Neuroendocrine and metabolic effects of adipocyte-derived hormones

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ABSTRACT

Obesity is characterized by an increase in adipose tissue mass. Contrary to the previous view of adipose tissue as simply an inert tissue devoted to energy storage, studies over the past decade have shown that adipose tissue is actively involved in regulating physiological processes and participates in disease. Adipose tissue secretes factors that exert local and systemic effects. Leptin, pro-inflammatory cytokines, resistin and proteins involved in haemodynamic regulation and coagulation are increased in obesity while adiponectin is reduced. The production of active corticosteroids is also increased in obesity. There is now growing evidence that adipocyte secretory factors regulate energy homoeostasis, as well as cardiovascular and immune systems. Some adipocyte hormones, most notably leptin, act in the brain to influence the neuroendocrine axis and energy balance, whereas adiponectin and resistin exert opposing effects on glucose and lipids. Understanding the actions of adipocyte hormones will provide novel insights into the pathophysiology and treatment of obesity.

ADIPOSE TISSUE

The rising incidence of obesity, diabetes and other associated diseases has focused attention on the biology of adipose tissue. WAT (white adipose tissue), the predominant type of adipose tissue, plays a vital role in the survival of humans and other mammals by providing an almost limitless capacity for energy storage in the form of triacylglycerol (triglyceride) [1]. WAT is composed mostly of adipocytes, is richly vascularized and innervated, and includes macrophages and other cell types in the stromovascular compartment. WAT blood vessels [2–4] and macrophages increase in obesity and are actively involved in controlling the nutrition and survival of adipocytes, as well as mediating inflammatory responses [5–7].

In times of surfeit, insulin, glucose and nutrients stimulate lipid synthesis in liver and storage in adipocytes [1]. Conversely, fasting triggers a breakdown of glycogen, lipids and protein via sympathetic activation and counter-regulatory hormones, in particular glucagon, adrenaline (epinephrine) and glucocorticoids [1]. This process ensures a constant glucose supply to the brain and vital organs. Fatty acids released by adipose tissue serve as

Key words: adiponectin, adipose tissue, hypothalamus, leptin, neuropeptide, resistin.

Abbreviations: AdipoR, adiponectin receptor; AGRP, agouti-related peptide; AMPK, AMP-activated protein kinase; CART, cocaine and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; ERK, extracellular-signal-regulated kinase; GnRH, gonadotropin-releasing hormone; HPA axis, hypothalamic–pituitary–adrenal axis; HSD, hydroxysteroid dehydrogenase; 11βHSD-1, 11βHSD type 1; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IL-6, interleukin-6; LRb, long leptin receptor; α-MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PTP1B, protein tyrosine phosphatase 1B; RBP4, retinol-binding protein 4; SHP-2, Src-homology protein tyrosine phosphatase-2; SOCS3, suppressor of cytokine signalling 3; STAT, signal transduction and activators of transcription; STAT3, signal transducer of transcription 3; TNF-α, tumour necrosis factor-α; TRH, thyrotropin-releasing hormone; vaspin, visceral adipose tissue-derived serpin; WAT, white adipose tissue.

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fuel substrates for muscle, liver and peripheral organs, in addition to providing ketones for use by the brain [1].

There has been a paradigm shift regarding the role of adipose tissue, from one in which adipocytes play a passive role in storing triacylglycerol, to a current model where adipose tissue actively participates in metabolism and mediates the complications of obesity [8]. Obesity is associated with histological and biochemical changes characteristic of inflammation. WAT from obese individuals contains a high number of activated macrophages which form giant cells and produce cytokines, e.g. TNF-\(\alpha\) (tumour necrosis factor-\(\alpha\)) and IL-6 (interleukin-6) [5]. CRP (C-reactive protein) is increased in obese compared with lean subjects [5]. Moreover, the expression of ICAM-1 (intracellular cell-adhesion molecule-1) and PECAM-1 (platelet/endothelial cell adhesion molecule-1) is increased in WAT endothelial cells and induces adhesion and migration of monocytes. Chemokines, such as MCP-1 (monocyte chemoattractant protein-1), are increased in obese WAT and contribute to monocyte recruitment [5]. These inflammatory changes coupled with increased production of coagulation factors, e.g. PAI-1 (plasminogen activator inhibitor-1), have been linked to the increased risk of cardiovascular complications and diabetes [5].

Adipocytes actively participate in energy homeostasis and regulation of insulin sensitivity and neuroendocrine, cardiovascular and immune systems by secreting proteins and other factors, as well as responding to neural, hormonal and nutrient signals [8]. In fact, the endocrine role of adipose tissue was predicted several decades ago by Kennedy [9], and later supported by the discovery of monogenic obese mice by Ingalls and co-workers [10] and parabiosis experiments by Coleman and Hummell [11]. As will be discussed in detail later, the adipocyte hormone leptin acts as an afferent signal in the brain and peripheral organs to regulate feeding and energy expenditure [8]. Leptin also links energy stores to hormonal adaptations during fasting and feeding [8]. Furthermore, leptin mediates structural and functional changes in neuronal circuits and immune and cardiovascular systems [8]. Thus leptin provides a unique model for unravelling the biology of adipocyte hormones.

In this review, we will discuss how adipocyte hormones integrate WAT into the overall physiological regulation, and how dysregulation of adipocyte hormone production and signalling underlies the pathophysiology of neuroendocrine abnormalities, diabetes and other metabolic complications of obesity.

**LEPTIN**

Leptin was discovered in 1994 through positional cloning of the \(\text{Lep}^{ob/ob}\) gene ([12], but see [12a]). Mice and humans homozygous for the leptin gene mutation develop a ravenous appetite, morbid early-onset obesity, severe insulin resistance, steatosis and a variety of neuroendocrine defects, in particular, hypothalamic hypogonadism, as well as immunosuppression [13]. Leptin is expressed mainly by WAT, although low levels are produced in the stomach, mammary gland, placenta and skeletal muscle [13].

Leptin has a relative molecular mass of 16 kDa and circulates in free or bound forms. Free leptin is thought to represent bioavailable hormone, whereas leptin bound to its soluble receptor or other leptin-binding proteins represents inactive hormone. The concentration of leptin correlates positively with the amount of body fat; hence, obese individuals have higher leptin levels than lean individuals [8,14]. Although adipocyte size, triacylglycerol content or lipid metabolites have all been suggested, the precise signal linking fat mass and leptin synthesis and secretion is unclear. Leptin is higher in females than males even after adjusting for BMI (body mass index), due in part to increased production by subcutaneous adipose tissue in females, inhibition by androgens and stimulation by oestrogens [8,14]. Insulin, chronic glucocorticoid exposure and cytokines, e.g. TNF-\(\alpha\) and IL-6, increase leptin, whereas cold exposure and adrenergic stimulation decrease leptin [14]. Like most hormones, leptin exhibits a diurnal rhythm, peaking at night in humans and in the morning in rodents [15,16]. This diurnal pattern is dependent on feeding. A pulsatile leptin rhythm has also been recognized in humans and other primates, although the underlying mechanisms and functional significance remain obscure [15–17].

Caloric deprivation decreases leptin concentration out of proportion to loss of weight or fat [8,16]. In contrast, leptin levels rise slowly several hours after feeding [8]. The nutritional dynamics of leptin appears to be coupled to insulin and perhaps glucose [8]. As will be discussed later, these acute changes in leptin play a crucial role in the neuroendocrine and metabolic responses to fasting.

The leptin receptor belongs to the class 1 cytokine receptor family [18]. At least five leptin receptor isoforms, LR\(a\)–LR\(e\), derived from alternate splicing of the \(\text{lepr}\) mRNA have been described [18]. LR\(a\) is the predominant ‘short leptin receptor’ lacking the cytoplasmic domain required for signalling through the Jak/STAT (signal transduction and activators of transcription) pathway. This receptor has a widespread distribution in the brain, especially capillary endothelium, and peripheral tissues, and is thought to be involved in leptin transport [19]. Additionally, studies in cell lines have suggested a potential for signalling via MAPK (mitogen-activated protein kinase) and ERK (extracellular-signal-regulated kinase) [19,20].

LR\(b\) (‘long leptin receptor’) mediates intracellular signalling [21] (Figure 1). Leptin enters the brain through a saturable transport system and directly acts on LR\(b\)-positive neurons in the arcuate nucleus, leading to
Figure 1  Leptin signalling via LRb
Leptin binds to LRb and autophosphorylates Jak2 and Tyr985 (Y985-P) and Tyr1138 (Y1138-P) on the cytoplasmic domain of LRb. LRb-phosphorylated Tyr1138 mediates the activation of STAT3, leading to transcription of neuropeptides and other target genes. SOCS3 is increased by STAT3 and terminates the leptin signal.

suppression of NPY (neuropeptide Y) and AGRP (agouti-related peptide) and increase in α-MSH (α-melanocyte-stimulating hormone), derived from POMC (pro-opiomelanocortin), and CART (cocaine and amphetamine-regulated transcript) [14] (Figure 2). α-MSH signals anorexia and thermogenesis through MC (melanocortin)-3 and -4 receptors in the paraventricular nucleus and other areas of the hypothalamus [14]. AGRP is an endogenous antagonist of α-MSH, whereas NPY stimulates feeding and reduces energy expenditure. Thus the net effect of leptin is to inhibit feeding and decrease weight [8,14]. Studies also indicate that leptin regulates glucose via hypothalamic and brain stem neuronal circuits [8,14].

Like other cytokine receptors, LRb does not have intrinsic enzymatic activity [21]. Rather, binding of leptin to LRb leads to association with Jak2, autophosphorylation of Jak2, phosphorylation of Tyr985 and Tyr1138 on LRb and phosphorylation and activation of STAT3 (signal transducer and activator of transcription 3) [21] (Figure 1). The latter acts as a transcription factor to regulate neuropeptides and various leptin target genes [21]. LRb-phosphorylated Tyr985 recruits the tyrosine phosphatase SHP-2 (Src-homology protein tyrosine phosphatase-2), which mediates activation of p21ras/ERK signalling [21]. Moreover, LRb-phosphorylated Tyr985 inhibits leptin signalling by inducing SOCS3 (suppressor of cytokine signalling 3) [21] (Figure 1). Binding of Jak2 to SOCS3 also contributes to termination of the leptin signal [21]. Studies have revealed a cross-talk between leptin and insulin signalling mediated through Jak2, PI3K (phosphoinositide 3-kinase) and IRS1 and IRS2 (insulin receptor substrate 1 and 2 respectively) [22]. As predicted, ablation of the arcuate hypothalamic nucleus, or loss of LRb or STAT3 in neurons, produces an obese phenotype similar to leptin deficiency (Lepob/ob) [23–25]. Ablation of LRb from POMC neurons results in modest weight gain [26]. In contrast, SOCS3 haploinsufficiency or neuron-specific ablation of SOCS3 enhances leptin sensitivity, decreases feeding and weight, and improves glucose and lipids in obese mice [27,28].

Role of leptin in energy homoeostasis: famine or feast?
Leptin was originally proposed to serve as a satiety signal in the brain to inhibit feeding and reduce weight and fat [8]. This negative feedback effect of leptin is consistent with development of hyperphagia and obesity in humans and rodents with congenital deficiency of leptin ([13,29,30], but see [30a]). As expected, leptin treatment reverses obesity in Lepob/ob, but not Leprob/db mice [13]. Similarly, leptin suppresses appetite and decreases body weight, specifically fat, in leptin-deficient patients ([29,30], but see [30a]). Moreover, patients who are heterozygote for leptin gene mutations have partial leptin
Leptin is secreted by adipose tissue, enters the brain via a saturable mechanism and directly activates neurons in the arcuate nucleus expressing α-MSH and CART. In contrast, NPY/AGRP neurons are suppressed. These neurons project to the paraventricular nucleus (PVN) and send relays to the cortex and brainstem, leading to appetite inhibition, increased thermogenesis and insulin sensitivity, stimulation of fatty acid oxidation and control of the neuroendocrine axis. The action of leptin is coupled to hypothalamic nuclei involved in regulation of circadian rhythm and sleep-wake cycles. LHA, lateral hypothalamic area; OXY, oxytocin; SCN, suprachiasmatic nucleus; SpVZ, subparaventricular zone; VMN, ventromedial nucleus.

Since leptin falls rapidly during fasting, we reasoned that the reduction in leptin served as a signal for the switch from fed to fasted states, leading to hyperphagia, reduction in energy expenditure, suppression of thyroid, reproduction and growth hormones, and immunosuppression [16] (Figure 3). The net effect of this leptin-mediated adaptation to fasting would be to limit the high-energy costs of reproduction, growth and immunity, and replenish energy stores [8]. From an evolutionary standpoint, this starvation response would be beneficial to survival. Although initially demonstrated in rodents, this idea has recently been extended to humans, where the fall in reproductive hormones, thyrotropin and growth hormone during short-term fasting or chronic nutritional deprivation was reversed by leptin replacement [32–34]. TRH (thyrotropin-releasing hormone) expression is decreased in the paraventricular nucleus, consistent with tertiary hypothyroidism [39]. These changes are reversed by leptin treatment, especially following direct injection in the brain [8]. In addition, leptin has trophic effects on brain development in rodents and humans and also regulates synaptic plasticity [40–43].

In contrast with the robust effects of low leptin level on the neuroendocrine axis and metabolism, the rise in leptin from the ad libitum-fed state to obesity elicits a minimal response [44] (Figure 3). The vast majority of obese animals have elevated leptin levels, and the failure of endogenous leptin to inhibit feeding and prevent obesity suggests ‘leptin resistance’ [8]. Rodents and humans with ‘common’ obesity as a result of polygenic factors and overeating are less responsive to exogenous leptin [8]. It has been suggested that leptin may fail to reach its targets in the brain parenchyma in obesity as a result of defective transport across the blood–brain barrier [45]. Leptin may fail to activate hypothalamic.
Adipocyte hormones and obesity

Figure 3  Dose effects of leptin during fasting and feeding

The fall in leptin during fasting stimulates hyperphagia, decreases energy expenditure, suppresses thyroid, growth and reproductive hormones and immunity, and activates the HPA axis. The leptin-mediated adaptation to fasting increases body weight and fat. The lack of functional leptin in Lepr<sup>ob/ob</sup> or leptin receptor in Lepr<sup>db/db</sup> mice produces an obese phenotype due to unmitigated fasting. In contrast with the robust metabolic and hormonal responses to fasting, the rise in leptin in diet-induced obesity (DIO) has minimal effects on feeding and energy expenditure. E<sub>2</sub>, oestradiol; GH, growth hormone; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine.

Neuronal circuits in diet-induced obesity, for example through induction of SOCS3 expression which decreases leptin signalling [21]. The activity of PTP1B (protein tyrosine phosphatase 1B), which normally terminates the leptin signal, may be increased in obesity [46]. This is in agreement with the increase in leptin sensitivity and leanness of PTP1B-deficient mice [46]. Leptin resistance may also involve the dysregulation of neuropeptide mediators, hormones other than leptin (e.g. insulin and ghrelin) and metabolic fuels (e.g. glucose and lipids) [8].

Teleologically, the skewed metabolic response in favour of low leptin is likely to have evolved as a safeguard against the threat of starvation, by optimizing feeding and energy storage [47]. This adaptation for energy efficiency is certain to have been advantageous when food shortage was the pre-eminent selection pressure over thousands of years of human evolution, but is thought to underlie the current epidemics of obesity, diabetes and other complications in modern societies where food is plentiful and sedentary lifestyle is normal.

Other neuroendocrine effects of leptin

Several lines of evidence suggest that leptin has an important role in reproduction and regulation of the hypothalamic–pituitary–gonadal axis [14]. Leptin stimulates the secretion of GnRH (gonadotropin-releasing hormone) during fasting, and is positively associated with GnRH and oestradiol pulsatility. Leptin-deficient mice and humans fail to undergo pubertal maturation and are invariably sterile. These defects are corrected by leptin treatment, whereas weight loss alone is ineffective [13,29]. Leptin supplementation has a permissive effect on reproduction in rodents and restores menstrual cycles in patients with functional or exercise-induced amenorrhea [32–48]. These effects appear to involve all levels of the reproductive axis, i.e. hypophysiotropic neurons, anterior pituitary and gonads [14].

Leptin prevents the fasting-induced suppression of proTRH mRNA in paraventricular nucleus neurons [39], reverses the inhibitory effect of fasting on pulsatile thyrotropin secretion [32] and blunts the decline in thyroid hormone levels during fasting [39]. However, leptin does not appear to affect the thyroid axis in the fed state [14]. Teleologically, the skewed metabolic response in favour of low leptin is likely to have evolved as a safeguard against the threat of starvation, by optimizing feeding and energy storage [47]. This adaptation for energy efficiency is certain to have been advantageous when food shortage was the pre-eminent selection pressure over thousands of years of human evolution, but is thought to underlie the current epidemics of obesity, diabetes and other complications in modern societies where food is plentiful and sedentary lifestyle is normal.
impaired in patients with a leptin receptor mutation [51]. In addition, these patients have low IGF-1 and IGFBP (IGF-binding protein)-3 levels and delayed growth during early childhood [51]. Leptin replacement blunts the fall in total IGF-1 but not free IGF-1 concentrations during fasting, but has no substantial effects on IGFBP-3 [32].

**ADIPONECTIN**

Adiponectin, a protein exclusively synthesized by adipocytes, was independently discovered by several laboratories, hence its various names: Acrp30 (adipocyte complement-related protein of 30 kDa), apM1 (adipose most abundant gene transcript 1), adipoQ and GBP28 (gelatin-binding protein of 28 kDa) [52]. The primary structure of adiponectin contains an N-terminal signal sequence, a variable domain, a collagen-like tail domain and a C-terminal globular head domain. Adiponectin shares strong sequence homology with C1q and types VIII and X collagen. Moreover, the globular domain resembles TNF-α. Adiponectin circulates at very high levels (µg/ml), in contrast with leptin and other polypeptide hormones which circulate at ng/ml concentrations [52]. Native adiponectin exists as homotrimers which form hexamers and high-molecular-mass complexes, which are thought to mediate the biological activity of adiponectin [52].

In contrast with leptin, adiponectin is decreased in obesity and inversely related to glucose and insulin. The effects of insulin-sensitizing thiazolidinediones [53] are mediated at least in part through adiponectin [52]. Importantly, ablation of the adiponectin gene in mice resulted in insulin resistance, glucose intolerance, dyslipidaemia and increased susceptibility to vascular injury and atherosclerosis [52,54]. Adiponectin reverses these abnormalities by stimulating oxidation of fatty acids, suppressing gluconeogenesis and inhibiting monocyte adhesion, macrophage transformation, proliferation and migration of smooth muscle cells in blood vessels [52,55,56]. These actions of adiponectin are associated with insulin receptor phosphorylation, activation of AMPK (AMP-activated protein kinase) and modulation of NF-κB (nuclear factor κB) [52,55,56].

Adiponectin receptors (AdipoR1 and R2) contain seven transmembrane domains, but are structurally and functionally distinct from GPCRs (G-protein-coupled receptors) ([57], but see [57a]). AdipoR1 is abundant in muscle and binds with high affinity to globular adiponectin and low affinity to the full-length protein. AdipoR2 is enriched in liver and has intermediate affinity for globular and full-length adiponectin. Both receptors mediate the phosphorylation and AMPK [58].

Peripheral adiponectin treatment decreases body fat by enhancing energy expenditure and fatty acid oxidation [58]. Chronic adiponectin treatment inhibits food intake in obese rats is association with reduction in weight, glucose and lipids [59–61]. Since both AdipoR1 and R2 are present in the brain, we hypothesized that adiponectin may act centrally to exert these metabolic actions ([62], but see [62a]). In agreement, the full-length adiponectin, the globular form and a mutant protein unable to form hexamers increased brown adipose thermogenesis, enhanced lipid oxidation and lowered glucose following injection into the lateral cerebral ventricle ([62], but see [62a]). Adiponectin potentiates the effect of leptin on thermogenesis and fatty acid oxidation. Both adipocyte hormones increased CRH expression and immunostaining of Fos protein in the paraventricular nucleus, suggesting an activation of hypothalamic sympathetic circuits. Moreover, dominant agouti (A/y/a) mice that are incapable of melanocortin signalling failed to respond to either leptin or adiponectin, implying an overlap in central neuronal targets ([62], but see [62a]). To date, our studies have not revealed significant effects of adiponectin on reproduction, thyroid hormone or HPA axis (R. S. Ahima, unpublished work).

**RESISTIN**

Resistin has a relative mass of 12 kDa and belongs to a family of cysteine-rich C-terminal domain proteins called RELMs (resistin-like molecules) [63,64]. Resistin was named for its ability to induce insulin resistance in rodents [63]. In contrast with the close homologies observed between human and rodent leptin and adiponectin, human resistin shares only 64% homology with murine resistin. Importantly, although rodent resistin is produced and secreted by WAT, human resistin is secreted by mononuclear cells and activated macrophages [65]. In rodents, multimeric complexes of resistin and RELMβ have been identified [66]. Each promoter consists of a C-terminal disulphide-rich β-sandwich head and an N-terminal α-helical tail. The latter associates with itself to form three-stranded coils. Interchain disulphide linkages form tail-to-tail hexamers. Resistin circulates as hexamers and trimers [66].

As predicted, systemic treatment or transgenic over-expression of resistin decreases the ability of insulin to suppress hepatic glucose output or increase glucose uptake by muscle [63,67,68]. Infusion of a mutant resistin protein lacking the intertrimer disulphide bonds was more potent, suggesting that these bonds be may be crucial to activation of resistin [66]. The effects of resistin on glucose are reversed by knockout of the resistin gene or reduction in resistin protein through antisense oligo-nucleotide treatment [69,70]. In contrast with leptin and adiponectin, resistin inhibits the phosphorylation and activation of AMPK in liver and muscle [67,69,70]. Resistin
induces SOCS3 in adipose tissue and liver, concomitant with its effect to inhibit insulin signalling [71].

So far, the role of resistin in glucose homeostasis in humans is unclear [72]. Resistin single nucleotide polymorphisms have been linked to obesity and diabetes in some studies [73]. Resistin has been reported to be elevated in adipose tissue and serum in obesity and insulin resistance, although other studies have failed to establish such a relationship [73–76]; for a review on the potential role of resistin in obesity and diabetes, see [76a]). Resistin appears to confer an increased risk of inflammation and atherosclerosis [77–79]. In rodents, resistin is decreased after fasting and increased after feeding, similar to leptin, and both are partly controlled by insulin and glucose [80]. Whereas the addition of resistin to preadipocytes inhibits adipogenesis, the loss of resistin function increases body weight and fat while enhancing insulin sensitivity [81,82]. Whether resistin plays a significant role in energy homeostasis and whether this occurs through a central or peripheral mechanism is as yet unknown.

**STEROID HORMONES**

Adipose tissue expresses enzymes involved in the metabolism of sex steroids, thereby influencing the bioactivity of these hormones [83,84]. For example, cytochrome P450-dependent aromatase is highly expressed in adipose tissue stromal cells and preadipocytes and mediates the conversion of androgens into oestrogens (i.e. androstenedione into oestrone and testosterone into oestradiol). On the other hand, 17βHSD (hydroxysteroid dehydrogenase) mediates the conversion of weak into strong sex steroids (i.e. androstenedione into oestrone and testosterone into oestradiol). These interconversions of sex steroids have been implicated in the sexual dimorphism of fat distribution, whereby young women have greater subcutaneous tissue and males and postmenopausal women have relatively higher abdominal (visceral) adipose tissue [83,84]. The level of 17βHSD is decreased relative to aromatase in subcutaneous adipose tissue, and the opposite is the case in visceral adipose tissue [84]. Interestingly, loss of the aromatase gene in mice and humans increases visceral fat, and the latter has been associated with features of the ‘metabolic syndrome’, including insulin resistance, hyperlipidaemia and steatosis [85–88].

The adrenal gland is the primary source of circulating glucocorticoids; however, adipose produces enzymes which activate or inactivate these steroid hormones [89]. The oxidoreductase 11βHSD-1 (11βHSD type 1) catalyses the conversion of inactive 11β-ketoglucocorticoid metabolites (i.e. cortisone in humans and 11-dehydrocorticosterone in mice) into active 11β-hydroxylated metabolites (i.e. cortisol in humans and corticosterone in mice). 11βHSD-1 is abundantly expressed in adipose tissue, especially visceral fat, and increases the local production of glucocorticoids without affecting systemic levels [89]. Studies in rodents have linked the dysregulation of glucocorticoid metabolism by 11βHSD-1 to the ‘metabolic syndrome’ [90,91]. Mice with transgenic overexpression of 11βHSD-1 in adipocytes have increased levels of corticosterone in visceral adipose tissue, central obesity, insulin resistance, increased lipids, hypertension and steatosis [90,91], whereas mice with deletion of 11βHSD-1 are resistant to diet-induced obesity, have preferential fat deposition in subcutaneous adipose tissue, improved glucose and insulin tolerance and are less prone to atherosclerosis [92,93]. Likewise, epidemiological, genetic and biochemical studies in humans have suggested a link between 11βHSD-1 activity and visceral adiposity, insulin resistance, dyslipidaemia and cardiovascular disease [94,95]. This raises the possibility that 11βHSD-1 may be useful as a marker for risk assessment and also targeted for the treatment of obesity-related complications.

**NEWER ADIPOCYTE HORMONES**

Visfatin was discovered as a secretory protein highly enriched in rodent and human visceral adipocytes, yet this protein is also expressed by liver, muscle, bone marrow and lymphocytes, where it was first identified as PBEF (pre-B-cell colony stimulating factor) [96,97]. The expression and secretion of visfatin is increased during the development of obesity; however, in contrast with inflammatory cytokines, the rise in visfatin does not decrease insulin sensitivity. Instead, visfatin exerts insulin-mimetic effects in cultured adipocytes, hepatocytes and myotubes and lowers plasma glucose in mice [96]. As expected, mice heterozygous for mutation in the visfatin gene have higher glucose levels than wild-type mice [96]. Visfatin binds to the insulin receptor with similar affinity but at a site distinct from insulin [96]. In contrast with insulin, visfatin levels do not change with feeding and fasting [96]. The discovery of visfatin may lead to novel therapies for diabetes; however, it remains to be determined if visfatin acts in concert with insulin to regulate metabolism and whether such interaction occurs via endocrine or paracrine mechanisms [96,97].

Vaspin (visceral adipose tissue-derived serpin) is a member of the serine protease inhibitor family isolated by from the visceral WAT of OLETF (Otsuka Long-Evans Tokushima fatty) rats, a model of abdominal obesity, insulin resistance and diabetes [98]. Rat, mouse and human vaspins exhibit approx. 40% homology with α1 antitrypsin. Vaspin expression increases by 30 weeks, coinciding with obesity and high insulin levels in OLETF rats, and declines as diabetes worsens and the rats lose weight by 50 weeks. Vaspin is restored by insulin or pioglitazone treatment [98]. Importantly, administration of vaspin to obese mice improves glucose tolerance and
insulin sensitivity and reverses the expression of half of the number of genes induced in WAT by diet-induced obesity [98].

A recent study revealed that RBP4 (retinol-binding protein 4) is elevated in insulin-resistant mice and humans with obesity and Type II diabetes [99]. RBP4 levels are normalized by rosiglitazone, establishing a link with insulin sensitization [99]. Transgenic overexpression of human RBP4 or injection of recombinant RBP4 induces insulin resistance in mice, whereas deletion of Rbp4 enhances insulin sensitivity [99]. RBP4 induces expression of the gluconeogenic enzyme PEPCK (phosphoenolpyruvate carboxykinase) and decreases insulin signalling in muscle. Interestingly, fenretinide, a synthetic retinoid that increases urinary RBP4 excretion, reduces serum RBP4 levels and improves insulin action in obese mice [99]. Thus lowering RBP4 could be a potential therapy for diabetes. The cell-surface protein megalin (gp320) is the only RBP4 receptor known so far, although the other lipophilic molecules that may mediate its effect on

CONCLUSIONS
This review emphasizes the roles of proteins secreted by adipose tissue. Leptin has well-defined effects on neuro-endocrine function, energy homoeostasis, immunity and other systems, supported by genetic and pharmacological evidence in rodents and humans. The mechanisms by which leptin is produced, transported and signals in the brain and peripheral organs provide useful models for understanding the biology of other proteins secreted by adipocytes and how they influence metabolism. Knowledge of specific signalling pathways of adipocyte hormones will benefit our understanding of obesity and associated metabolic diseases.

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REFERENCES


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