al*. 1999; Bastard *et al*. 2000; Das, 2001; Festa *et al*. 2001; Engström *et al*. 2003). The basis for this view is that the circulating level of several markers of inflammation, such as IL-6,

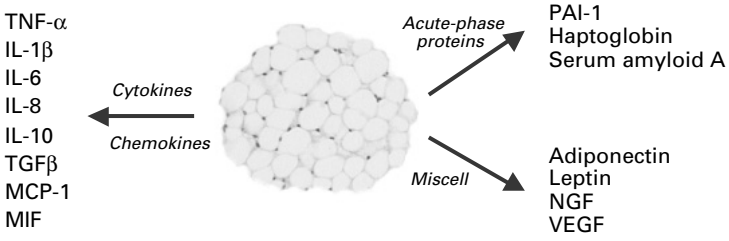

Fig. 3. Adipokines related to inflammation. TGFβ, transforming growth factor β; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; miscell, miscellaneous; PAI-1, plasminogen activator inhibitor-1; NGF, nerve growth factor; VEGF, vascular endothelial growth factor.

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C-reactive protein and haptoglobin, are elevated in obesity and are reduced with weight loss (Yudkin *et al*. 1999; Festa *et al*. 2001; Chiellini *et al*. 2004). Given that WAT secretes a wide range of inflammation-related proteins, it is probable that it is the source of at least some of the increase in these factors in obese subjects. The quantitative importance of WAT relative to other potential sources is, however, unclear.

A key hypothesis is that adipose tissue-derived inflammatory factors may play a causal role in the development of the insulin-resistance and associated pathologies (the metabolic syndrome) of obesity (Hotamisligil, 2003; Yudkin, 2003). There is increasing support for such a concept, and both the circulating levels and adipose tissue expression of several adipokines are increased in obese subjects, including leptin, plasminogen activator inhibitor-1, IL-6, TNF-α and haptoglobin (Considine *et al*. 1996; Ostlund *et al*. 1996; Mohamed-Ali *et al*. 1997; Alessi *et al*. 2000; Bastard *et al*. 2000; Búllo *et al*. 2003; Chiellini *et al*. 2004). In contrast, the production and circulating level of adiponectin, which has been reported to have an anti-inflammatory effect (Yokota *et al*. 2000), is reduced in obesity (Arita *et al*. 1999; Hotta *et al*. 2000).

A major question is why the secretion of cytokines and other inflammation-related proteins from WAT rises sharply as the tissue mass expands? This question has not yet been addressed, but it has recently been proposed (Trayhurn & Wood, 2004) that it is a response to relative hypoxia within clusters of adipocytes remote from the vascular supply in the expanding tissue. Hypoxia leads to the expression of hypoxia-inducible factor-1α, which when combined with hypoxia-inducible factor-1β (which is constitutively expressed) forms the transcription factor hypoxia-inducible factor-1 (Semenza, 2001; Wenger, 2002; Höpfl *et al*. 2004). The transcription of a number of genes, including those encoding the GLUT1 facilitative glucose transporter, glycolytic enzymes (such as lactate dehydrogenase) and inflammation-related proteins, has been shown in several tissues to be stimulated during hypoxia through the medium of hypoxia-inducible factor-1 (Wenger, 2002; Höpfl *et al*. 2004).

Coda

It is now evident that WAT is an important player in overall metabolic and physiological control, secreting a wide range of factors that communicate with other tissues and organs. Thus, there is extensive cross talk between adipocytes and tissues such as the brain and skeletal muscle. The interaction with the brain relates particularly to leptin and the sympathetic nervous system, while that with muscle includes leptin and IL-6. Recent work suggests that IL-6 is secreted from skeletal muscle in considerable amounts during exercise, which results in a cytokine-induced stimulation of lipolysis in WAT (Pedersen *et al*. 2001, 2004), providing two-way communication between adipocytes and muscle. This communication process raises the question of whether there is a range of secreted proteins from myocytes (myokines; Pedersen *et al*. 2004) analogous to the release of adipokines from white fat.

WAT is now very much at the centre of the biology of obesity, both in relation to the fundamentals of energy balance and the consequences of being obese. In essence (courtesy of Hans Christian Anderson) the 'Ugly Duckling' has become a 'very fine Swan indeed'.

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