Review

Adipokines as novel modulators of lipid metabolism

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In the mid-1990s, interest in adipose tissue – until then generally regarded as a mere energy reserve – was revived by the discovery of leptin. Since then numerous other cytokine-like hormones have been isolated from white adipose tissue. These adipokines have been investigated in relation to obesity, metabolic syndrome, insulin resistance and other pathological conditions and processes. In addition, it is now established that adipokines play a role in the maintenance of an inflammatory state in adipose tissue and in the development of obesity and comorbidities. The contributions of individual adipokines in the pathophysiological features of obesity have yet to be determined in full, but recent data highlight important roles for adipokines in lipid metabolism.

Adipokines: a brief historical remark

In all animal species, the maintenance of energy reserves is essential. The absence of such reserves leads rapidly to death, and animals have evolved the capacity to store energy as fat that can be used to survive food shortages. However, not only starvation, but also obesity, is pathological, and the abundance of food in today's industrialized societies has led to obesity becoming endemic [13]. Childhood obesity is of particular concern, causing health problems once seen only in adults, including diabetes, high blood pressure and high cholesterol levels.

The increase in obesity has prompted intense research into its pathogenesis and metabolic consequences. It is quite clear that the development of obesity requires a state of positive energy balance, as well as the existence of a strong link between excess fat mass and diabetes. Paradoxically, the absence of white adipose tissue (WAT), as seen in lipodystrophy, or the ablation of adipose tissue by overexpression of either the diphtheria toxin, the transcription factor SREBP-1c, uncoupling protein-1, or transforming growth factor-β1 in adipocytes induces insulin resistance and, in some cases, diabetes [1]. Therefore, maintenance of an adequate amount of adipose tissue, and thus physiological levels of adipokines, is required to maintain whole-body metabolic homeostasis.

Energy homeostasis requires fine regulation of food intake, nutrient absorption, energy storage and fuel expenditure. An essential role in the coordination of these processes is played by structures of the brainstem and other areas of the central nervous system that integrate relevant afferent information into signals controlling homeostatic adjustments. The complex details of these interactions and of their pathological alterations are beginning to be elucidated.

Experimental results suggesting the existence of a circulating marker of fat reserves date back to the 1950s [2], whereas in the 1980s the existence this marker was supported by results from studies of obese mutant mice in parabiotic pairs. Finally, the compound was identified in the mid-1990s when Friedman and co-workers cloned the mouse gene *ob* [3] and confirmed the anorexigenic, appetite suppressive, effects of its protein product, which they named leptin (from the Greek *leptos* for thin). Since then, our knowledge of the secretory activities of WAT has increased exponentially, with more than 50 adipocyte-derived products isolated and characterized. Most of these compounds act as cytokines and have been collectively named adipokines. However, the contributions of individual adipokines to the pathophysiological features of obesity remain to be fully clarified. It has become evident that the metabolic alterations triggered by circulating adipokines have important effects on muscle and liver, which, together with other effects such as those exerted on endothelium and immune function, can lead to the development of metabolic syndrome. In this context, recent data have highlighted the important roles of adipokines in lipid metabolism, which is the focus of this review (Figures 1 and 2, and Table 1).

Adipokine regulators of lipid metabolism

In the following sections, we highlight why and how members of this newly recognized heterogeneous family of proteins can fundamentally influence lipid metabolism in several target tissues. Current evidence indicates that adipose tissue secretes several adipokines and that the absence or excess of individual adipokines can cause severe

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Glossary

5′-AMP-activated protein kinase (AMPK): heterotrimeric protein with α, β, and γ subunits. Each of these three subunits has a specific role in AMPK stability and activity. The enzyme is conserved from yeast to humans and plays a role in cellular energy homeostasis. It is expressed in several tissues, including the liver, brain and skeletal muscle. The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, triglyceride synthesis and adipocyte lipolysis, stimulation of skeletal-muscle fatty acid oxidation and glucose uptake, and modulation of insulin secretion by pancreatic β-cells.
Adipostatin: through complex mechanisms, this molecule maintains the level of body fat within a narrow range despite considerable variations in dietary fat intake and physical activity.
Angiogenesis: formation of new blood vessels by branching morphogenesis.
Angiotensin II: protein with vasoconstrictive activity that is composed of eight amino acid residues and is the physiologically active form of angiotensin.
Apolipoprotein B (APOB): primary apolipoprotein of low-density lipoprotein (LDL), which is responsible for carrying cholesterol to tissues.
Apolipoprotein E (APOE): apolipoprotein found in chylomicron and intermediate-density lipoproteins, which binds to a specific receptor on liver cells and peripheral cells. It is essential for normal catabolism of triglyceride-rich lipoprotein constituents.
Autocrine: a secreted substance which acts on surface receptors of the same cell.
Brainstem nuclei: groups of neuronal cell bodies present in the hindbrain that form connections with other parts of the central nervous system.
Catecholamines: any of various amines (e.g. epinephrine, norepinephrine and dopamine) that contain a dihydroxy benzene ring, are derived from tyrosine and function as hormones and/or neurotransmitters.
$CD4^+$ T-lymphocytes: group of T-helper lymphocytes that express a large glycoprotein that usually facilitates recognition by helper T-cell receptors of antigens forming complexes with molecules of a class that are found on the surface of antigen-presenting cells (such as B-cells and macrophages) and are the product of genes of the major histocompatibility complex.
Class I cytokine receptor family: includes receptors for IL-2 (β-subunit), IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, EPO, GM-CSF, G-CSF, LIF, CNTF, thrombopoietin, growth hormone, leptin and prolactin. Other members of this protein family include commonly shared signal transducing components such as GP130, common β (AIC2A), common γ, and the γ chain of the IL2 receptor. Members of the type 1 cytokine receptor family lack intrinsic protein tyrosine kinase activity and form homodimers or heterodimers (trimers in a few cases) and the intracellular receptor domains associate with a variety of signalling molecules, in particular cytoplasmic tyrosine kinases (e.g., Janus kinases) and latent cytoplasmic transcriptional activators (e.g., STAT proteins).
Corticosterone: steroid hormone of the corticosteroid type produced in the adrenal cortex.
***db/db* mice**: mice homozygous for the diabetes spontaneous mutation ($Lepr^{db}$) that become obese at approximately 3–4 weeks of age. In rats, the equivalent model is *fa/fa*.
Dyslipidaemia: condition marked by abnormal concentrations of lipids or lipoproteins in the blood.
Extracellular signal-regulated kinases (ERKs): widely expressed protein kinase intracellular signalling molecules which are involved in functions including the regulation of meiosis, mitosis, and post-mitotic functions in differentiated cells.
Fatty-acid-binding proteins (FABPs): family of carrier proteins for fatty acids and other lipophilic substances such as eicosanoids and retinoids. These proteins are thought to facilitate the transfer of fatty acids between extra- and intra-cellular membranes. Some family members are also believed to transport lipophilic molecules from the plasma membrane to certain intracellular receptors such as PPAR.
Hyperleptinaemia: increased circulating levels of leptin.
Hyperphagia: abnormally increased appetite for and consumption of food.
Hypothalamic-pituitary-adrenal axis: The hypothalamic-pituitary-adrenal axis (HPA), also known as the limbic-hypothalamic-pituitary-adrenal axis (LHPA axis), consists of a complex set of direct influences and feedback interactions between the hypothalamus, the pituitary, and the adrenal (or suprarenal) glands. The HPA axis forms a major part of the neuroendocrine system that controls reactions to stress and regulates many physiological processes, including digestion, immunity, mood and emotions, sexuality, and energy storage and expenditure.
IκB kinase (IKK): enzyme complex that is part of the upstream NF-κB signal transduction cascade. The inhibitor of κB (IκBα) protein inactivates NF-κB by masking the nuclear localization signals (NLS) of NF-κB proteins and keeping them sequestered in an inactive state in the cytoplasm. IKK specifically phosphorylates the inhibitory IκBα protein. This phosphorylation event results in dissociation of IκBα from NF-κB, thereby activating NF-κB.
JAK-STAT signalling pathway: takes part in the regulation of cellular responses to cytokines and growth factors. Using JAKs and STATs, the pathway transduces the signal carried by these extracellular polypeptides to the cell nucleus, where activated STAT proteins modify gene expression.
Janus kinases (JAK1 and JAK2): family of intracellular non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway.
c-Jun N-terminal kinases (JNKs): originally identified as kinases that bind and phosphosphorylate c-Jun on Ser63 and Ser73 within its transcriptional activation domain, JNKs are mitogen-activated protein kinases that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock and osmotic shock, and are involved in T-cell differentiation and apoptosis.
Leptin resistance: sustained high concentrations of leptin from enlarged adipose stores resulting in leptin desensitization.
Lipogenesis: normal deposition of fat or the conversion of carbohydrate or protein to fat.
Lipopolysaccharides (LPS, also known as lipoglycans): large molecules consisting of a lipid and a polysaccharide joined by a covalent bond. They are found in the outer membrane of Gram-negative bacteria, acting as endotoxins and elicit strong immune responses in animals.
Lipotoxicity: excess fatty acids accompanied by triglyceride accumulation in parenchymal cells of many tissues including skeletal and cardiac myocytes, hepatocytes and pancreatic β cells, resulting in chronic cellular dysfunction and injury.
Metabolic syndrome: constellation of abnormalities associated with an increased risk of the development of obesity, type 2 diabetes and atherosclerotic vascular disease (leading, for example, to heart disease and stroke).
Neuropeptide Y: neurotransmitter found in the brain and autonomic nervous system associated with a number of physiological processes, including the regulation of energy balance.
Nuclear factor κ-light-chain-enhancer of activated B-cells (NFκB): protein complex that acts as a transcription factor. NF-κB is found in almost all animal cell types and particpates in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Consistent with this role, abnormal regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection and inappropriate immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory.
ob/ob: mouse model harboring a deletion of the leptin gene.
Orexigenic: having a stimulating effect on appetite.
β-Oxidation: process in which fatty acids, in the form of acyl-CoA molecules, are broken down in mitochondria and/or in peroxisomes to generate acetyl-CoA.
Parabiosis: natural or surgical union of anatomical parts of two organisms, usually involving exchange of blood.
Paracrine: mode of hormone action in which a hormone binds to receptors on and affects the function of cells near to the cell that produced it.
Peroxisome proliferator-activated receptors (PPARs): group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. PPARs play essential roles in the regulation of cellular differentiation, development and metabolism (carbohydrate, lipid and protein) of higher organisms.
Protein kinase A (PKA): family of enzymes for which activity depends on the level of cAMP in the cell; also known as cAMP-dependent protein kinase. PKA has several functions in the cell, including regulation of glycogen, sugar and lipid metabolism.
Signal transducer and activator of transcription (STAT) proteins: originally described as latent cytoplasmic transcription factors that require phosphorylation for nuclear retention. Unphosphorylated STAT proteins shuttle between the cytosol and the nucleus until an activation signal is received. Once the activated transcription factor reaches the nucleus it binds to a consensus DNA-recognition motif known as a γ-activated site (GAS) in the promoter region of a cytokine-inducible gene and activates transcription of this gene.
Somatostatin: polypeptide neurohormone found especially in the hypothalamus and inhibits the secretion of several other hormones (e.g. growth hormone, insulin, and gastrin).
Steatosis: a process of tissue degeneration marked by the deposition of fat globules within the cells.
Suppressor of cytokine signalling 3 (SOCS-3): candidate leptin resistance factor. SOCS-3 overexpression results in inhibition of leptin-induced JAK2 tyrosine phosphorylation.
T3: crystalline iodine-containing hormone ($C_{15}H_{12}I_3NO_4$), an amino acid derived from thyroxine and used mainly in the form of its soluble sodium salt ($C_{15}H_{11}I_3NNaO_4$) for the treatment of hypothyroidism and metabolic insufficiency.
Thiazolidinediones: a class of drug (including pioglitazone and rosiglitazone) that are thiazolidine derivatives. As PPARs agonists, they are used therapeutically in type 2 diabetes mellitus and related diseases.
Tumour necrosis factor α (TNF-α): cytokine involved in systemic inflammation; member of a group of cytokines that stimulate the acute phase reaction.
Uncoupling protein: mitochondrial inner-membrane protein that dissipates the proton gradient before membrane utilization to provide energy for oxidative phosphorylation.

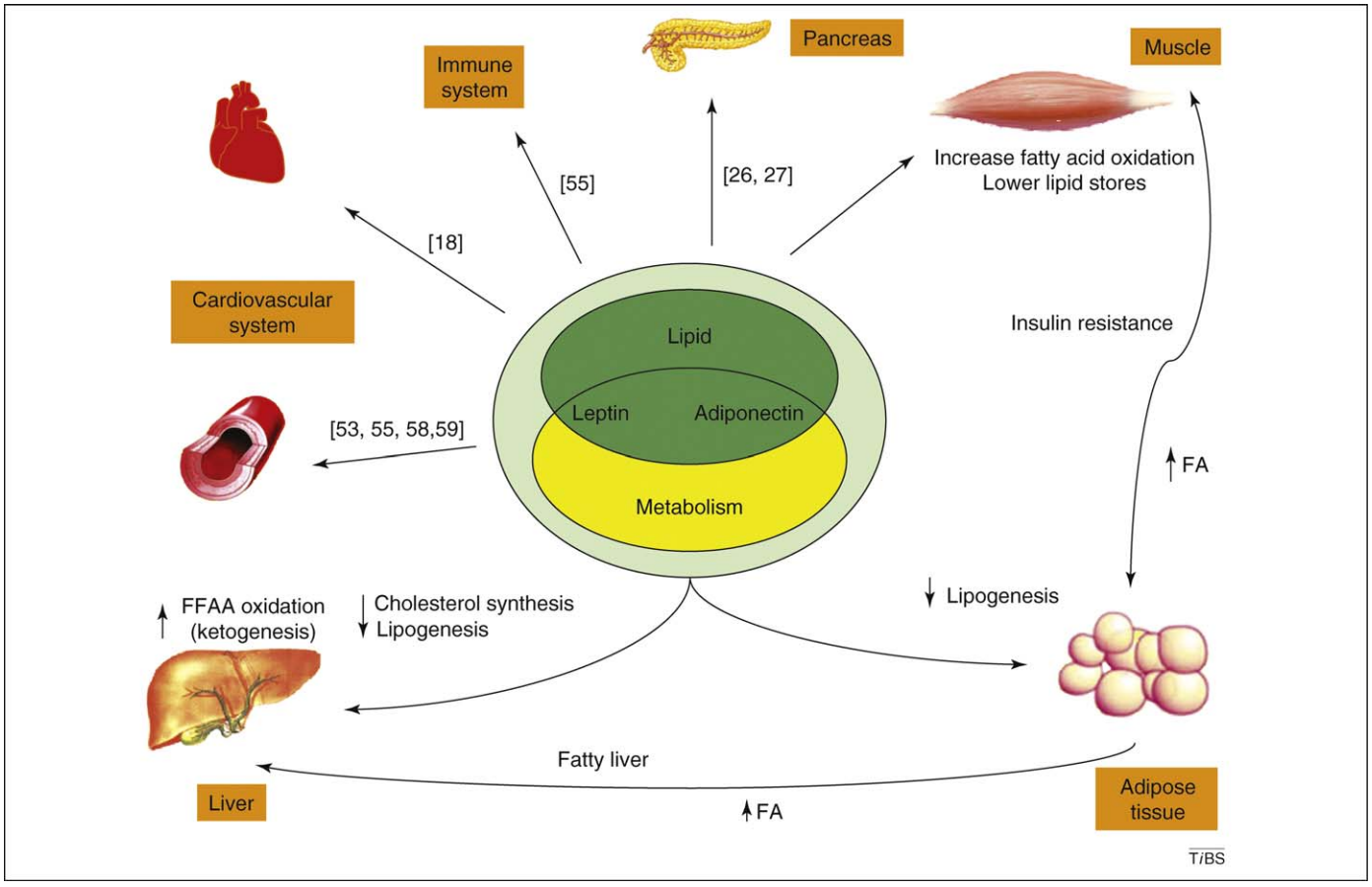

Figure 1. Schematic representation of the roles of leptin and adiponectin in lipid metabolism. Leptin and adiponectin control lipid metabolism in muscles, liver and adipose tissue. In these locations, the most relevant actions of both hormones are the decrease in lipogenesis and the induction of fatty acid oxidation. These adipokines have additional targets such as the immune system, pancreas and cardiovascular system.

alterations in carbohydrate or lipid metabolism. Recent data have revealed molecular mechanisms related to the interrelationship between adipokines and lipid metabolism. These findings are important because of their obvious implications in terms of fatty acid deposition and mobilization, which in turn are a critical factor in obesity-induced comorbidities.

Leptin

Leptin is a 16-kDa non-glycosylated peptide that belongs to the cytokine class 1 super family [3] (encoded by *LEP* in humans; *Lep* in mice). It is mainly produced by adipocytes and circulating leptin levels are directly correlated with WAT mass. Leptin decreases food intake and increases energy consumption by acting on hypothalamic cell populations, inducing anorexigenic factors (cocaine- and amphetamine-regulated transcripts and pro-opiomelanocortin) and inhibiting orexigenic neuropeptides (neuropeptide Y, Agouti-related protein and orexin) [4,5]. Leptin levels are negatively correlated with glucocorticoid levels [6] and positively with insulin levels [7]. Nevertheless, the role of glucocorticoids as modulators of leptin secretion

Table 1. Metabolic effects of adipokines.

Hormones & cytokines	Leptin	Adiponectin	Vaspin	Apelin	Visfatin	Omentin	Chemerin	FABP
Insulin	+	+/–	+	+	–/=	–	nd	+
Catecholamines	–	–	nd	–	–	nd	nd	nd
Glucocorticoids	–/+	–	nd	–	+	nd	nd	+
TNF-α (long exposure)	–	nd	nd	nd	nd	nd	nd	nd
TNF-α (acute exposure)	+	–/=	nd	+/=	–	nd	nd	–
Interleukin-6	+	=	nd	+	–	nd	nd	nd
Testosterone	–	–	–	nd	–/=	–	nd	=
Ovarian steroids	+	+	+	nd	–/=	+	nd	=
IGF-1	nd[a]	–	nd	nd	nd	nd	nd	+
PPARγ agonists	–	+	+	=	–	nd	nd	+
High energy status	+	–	+	+	–	–	+	+
Low energy status	–	+	–	–	+	+	–	–
References	[6,8,9,12,18,39, 40,42,102–104]	[18, 105–112]	[76,78, 126]	[72,104, 113–116]	[117–119, 127]	[120, 128]	[97]	[79, 121–125]

[a]Not determined.

remains a matter of debate [8,9]. Leptin synthesis is mainly regulated by food intake and eating-related hormones, but also depends on energy status, sex hormones (being inhibited by testosterone and increased by ovarian sex steroids) and a wide range of inflammation mediators [10,11] (being increased or suppressed by pro-inflammatory cytokines, depending on whether their action is acute or chronic). As a result of the effects of sex hormones, leptin levels are higher in women than in men, even when adjusted for body mass index (BMI), which could be relevant to the influence of sex on the development or frequency of certain diseases [12]. Leptin seems to act not only as an adipostatin, the function in relation to which it was discovered, but also as a general signal of energy reserves [13] that is involved in a wide variety of other functions, including glucose metabolism, glucocorticoid synthesis, $CD4^+$ T-lymphocyte proliferation, cytokine secretion, phagocytosis, regulation of the hypothalamic–pituitary–adrenal axis, reproduction and angiogenesis [14].

Leptin exerts its biological actions by binding to a class I cytokine receptor encoded by *LEPR* in humans (formerly *OBR*) and *Lepr* in mice(formerly *Obr* or *db* for *diabetes; db* now refers to the original non-functional mutant allele). Alternative splicing of *Lepr* gives rise to six receptor isoforms, only one of which, LEP-Rb (found in almost all tissues), has the long cytoplasmic domain that is necessary for transduction of the leptin signal [15]. Like other class I cytokine receptors, LEP-Rb seems to transmit the extracellular signal it receives mainly through JAK-STAT signalling pathways [15], which involve JAK2 phosphorylating tyrosines in the cytoplasmic domain of the receptor. In particular, replacing the intracellular tyrosine Y1138 of murine LEP-Rb with a serine residue prevents STAT3 activation and results in hyperphagia, obesity and impaired thermoregulation. However, because Y1138S knockin mice do not exhibit the other defects of *db*/*db* mice, such as infertility, the role of leptin in the processes that are disrupted in the latter conditions must be independent of STAT3 [16]. Rats that are heterozygous for the mutant leptin receptor allele display intermediate phenotypes between wild-type and homozygous rats in terms of adiposity and lipogenesis [17]. In both humans and rodents, leptin levels correlate closely with BMI and defects of the leptin and leptin receptor genes cause severe obesity and diabetes [18]. Leptin treatment of *ob*/*ob* mice induces a reduction in food intake, an increase in metabolic rate and weight loss, and in the few known cases of human patients with mutant *LEP* or *LEPR*, leptin treatment has likewise ameliorated all the problems associated with leptin deficiency [18]. Leptin therapy is not effective against morbid obesity that is not due to congenital deficiency of leptin or leptin receptors; in these non-congenital types of obesity, leptin concentrations are already high because of increased fat mass. The persistence of obesity in spite of high leptin levels suggests that high leptin levels can induce leptin resistance. This could involve a leptin-induced increase in SOCS-3, which blocks intracellular transmission of the leptin signal [19], but our understanding of leptin resistance is still limited.

Leptin not only influences energy homeostasis through its actions in the central nervous system, but also has autocrine or paracrine actions in triacylglycerol-storing tissues, where it influences the rates of synthesis and degradation of lipids, at least *in vitro*. (It should of course be borne in mind that extrapolation of the interpretation of *in vitro* findings to *in vivo* conditions is complicated by the presence of many other regulating factors.) The autocrine or paracrine effect of leptin on lipolysis was first shown when the rate of lipolysis in isolated lean wild-type mouse adipocytes (34–40% faster than those of *ob*/*ob* and *db*/*db* adipocytes) increased by 28% when treated with leptin, whereas the corresponding increase in *ob*/*ob* adipocytes was 123% and *db*/*db* adipocytes (which lack a functional leptin receptor) were unaffected [20]. Similar results were obtained when lipolysis rates were measured *ex vivo* in adipocytes from wild-type rats and *fa*/*fa* rats (rat equivalent of *db*/*db* mice) [21]. In another study, lean *ob*/*ob* and *db*/*db* mice were treated with three different doses of leptin before samples of adipocytes were excised and their lipolysis rates measured. The lipolysis rate was unaffected by leptin treatment in *db*/*db* adipocytes, was only increased by the largest dose of leptin in wild-type cells and was increased by the two largest doses in *ob*/*ob* cells [22]. The stronger effect of leptin on *ob*/*ob* adipocytes than on wild-type adipocytes in these experiments suggests that the leptin receptor is strongly upregulated in the absence of a functional leptin protein. Notably, leptin directly stimulates phosphorylation and activation of the α-2 catalytic subunit of AMP-activated protein kinase (AMPK) in skeletal muscle, increasing phosphorylation of acetyl-CoA carboxylase (ACC) and fatty acid oxidation (at least in the early phases of AMPK activation (Figure 2), with later-phase activation depending on leptin functioning through the hypothalamic–sympathetic nervous system axis) [23].

Although the autocrine or paracrine role of leptin in fatty acid metabolism has not yet been fully elucidated at the molecular level, it is known that leptin in adipocytes inhibits the synthesis of ACC, an enzyme essential (and rate-limiting) in the conversion of carbohydrates to long-chain fatty acids and hence in the storage of energy as triacylglycerol. Differentiating wild-type adipocytes starved by culture in the absence of serum have lower ACC levels and lower rates of fatty acid and triacylglycerol synthesis than *ob*/*ob* cells [24]. In addition, long-term treatment of wild-type mice with large leptin doses increases mRNA levels of the key lipolytic enzyme hormone-sensitive lipase but reduces those of the lipogenic enzyme fatty acid synthase [25]. Hormone-sensitive lipase levels are more immediately controlled by cellular levels of cAMP, so it seems that leptin, like glucagon and catecholamines, might stimulate lipolysis primarily by increasing cAMP concentrations [26].

Leptin-driven control of lipid metabolism has been observed not only in adipocytes, but also in other tissues that store triacylglycerol. In particular, leptin treatment of pancreatic islets isolated from rats causes an increase in fatty acid oxidation and a decrease in esterification, and hence a reduction in intracellular triacylglycerol content [26,27]. In addition, the pancreatic islets of *fa*/*fa* rats

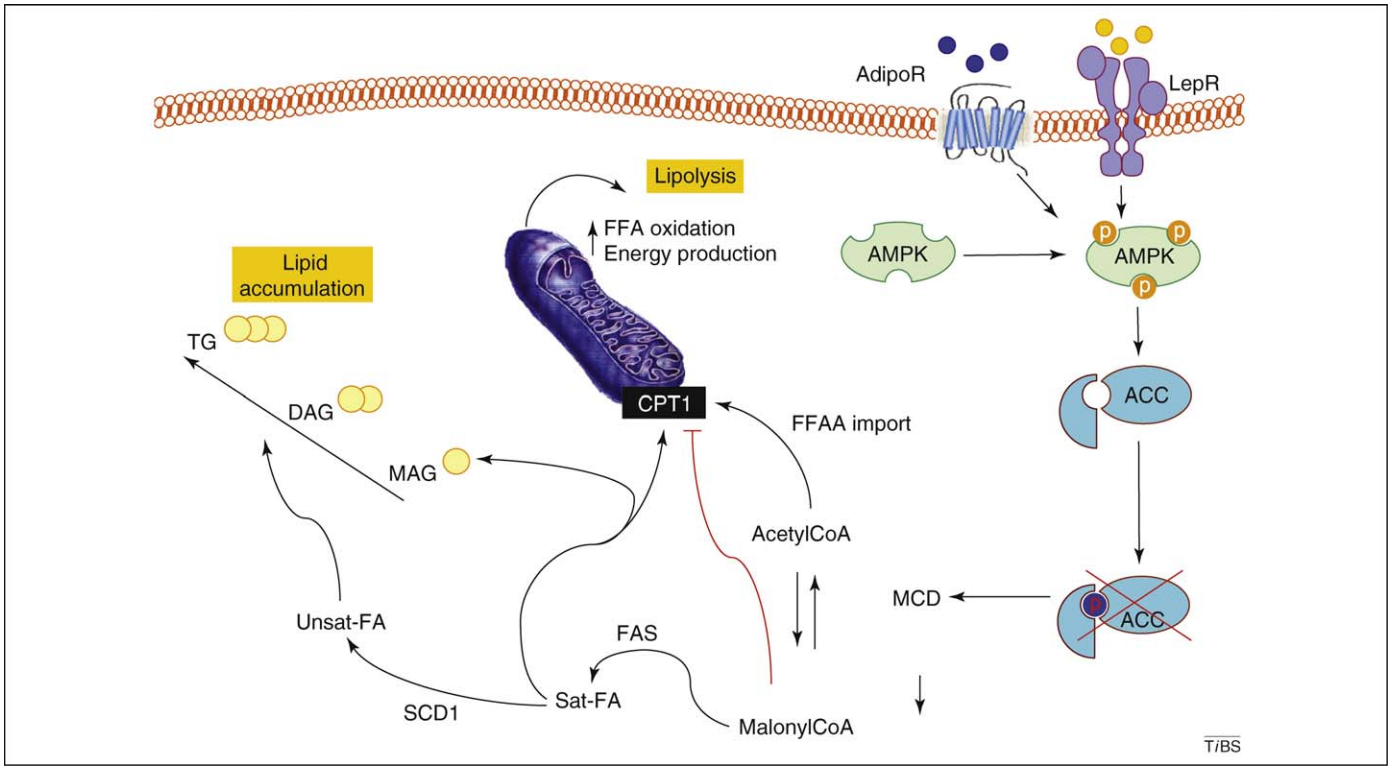

Figure 2. The leptin and adiponectin signalling pathway involved in the control of lipid metabolism. Leptin and adiponectin cause phosphorylation of AMPK, which in turn phosphorylates ACC, inactivating it. Leptin and adiponectin thus inhibit malonyl CoA synthesis, leading to increased mitochondrial import and consumption of fatty acids, so that fatty acid oxidation occurs rather than lipid accumulation.

contain as much as 20 times the amount of triacylglycerol found in lean rats [28]. Furthermore, rats lacking functional leptin receptors have high levels of acyl-CoA synthetase and glycerol-3-PO_4 acyltransferase (two enzymes required for lipogenesis), but low levels of acyl-CoA oxidase (ACO) and carnitine palmitoyl transferase I (two enzymes involved in fatty acid oxidation). In view of these enzyme levels and of the high lipid contents of *fa/fa* non-adipocytes, it has been hypothesized that one of the functions of leptin is to keep the triacylglycerol content of non-adipocytes low, thereby protecting them from steatosis and lipotoxicity [29].

An indirect effect of leptin on lipid metabolism is its reduction of the lipogenic effects of insulin: addition of insulin to cultured leptin-deficient adipocytes increases the synthesis of ACC, fatty acids and triacylglycerol to a greater extent than in adipocytes that do produce leptin [24], possibly due in part to leptin inhibition of insulin–adipocyte binding [30]. Like the direct effects of leptin, this action also extends to non-adipocytes: the insulin-induced increase in triacylglycerol synthesis and decrease in fatty acid oxidation in isolated mouse skeletal muscle are reduced by simultaneous administration of leptin [31]. Leptin counteraction of insulin in both adipocytes and muscle suggests that, *in vivo*, high leptin levels probably depress the temporary postprandial lipogenic effect of insulin; this implies that in obesity, for example, triacylglycerol synthesis might not be fully activated even when lipogenic hormones are present. However, leptin does not seem to modulate the effects of insulin on glycogen synthesis, glucose oxidation or lactate production in non-adipocytes [31] and therefore probably does not interfere with the primary function of insulin, which is to reduce high circulating levels of glucose by upregulating glycogenesis in muscle and liver. In fact, it is well established that *in vivo* leptin can increase insulin sensitivity, with insulin resistance induced by an acute lipid infusion prevented by hyperleptinaemia [32]. The actions of leptin are also intertwined with those of numerous metabolic hormones besides insulin. Notably, leptin forms a negative feedback loop with T3, which is promoted by leptin [33] and in turn reduces circulating leptin levels [34]. Within adipocytes, there might also be feedback between leptin and certain transcription factors, namely peroxisome-proliferator-activated receptors (PPARs). Thus, leptin has been found to upregulate PPAR-α and PPAR-γ [4], which both upregulate fatty acid binding proteins (FABPs); PPAR-α also seems to regulate fatty acid oxidation enzymes [35] and uncoupling protein-3 (UCP3) [36]. However, findings have differed as to whether PPARs can regulate leptin gene expression.

Leptin has a complex relationship with growth hormone (GH). Obese subjects have low plasma GH levels [37], which suggests that high leptin levels can depress GH production. However, administration of anti-leptin serum to adult rats reduces spontaneous GH secretion and leptin prevents the decrease in plasma GH levels on fasting [38]. The effect of leptin on GH seems to be usually exerted at the hypothalamic level by regulation of the production of GH-releasing hormone, somatostatin and neuropeptide Y. However, any interpretation of the effects of leptin must take into account the influence on GH secretion of another adipocyte-derived signal, free fatty acid (FFA) [38], which seems to inhibit GH secretion mainly by acting on the pituitary.

Leptin levels are modulated not only by T3, but also by tumour necrosis factor α (TNF-α), a classic cytokine with lipolytic activity that, like leptin, is secreted by adipocytes. However, *in vivo–in vitro* contradictions are abundant in this area: treatment of rodent and human adipocytes with TNF-α *in vitro* reduces leptin secretion and mRNA levels [39], whereas *in vivo* treatment causes a corresponding increase [40] and TNF-α-deficient mice have lower circulating leptin levels than wild-type mice. These discrepancies might be due to differences in the experimental models or to interspecies differences.

As noted at the beginning of this section, leptin synthesis is mainly regulated by food intake. During fasting and caloric restriction, circulating leptin levels decrease regardless of weight loss [4] and are clearly uncoupled from the control of lipolysis and fatty acid oxidation, which increase [41]. However, the decrease in energy expenditure that occurs during fasting is in keeping with the decrease in leptin, as is the decrease in T3 levels that occurs under these circumstances and to which the decline in metabolic rate has been attributed (although it has also been hypothesized that a decrease in leptin levels reduces energy expenditure through its effects on thyroid function and uncoupling proteins [33]). It is not yet known what triggers the decrease in leptin itself (which seems to be initially due to decreased leptin secretion rather than decreased transcription [42]), although a possible clue is the finding that it is preceded by a decrease in plasma insulin concentration and increases in FFA and corticosterone levels.

Adiponectin

Adiponectin is a 244-residue protein that is produced mainly by WAT. It increases fatty acid oxidation and reduces glucose synthesis in the liver [43]. Ablation of the adiponectin gene has no dramatic effect on knockout mice on a normal diet, but when placed on a high-fat, high-sucrose diet these mice develop severe insulin resistance and exhibit lipid accumulation in skeletal muscle [44]. Circulating adiponectin levels tend to be low in morbidly obese patients and increase with weight loss or with the use of thiazolidinediones, which enhance sensitivity to insulin [45].

Adiponectin acts mainly via two receptors, one (ADIPOR1) found mainly in skeletal muscle and the other (ADIPOR2) in the liver. Consistent with a beneficial role of adiponectin in insulin sensitivity, simultaneous disruption of both ADIPOR1 and ADIPOR2 abolishes adiponectin binding and activity, resulting in insulin resistance and marked glucose intolerance [46]. Transduction of the adiponectin signal by ADIPOR1 and ADIPOR2 involves activation of AMPK (Figure 2), PPARα and PPARγ. Adiponectin exhibits structural homology with collagen VIII and X and complement factor C1q, and circulates in the blood in relatively large amounts in oligomeric forms (mainly trimers and hexamers, but also 12–18-mer forms) [47]. Whether these oligomers have different activities is somewhat controversial and could depend on target cell type: authors working with myocytes have reported that trimers activate AMPK whereas larger oligomers activate NFκB, but it has been reported that 12–18-mers promote AMPK in hepatocytes [18].

It has been hypothesized [48,49] that the development of atherosclerosis and cardiovascular diseases in obese patients is partly caused by low adiponectin levels [50]. Indeed, adiponectin seems to play both direct and indirect roles in protection against cardiovascular disease [51] and there is increasing evidence that these effects are due to its involvement in the regulation of both lipid and carbohydrate metabolism. For example, low adiponectin levels have been linked to small dense LDL and high APOB and triglyceride levels [52]. It has also been reported that adiponectin has direct actions on vascular endothelium that could protect against cardiovascular disease in part by suppressing lipid accumulation in macrophages [53–55]. Ablation of the adiponectin gene had no obvious metabolic effects in mice fed a normal chow diet; however, when they were fed a high-fat, high-sucrose diet, these knockout mice developed severe insulin resistance accompanied by increased lipid deposition in muscle [56]. Adipose and plasma TNF-α levels were increased as a result of adiponectin deficiency and these changes were reversed by adiponectin treatment [56]. Furthermore, knockout mice lacking adiponectin exhibit an enhanced inflammatory response to vascular injury [57] and adiponectin administration prevents atherosclerosis in APOE-deficient mice [58,59]. Intriguingly, adiponectin transgenic mice crossed with *ob/ob* mice show partial amelioration of insulin resistance and diabetes, but not of obesity. These data suggest that chronic elevation of globular adiponectin has a direct insulin-sensitizing effect independent of WAT mass [60]. Therefore, in addition to adiponectin expression and plasma levels, expression of ADIPOR1 and ADIPOR2 in target tissues could play a relevant role in the modulation of metabolic homeostasis. The physiological relevance of these two receptors is further supported by the fact that ADIPOR1 deficiency results in increased adiposity associated with decreased glucose tolerance, physical activity and energy expenditure, effects that in part overlap with the phenotype described for adiponectin-deficient mice [46]. By contrast, ADIPOR2 deficiency leads to resistance to obesity induced by a high-fat diet and to glucose intolerance associated with increased physical activity and energy expenditure and decreased plasma cholesterol levels [61].

It is noteworthy that recent data point to liver ADIPOR2 as a promising target for the treatment of non-alcoholic steatohepatitis (NASH). Indeed, inhibition of hepatic ADIPOR2 expression aggravates the pathological state of NASH at all stages, including fatty changes, inflammation and fibrosis. By contrast, enhancement of ADIPOR2 expression in the liver improves NASH at every stage, from early fatty changes to progressive fibrosis. In a recent study, inhibition of ADIPOR2 signalling in the liver led to lower PPAR-α signalling, with decreased expression of ACO and catalase and a subsequent increase in lipid peroxidation. ADIPOR2 overexpression had the opposite effect [62].

Several genes linked to circulating adiponectin levels also have pleiotropic effects on serum HDL and triglyceride levels [63]. Moreover, the results of two large cross-sectional studies suggest that, after adjusting for gender and body adiposity, circulating adiponectin concentrations are

closely and positively correlated with plasma HDL concentrations, but negatively correlated with triglyceride levels [64,65].

Pro–inflammatory adipokines

The inflammatory cytokines secreted by adipose tissue include TNF-α and several interleukins (among them IL-2 and IL-6) that adversely affect both glucose and lipid metabolism. TNF-α is a paradigmatic pro-inflammatory cytokine produced mainly by macrophages and lymphocytes, but also by numerous other cell types, including adipocytes. In rodents, TNF-α is involved in the pathophysiology of insulin resistance [66], but human adipose tissue produces less TNF-α than that of rodents and the role of TNF-α in human dyslipidaemia is less clear. It could participate in crosstalk between adipocytes and invading stromal mononuclear cells (infiltrating macrophages constitute the major source of inflammatory agents in adipose tissue), mediating their synergistic amplification of local and systemic inflammation [67].

TNF-α acts at several levels on adipocyte lipid metabolism. First, it inhibits FFA uptake through a mechanism that probably involves downregulation of fatty acid transport protein, fatty acid translocase and FABP4 (aP2). TNF-α also regulates lipoprotein lipase expression (although results are discordant [68]) and reduces the transcript levels and synthesis of many proteins involved in glyceroneogenesis, *de novo* fatty acid synthesis and esterification. All these effects lead to impaired triglyceride storage in adipose tissue. Notably, most of the relevant genes are regulated by PPARγ, which suggests that the effects of TNF-α could be primarily due to its inhibition or downregulation of this transcription factor.

TNF-α also induces lipolysis in the absence of insulin by a complex, ill-understood mechanism that might depend on nutritional state and that involves downstream signals such as ERK1/2, JNK, AMPK, IκK and PKA following the activation of type-1 TNF receptors by TNF-α binding [69]. Other actions of TNF-α on lipid storage and oxidation in WAT, through the regulation of gene transcription and other mechanisms, have been reviewed by Cawthorn and Sethi [68].

Acylation-stimulating protein

Acylation-stimulating protein (ASP) is a complement-derived adipokine that increases triglyceride clearance and triacylglycerol storage and enhances insulin sensitivity by increasing the transport of glucose into adipocytes. ASP also inhibits lipolysis by decreasing hormone-sensitive lipase levels [70]. ASP levels are increased in human obesity, for which it can be regarded, like leptin, as a marker [71].

Apelin

Apelin is a recently discovered adipokine that is present at higher levels during adipocyte differentiation and, particularly when associated with insulin resistance, in obesity [72]. It seems to regulate adiposity and lipid metabolism in both lean and obese mice. It increases *Ucp1* mRNA levels (a marker of peripheral energy expenditure) in brown adipose tissue [16] and *Uco3* mRNA levels (a regulator of fatty acid export) in skeletal muscle [73]. Apelin also promotes endothelial vasodilation by stimulating nitric oxide [74] and acts as an anti-inflammatory secretagogue and angiotensin II antagonist, decreasing vascular tone and angiogenesis [75].

Vaspin

Vaspin, an adipokine with potential anti-protease properties, is a member of the largest and most widely distributed family of serine protease inhibitors. It was identified as an adipokine with insulin-sensitizing effects and some results suggest that it could play a role in the development of obesity and metabolic disorders. Vaspin was identified using a PCR-based cDNA subtraction method in visceral WAT in the Otsuka Long–Evans Tokushima fatty (OLETF) rat, an animal model characterized by abdominal obesity, dyslipidaemia, insulin resistance and hypertension [76]. Vaspin gene expression has been detected in mature adipocytes isolated from epididymal, retroperitoneal, mesenteric and subcutaneous abdominal WAT from 30-week-old OLETF rats. In addition, vaspin expression is specific to adipocytes in visceral WAT and is not detected in stromal endothelial or vascular cells. Levels of circulating vaspin and transcripts within adipocytes of visceral adipose tissues were significantly increased in OLETF rats compared with their non-mutant counterparts (Long–Evans Tokushima Otsuka rats) at 30 weeks, when obesity and insulin plasma concentrations reach their peak. Pioglitazone and insulin treatment significantly upregulated levels of vaspin mRNA in OLETF rats at 50 weeks of age compared with placebo treatment [77].

Insulin resistance and obesity are associated with high levels of expression of vaspin, both in humans and in OLETF rats, whereas in the latter vaspin expression also significantly decreases with the progression of diabetes and concomitant loss of body weight. Visceral expression of vaspin mRNA significantly correlates with percentage body fat, BMI and plasma glucose levels following a 2-h oral glucose tolerance test, whereas similar correlations have not been detected in lean subjects (BMI$<$25) [77]. Similar to other adipokines such as leptin and adiponectin, serum concentrations of vaspin in humans show gender-dependent regulation and are significantly higher in female than male subjects [78]. Vaspin administration to obese mice improved glucose tolerance and insulin sensitivity and modified the expression of genes involved in the pathogenesis of insulin resistance, such as resistin, leptin and adiponectin, suggesting a link between vaspin and glucose metabolism [76]. The physiological and pathophysiological mechanisms of the action and regulation of vaspin remain to be defined.

Fatty acid-binding proteins

Molecular pathways linking obesity to metabolic and atherosclerotic defects are being intensively explored. Dysregulation of lipid metabolism with increased FFA plasma concentrations is consistently associated with metabolic syndrome, in which elevated FFAs modify glucose and lipid metabolism. FFAs are transported in the circulation bound to albumin and their cellular uptake can occur by passive

diffusion or by protein-mediated binding and translocation mechanisms; intracellularly, FABPs are carriers for FFAs [79]. In particular, adipocyte-specific FABPs have attracted much attention in recent years because studies in FABP-deficient mouse models suggested that they play a role in insulin resistance, type-2 diabetes and atherosclerosis [80].

FABPs are small (14–15 kDa) cytoplasmic proteins that bind reversibly with high affinity to hydrophobic ligands, such as saturated and unsaturated long chain fatty acids, eicosanoids and other lipids. FABPs can be found across all animal [81] species, demonstrating high evolutionary conservation [81]. At least nine tissue-specific cytoplasmic FABPs have been identified to date. Their functions include enhancement of FFA solubility and transport of FFAs to specific enzymes and cellular compartments (namely to the mitochondria and peroxisomes for oxidation, to the endoplasmic reticulum for re-esterification, to lipid droplets for storage or to the nucleus for regulation of gene expression) [81,82]. Overexpression and antisense studies have suggested FABP roles in FFA import, storage and export, as well as in cholesterol and phospholipid metabolism [83].

Via modulation of FFA availability, FABPs have an indirect regulatory effect on various cellular processes in which FFAs are involved, such as signal transduction. FFAs transmit a stress response through activation of Protein kinase C θ, Inhibitor of κ kinase (IκK), or c-jun NH_2-terminal kinase (JNK), which have all been linked to insulin resistance and metabolic syndrome [80]. In addition, the role of FFAs in gene transcription regulatin is well characterized, especially for genes encoding proteins involved in lipid metabolism, e.g. acyl-CoA synthase, acyl-CoA oxidase, stearoyl-CoA desaturase, carnitine-palmitoyl transferase and FABP itself [81]. Several mechanisms of FFA-mediated regulation of gene transcription have been proposed: binding to and activation of a transcription factor, modification of mRNA stability and regulation of transcription factor expression. Moreover, FABPs cooperate with transcription factors of the PPAR family by inducing ligand-dependent transactivation of PPARs [11,84]. Although experimental data for knockout mice and pharmacological inhibition of FABPs provide insight into their central regulatory role in metabolic syndrome (which is related to insulin sensitivity), evidence from humans is not as consistent as that from the animal models used. FABPs clearly link several mechanisms and pathways that are involved in the development of obesity, metabolic syndrome and atherosclerosis. Translation of these important data from mouse models to humans, however, will require further comprehensive investigations. Whether a circulating adipocyte or macrophage FABP represents a biomarker of obesity, metabolic syndrome and/or atherosclerosis or whether it is a causative factor of metabolic and inflammatory dysregulation that can be effectively and safely counteracted remains to be elucidated.

Other regulators

Finally, we mention here a number of secreted proteins with reported involvement in energy metabolism that are of uncertain source, function and/or relevance to humans [85].

Visfatin Pre-β-cell colony-enhancing factor 1, a cytosolic nicotinamide phosphoribosyl transferase involved in the biosynthesis of nicotinamide adenine dinucleotide (a key factor in cell survival and in the regulation of insulin secretion in β-cells), was recently renamed visfatin when it was revealed that it is produced abundantly by visceral fat and mimics the action of insulin [86]. However, the insulin-mimetic role of visfatin was recently questioned [87]. Studies on human subjects have led to conflicting results regarding the insulin mimetism of visfatin and its relationship to adiposity, subcutaneous versus visceral fat distribution and insulin resistance [88–91]. Although ubiquitous within the body, visfatin gene expression in humans is greatest in the liver and peripheral blood leukocytes. Adipocytes and adipose tissue seem not to be the major contributors to the high visfatin levels normally found in the human circulation (10–40 ng/ml) and the failure to recognize this could partly account for discrepancies between different authors regarding the relationship that visfatin might have with insulin resistance and adiposity.

Circulating visfatin is associated with HDL-cholesterol [92,93] and it seems that visfatin could influence lipid metabolism through its role in the biosynthesis of NAD because the NAD precursor nicotinic acid is able to increase HDL-cholesterol considerably [94]. Interestingly, early studies showed that in experimental inflammation and clinical sepsis visfatin was strongly induced in white blood cells by cytokines and lipopolysaccharides. In addition, lipopolysaccharides and sepsis affect a wide range of apolipoproteins, plasma enzymes, lipid transfer factors and receptors that are involved in HDL metabolism.

Omentin Omentin is another protein that has recently been rediscovered in visceral adipose tissue [95]. Under the name intelectin 1, it is known to take part in defence mechanisms by binding to galactofuranoses on bacteria [96]. Omentin is not secreted by adipocytes, but by stromal vascular cells, and is abundant in human vasculature, the small intestine, colon, heart and thymus. Although it is not clear whether it contributes to the development of obesity and insulin resistance, omentin nevertheless seems to contribute to the regulation of lipid metabolism and to the physiological difference between visceral and subcutaneous adipose tissue.

Chemerin The plasma level of chemerin, which was discovered in 2007 [97,98], is closely associated with several key aspects of metabolic syndrome. Chemerin also influences adipocyte function, inducing lipolysis [99], enhancing insulin signalling and potentiating insulin-stimulated glucose uptake [100]. The chemerin receptor was previously characterized as an orphan G protein-coupled receptor (i.e. one for which no ligand had been described), activation of which stimulated intracellular calcium release, phosphorylated ERK1 and ERK2, and inhibited cAMP accumulation through binding of G_i–coupled heterotrimeric G proteins [101].

Concluding remarks

The discovery of leptin nearly 15 years ago opened a vast new field of research. It was eventually shown that this adipocyte-derived peptide not only regulates energy production, but also acts in other ways on a large number of peripheral tissues. However, its role in lipid metabolism is central to its significance for the pathogenesis of obesity and the physiological function of adipose tissue as an endocrine organ regulating overall metabolism. The metabolic roles of leptin, and those of other adipokines, are still being elucidated. Apart from the adipokines considered in this review, numerous other recently identified adipocyte-derived factors, such as vaspin and hepcidin, might also modulate lipid metabolism in health or disease. A pressing challenge is to determine how leptin, adiponectin and other adipokines are involved in metabolic disorders. This question overlaps with the more general issue of how the various adipokines interact with each other because the net effect of the simultaneous release of several agents with diverse biological properties is not readily predictable. Addressing such problems will require the development of new pharmacological tools that target specific adipokine systems. As a consequence, we anticipate that new therapeutic targets will be identified to realize control of these systems.

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