Adipose Tissue as an Endocrine Organ

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Abstract

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Adipose tissue plays a critical role in energy homeostasis, not only in storing triglycerides, but also responding to nutrient, neural, and hormonal signals and secreting adipokines that control feeding, thermogenesis, immunity, and neuroendocrine function. A rise in leptin signals satiety to the brain through receptors in hypothalamic and brainstem neurons. Leptin activates tyrosine kinase, Janus kinase 2, and signal transducer and activator of transcription 3, leading to increased levels of anorexigenic peptides, e.g., α-melanocyte stimulating hormone and cocaine- and amphetamine-regulated transcript, and inhibition of orexigenic peptides, e.g., neuropeptide Y and agouti-related peptide. Obesity is characterized by hyperleptinemia and hypothalamic leptin resistance, partly caused by induction of suppressor of cytokine signaling-3. Leptin falls rapidly during fasting and potently stimulates appetite, reduces thermogenesis, and mediates the inhibition of thyroid and reproductive hormones and activation of the hypothalamic–pituitary–adrenal axis. These actions are integrated by the paraventicular hypothalamic nucleus. Leptin also decreases glucose and stimulates lipolysis through central and peripheral pathways involving AMP-activated protein kinase (AMPK). Adiponectin is secreted exclusively by adipocytes and has been linked to glucose, lipid, and cardiovascular regulation. Obesity, diabetes, and atherosclerosis have been associated with reduced adiponectin levels, whereas adiponectin treatment reverses these abnormalities partly through activation of AMPK in liver and muscle. Administration of adiponectin in the brain recapitulates the peripheral actions to increase fatty acid oxidation and insulin sensitivity and reduce glucose. Although putative adiponectin receptors are widespread in peripheral organs and brain, it is uncertain whether adiponectin acts exclusively through these targets. As with leptin, adiponectin requires the central melanocortin pathway. Furthermore, adiponectin stimulates fatty acid oxidation and reduces glucose and lipids, at least in part, by activating AMPK in muscle and liver.

Key words: adipokine, leptin, adiponectin, hypothalamus, metabolism

Adipose Tissue

There has been a paradigm shift from the notion of adipose tissue merely as a storage site for energy to one where adipose tissue plays an active role in energy homeostasis and various processes (1). The predominant type of adipose tissue, commonly called "fat" in mammals is white adipose tissue (WAT).[1] WAT is comprised of mostly adipocytes, surrounded by loose connective tissue that is highly vascularized and innervated, and contains macrophages, fibroblasts, adipocyte precursors, and various cell types. The largest WAT depots are found in the subcutaneous region and around viscera. WAT provides a limitless capacity for triglyceride storage vital for survival. The concurrent rise in insulin, glucose, and lipids during meals stimulates triglyceride formation and storage in liver and WAT. Conversely, the fall in insulin during fasting triggers glycogen breakdown and lipolysis through activation of the sympathetic nervous system and elevation of glucagon, epinephrine, and glucocorticoids. The latter maintain glucose supply to the brain and vital organs. Fatty acids released from adipose tissue during fasting are partially oxidized by muscle and liver, generating ketones that serve as alternate fuels for the brain and peripheral organs. As will be discussed later, adipocytes actively participate in energy homeostasis by secreting leptin, adiponectin, acylation stimulating protein, and other factors (Table 1).

The increase in WAT mass in obesity is associated with profound histological and biochemical changes characteris-

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[1] Nonstandard abbreviations: WAT, white adipose tissue; TNF, tumor necrosis factor; IL, interleukin; 11β-HSD-1, 11β-hydroxysteroid dehydrogenase type 1; CNS, central nervous system; LR, leptin receptor; BBB, blood–brain barrier; PVN, paraventricular nucleus; LHA, lateral hypothalamic area; NPY, neuropeptide Y; AGRP, agouti-related peptide; MCH, melanin-concentrating hormone; α-MSH, α-melanocyte stimulating hormone; POMC, pro-opiomelanocortin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; AMPK, AMP kinase; HMW, high molecular weight; AdipoR, adiponectin receptor.

Table 1. Factors produced by WAT

Secreted proteins	Receptors	Enzymes and transporters
Leptin	Peptide and glycoprotein	Lipid metabolism
Adiponectin	Insulin	Lipoprotein lipase
Resistin (in rodents)	Glucagon	Apolipoprotein E
Angiotensinogen	Thyroid stimulating hormone	Cholesterol ester transfer protein
TNF-α	Growth hormone	Adipocyte fatty acid binding protein
IL-6	Angiotensin-II	CD36
Adipsin	Gastrin/cholecystokinin B	
Acylation stmulating protein	Adiponectin	Glucose metabolism
Fasting-induced adipose factor	Cytokine	Insulin receptor substrate 1,2
PAI-1	IL-6	Phosphatidylinositol 3-kinase
Tissue factor	TNF-α	Protein kinase B (Akt)
Monocyte chemoattractant protein-1	Leptin	GLUT4
Tranforming growth factor-β		Protein kinase λ/ζ
Visfatin	Nuclear	
Vaspin	PPARγ	Glycogen synthase kinase-3α
Retinol binding protein-4	Glucocorticoid	
	Estrogen	Steroid metabolism
	Progesterone	Aromatase
	Androgen	11β-hydroxysteroid dehydrogenase type 1
	Thyroid	17β-hydroxysteroid dehydrogenase
	Vitamin D	
	Nuclear factor-κB	

WAT, white adipose tissue; TNF, tumor necrosis factor; IL, interleukin; PPAR, peroxisome proliferator-activated receptor; GLUT4, glucose transporter 4.

tic of inflammation (2,3). Studies in obese humans and rodents have shown an increase in activated macrophages that form giant cells and produce tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) and various cytokines (2,3). C-reactive protein is increased in obesity. Intracellular adhesion molecule 1 and platelet-endothelial cell adhesion molecule-1, which induce adhesion and migration of monocytes, are both increased in WAT endothelium in obesity. Monocyte chemoattractant protein 1 and various chemokines are increased in obese WAT and contribute to monocyte recruitment (2,3). Obesity also results in an increase in fibrinogen, plasminogen activator inhibitor-1 and various coagulation factors (4). WAT inflammation and hypercoagulation have been linked to increased cardiovascular risk in obesity (5).

It is well established that adipose tissue controls the levels and bioactivity of sex steroids (6). Cytochrome P450–dependent aromatase produced by adipose stromal cells and preadipocytes mediates androgen to estrogen conversion, i.e., androstenedione to estrone and testosterone to estradiol. 17β-hydroxysteroid dehydrogenase converts weak sex steroids to strong ones, i.e., androstenedione to testosterone and estrone to estradiol. Changes in the local levels of these hormones are thought to underlie the sex differences in fat distribution, by which young women have greater subcutaneous WAT in contrast to a predominance of abdominal/visceral WAT in men and postmenopausal women (7). Visceral adiposity in the latter has been associated with cardiovascular disease (7).

The oxidoreductase 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) catalyzes the conversion of inactive 11β-ketoglucocorticoid metabolites, i.e., cortisone in humans and 11-dehydrocorticosterone in rodents, to active 11β-hydroxylated metabolites, i.e., cortisol in humans and corticosterone in mice (8). 11β-HSD-1 is abundantly expressed in visceral WAT and increases the local production of cortisol and corticosterone without affecting circulating levels (8). Studies in rodents have linked increased 11β-HSD-1 activity in WAT to the metabolic syndrome, a cluster of conditions characterized by central obesity, insulin resistance, steatosis, hypertension, and cardiovascular abnormalities (9–11). As predicted, transgenic 11β-HSD-1

overexpression in WAT increased local corticosterone level and resulted in central obesity, insulin resistance, hyperlipidemia, hypertension, and steatosis (10,11). Conversely, ablation of 11β-HSD-1 prevented central obesity (11). Instead, WAT formation increased in the subcutaneous region and was associated with improvement in glucose and lipid metabolism and reduced incidence of atherosclerosis (11). Increases in 11β-HSD-1 activity in visceral WAT has been linked to obesity, insulin resistance, dyslipidemia, and cardiovascular disease in humans (12,13).

In addition to the above hormones, WAT secretes resistin, complement factors, angiotensinogen, and various hormones and paracrine factors (Table 1). Moreover, enzymes involved in lipid metabolism and receptors for amines, steroid, and peptide hormones are expressed in WAT, highlighting the complexity of this organ system (Table 1).

Leptin

Leptin is produced mainly by adipocytes and in low levels by the gastric fundic epithelium, intestine, placenta, skeletal muscle, mammary epithelium, and brain (1). Leptin levels in WAT and plasma are related to energy stores, such that leptin increases in obesity and decreases during fasting. The precise signals mediating these nutritional changes in leptin are unclear, although studies have suggested an important role for insulin (14). Congenital leptin deficiency has been associated with hyperphagia, impaired thermogenesis, insulin resistance, hyperlipidemia, and central hypogonadism, all reversed by leptin treatment (15,16). In normal humans and rodents, leptin falls in concert with insulin during fasting and mediates the suppression of thyroid, growth, and reproductive hormones, stimulation of appetite, and inhibition of sympathetic nerve activity, thermogenesis, and immunity (17–19). Moreover, chronic weight loss in females and obese patients on dietary restriction decreases leptin, resulting in suppression of reproductive hormones, disruption of menstrual cycles, and reduction in sympathetic nerve activity and fuel use by muscle (20,21). Obesity is associated with leptin production and high plasma leptin concentration (22). Soon after its discovery, it was realized that the rise in endogenous leptin or exogenous leptin treatment was unable to prevent weight gain in obese humans and rodents (1,22). This apparent "leptin resistance" may result from a decrease in brain transport or attenuation of leptin signaling in the hypothalamus and other central nervous system (CNS) targets (1,23).

The leptin receptor (LR) belongs to the cytokine receptor class I family, containing extracellular ligand–binding, transmembrane, and cytoplasmic signaling domains (23,24). Various leptin receptor isoforms (LRa–LRe) are derived from alternate splicing of *lepr* transcript; however, leptin's effects on energy homeostasis and other systems are thought to involve the long receptor LRb, especially in the brain (1). Leptin crosses the blood–brain barrier (BBB) through a saturable mechanism, but the precise nature of the "leptin transporter" is unknown (25,26). BBB leptin transport falls in parallel with plasma level during fasting and increases in response to feeding (27). These BBB adaptations, which may involve lipids or other nutritional factors, enable leptin to function as both a fasting and satiety signal (27). In rodents, BBB leptin transport is decreased in diet-induced obesity and aging and may contribute to leptin resistance (27). The high uptake of leptin in hypothalamus is consistent with the role of this brain region in energy homeostasis, but the biological significance of leptin uptake in hippocampus, olfactory tubercle, thalamus, and cerebral cortex is unclear (27).

Leptin controls specific neuronal groups within the hypothalamus, brainstem, and other regions of the CNS (1). High LRb expression is present in the arcuate, dorsomedial, ventromedial, and ventral premamillary hypothalamic nuclei, moderate LRb expression is present in the periventricular region and posterior hypothalamic nucleus, and low LRb levels are expressed in the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). LRb is also localized in the nucleus tractus solitarius, lateral parabrachial nucleus, and motor and sensory nuclei and brainstem areas not normally associated with energy balance (1,28). An increase in leptin directly suppresses the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AGRP) in the arcuate nucleus. Melanin-concentrating hormone (MCH) and orexins expressed in LHA are inhibited indirectly by leptin. Leptin increases the levels of anorectic peptides, α-melanocyte stimulating hormone (α-MSH) derived from proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript, produced by neurons in the lateral arcuate nucleus. These project to the PVN to increase corticotropin-releasing hormone, thyrotropin-releasing hormone, and oxytocin (Figure 1). The net action of leptin is to inhibit appetite, stimulate thermogenesis, enhance fatty acid oxidation, decrease glucose, and reduce body weight and fat (Figure 1). Suppression of AGRP by leptin relieves the antagonism of α-MSH by AGRP at the melanocortin-4 receptor. The importance of these central neuronal circuits has been confirmed using neuroanatomic and genetic techniques. Ablation of the arcuate nucleus disrupts the negative feedback action of leptin, and LRb ablation recapitulates the obese phenotype of $Lepr^{db/db}$ mice, whereas LRb expression in the arcuate nucleus reverses obesity in Koletsky rats lacking all membrane-bound forms of LR (29–31). LRb ablation in POMC neurons attenuates leptin action, resulting in obesity (32). Ablation of NPY or MCH partially reverses hyperphagia, thermoregulatory defect, obesity, and hormonal abnormalities in $Lep^{ob/ob}$ mice (33,34).

As discussed in detail by Leshan et al. (24), the leptin signal is transmitted by the Janus kinase (JAK)-signal trans-

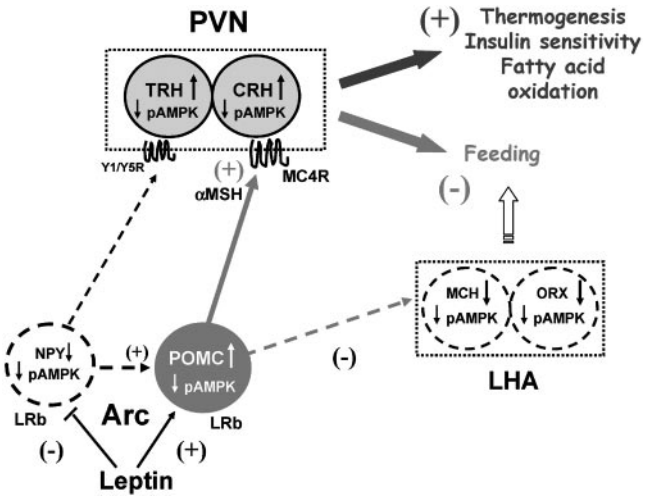

Figure 1: Hypothalamic neuronal circuit for leptin. Leptin directly suppresses NPY and AGRP and stimulates POMC and cocaine- and amphetamine-regulated transcript neurons in the arcuate nucleus, which project to the PVN and LHA to regulate thyrotropin-releasing hormone/corticotropin-releasing hormone and MCH/orexins, leading to inhibition of feeding, increased thermogenesis, and reduction in glucose and lipids. NPY controls feeding through Y1 and Y5 receptors. AGRP antagonizes the anorectic action of α-MSH action at MC4 receptors. Leptin inhibits AMPK, resulting in stimulation of fatty acid oxidation and weight loss.

ducer and activator of transcription (STAT) pathway. Binding of leptin to LRb results in autophosphorylation of JAK1 and 2, tyrosyl-phosphorylation of the cytoplasmic domain of LRb, and phosphorylation and activation of STAT3. Tyrosyl-phosphorylated STAT3 undergoes homodimerization, is translocated to the nucleus, and regulates expression of neuropeptides and other genes. The Myers laboratory showed the importance of the tyrosine at position 1138 by replacing this amino acid with serine (35). Y1138S (*Lepr*^{S1138}) mutation disrupted STAT3 activation, resulting in hyperphagia, impairment of thermoregulation, and obesity (35). In contrast to *Lepr* $^{db/db}$ mice, *Lepr*^{S1138} homozygotes had normal sexual maturation and growth and were less hyperglycemic, indicating distinct roles of the leptin–STAT3 interaction in energy balance, reproduction, growth, and glucose regulation (35).

Leptin acting through LRb has also been shown to regulate insulin receptor substrate-1 and 2, mitogen-activated protein kinase, extracellular signal-regulated kinase, Akt, and PI3 kinase, raising the possibility of cross-talk between leptin and insulin (36). The ability of leptin to inhibit feeding is related to activation of PI3 kinase in the hypothalamus (36). Blockade of PI3 kinase activity prevents the anorectic action of leptin. The leptin signal is terminated through induction of suppressors of cytokine signaling (SOCS)-3, a member of a family of proteins that inhibits JAK-STAT signaling (1). SOCS-3 haploinsufficiency enhances leptin sensitivity and prevents obesity (37). More specifically, SOCS3 ablation in neurons enhances leptin action, resulting in STAT3 activation, increase in hypothalamic POMC expression, and reduction in food intake and weight (38). Protein-tyrosine phosphatase-1B, which is well known to terminate insulin action, also inhibits leptin signaling through inactivation of JAK2 (1). In agreement, protein-tyrosine phosphatase-1B–deficient mice exhibit greater leptin sensitivity, increased hypothalamic STAT3 phosphorylation, and resistance to obesity (39).

AMP-activated protein kinase (AMPK) is another leptin target of interest (40). AMPK is phosphorylated and activated in response to energy deficit during fasting or cellular stress, leading to stimulation of fatty acid oxidation. AMPK is colocalized with STAT3 and hypothalamic peptides implicated in energy balance. Hypothalamic AMPK phosphorylation and activity are increased by fasting and decreased by leptin, insulin, and various anorectics (41). Interestingly, leptin's ability to regulate AMPK in the hypothalamus is dependent on melanocortin-4 receptor signaling (41).

Leptin acting through the JAK-STAT pathway does not provide a mechanism for neurotransmission. Earlier studies showed that leptin rapidly inhibited NPY secretion from hypothalamic explants, an effect that could not be attributed to gene expression (42). Leptin depolarizes hypothalamic POMC neurons partly through a non-specific cation channel, as well as decreasing the inhibitory tone of γ-aminobutyric acid released from NPY terminals in the arcuate nucleus (43). Conversely, leptin hyperpolarizes and inactivates NPY neurons in the arcuate nucleus (43). Falling leptin level during fasting increases the action potential frequency of NPY/AGRP neurons, similar to *Lep*$^{ob/ob}$ and *Lepr*$^{db/db}$ mice, and this may explain the why these conditions are characterized by hyperphagia (44). As discussed by Horvath (45), there are significant differences in excitatory and inhibitory synapses in the arcuate nucleus of *Lep*$^{ob/ob}$ and normal mice. Leptin treatment reverses this synaptic defect and hyperphagia in *Lep*$^{ob/ob}$ mice within hours, suggesting a short-term role in modulating synaptic plasticity (45).

We have previously reported that congenital leptin deficiency in rodents is associated with reduced brain weight, impaired myelination, and reduction of several neuronal and glial proteins (46). These structural and chemical abnormalities were partially reversible in adult *Lep*$^{ob/ob}$ mice by leptin treatment (46). The Simerly laboratory later confirmed that *Lep*$^{ob/ob}$ mice have a defective maturation of neuronal projections from the arcuate nucleus to PVN that is reversible by leptin treatment (47). This trophic action of leptin also occurs in the human brain (48). Leptin replacement therapy by daily subcutaneous injections of recombinant methionyl human leptin reduced body weight in patients with congenital leptin deficiency (48). Volumetric T1-weighted magnetic resonance imaging revealed an increase in gray matter tissue in the anterior cingulate gyrus,

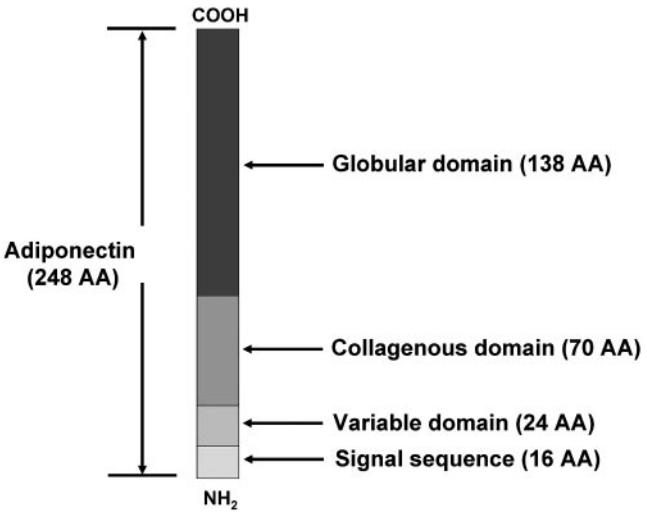

Figure 2: Primary structure of adiponectin.

the inferior parietal lobule, and cerebellum 6 months after leptin treatment, and these increases were maintained over 18 months (48).

Leptin enhances peripheral insulin action when administered by intravenous and intracerebroventricular infusion (49,50). Acute insulin infusion in the cerebral ventricle inhibits endogenous glucose production, in contrast to leptin infusion, which stimulates gluconeogenesis but does not affect glucose production as a result of a compensatory decrease in glycogenolysis (50). Blockade of the central melanocortin pathway prevents the effects of leptin on gluconeogenesis and suppresses glycogenolysis and glucose production (50). Overall, leptin seems to control hepatic glucose fluxes through a melanocortin-dependent pathway that stimulates gluconeogenesis and a melanocortin-independent pathway that inhibits glucose production and glycogenolysis. These data establish a crucial role for leptin in the CNS regulation of glucose metabolism that may relate to the pathogenesis of insulin resistance and type 2 diabetes associated with obesity (49,50).

Adiponectin

Adiponectin is produced exclusively by mature adipocytes and circulates at >1000 times the concentration of polypeptide hormones (51). The primary structure of adiponectin contains an N-terminal signal sequence, a variable domain, a collagen-like (tail) domain, and C-terminal globular (head) domain (Figure 2). Adiponectin shares strong sequence homology with C1q and types VIII and X collagen. The tertiary structure of the globular domain resembles TNF-α (52). Native adiponectin exists as homotrimers that form dimers of trimers (hexamers) and high molecular weight (HMW) complexes (51). (Figure 3). The potency of adiponectin has been linked to HMW complex and post-

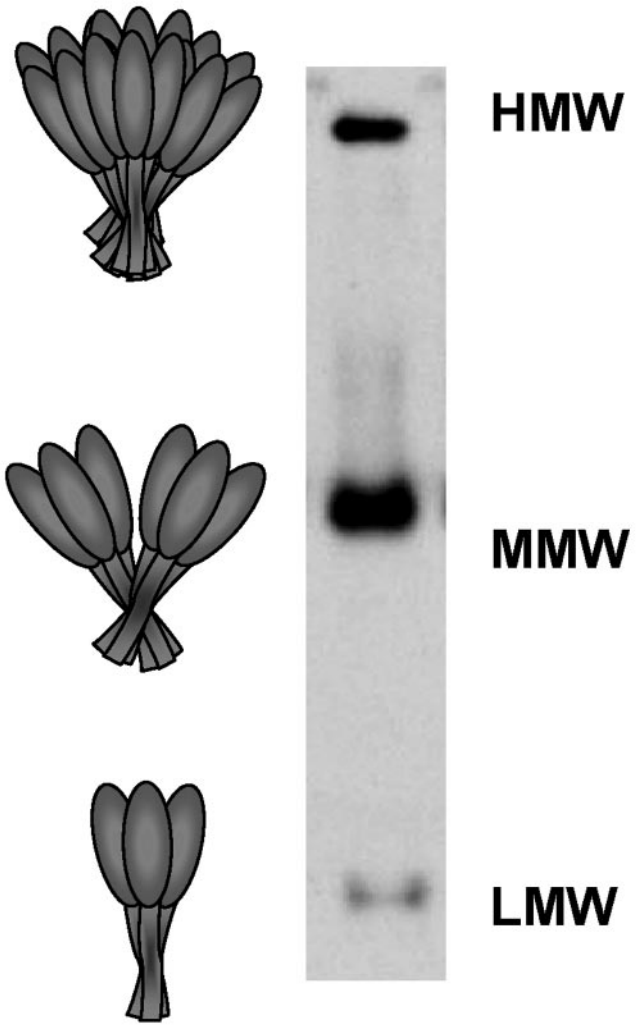

Figure 3: Multimeric structure of adiponectin. HMW, middle molecular weight, and low molecular weight are detected in mouse serum resolved on 4% to 20% sodium dodecyl sulfate polyacrylamide gel electrophoresis.

translational modifications, e.g., glycosylation and hydroxylation (53). As is the case with leptin, adiponectin is higher in women than men, but in contrast to leptin, adiponectin is reduced in obesity and increases in response to severe weight loss (51). Reduction of adiponectin has been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans and rodents (51). A longitudinal study in non-human primates revealed a strong relation between low adiponectin level and development of the metabolic syndrome (54). Adiponectin-deficient mice develop insulin resistance, glucose intolerance, and hyperlipidemia and increased susceptibility to vascular injury and atherosclerosis (55,56). Ablation of adiponectin in mice increases hepatic insulin resistance, whereas adiponectin replacement reverses these glucose, lipid, and vascular abnormalities (55–57).

The pharmacological effect of thiazolidinediones to improve insulin sensitivity involves an increase in total as well as HMW adiponectin (53). While globular adiponectin enhances lipid catabolism, it is important to stress that this form of adiponectin is expressed by bacteria but not mammals under normal conditions (51). Adiponectin stimulates fatty acid oxidation, suppresses hepatic gluconeogenesis, and inhibits monocyte adhesion, macrophage transformation, proliferation, and migration of smooth muscle cells in blood vessels (51). These metabolic and anti-inflammatory actions are closely associated with activation of AMPK and modulation of nuclear factor-κB. Putative adiponectin receptors (AdipoR) 1 and 2 containing seven-transmembrane domains, but structurally and functionally distinct from G protein–coupled receptors, are expressed widely in peripheral tissues and brain (58). AdipoR1 is abundant in muscle and binds with high affinity to globular adiponectin and with low affinity to full-length adiponectin. AdipoR2 is expressed mainly in liver and has intermediate affinity for both globular and full-length adiponectin. AdipoRs mediate the phosphorylation of AMPK and its downstream target acetyl CoA carboxylase. We have found that both AdipoR1 and R2 are highly expressed in the PVN, amygdala, area postrema, and diffusely localized in periventricular areas (unpublished observations). T-cadherin binds to adiponectin and may modulate its kinetics but is unlikely to mediate the signal transduction of adiponectin (59).

Peripheral adiponectin treatment decreases body weight, specifically fat, by increasing stimulating oxidation of fatty acids (60). Chronic adeno-associated virus–adiponectin treatment inhibits food intake in obese rats concomitant with reduction of body weight, glucose, and lipids (61). Seasonal reciprocal changes in leptin and adiponectin have been observed in mammalian hibernators (62). In marmots (*Marmota flaviventris*), leptin is positively associated with increasing WAT mass and adipocyte size, in contrast to adiponectin, which is negatively associated with WAT mass (62). These findings are consistent with the putative roles of low and high leptin, respectively, in mediating the switch from lipogenesis to lipolysis between winter and summer. To examine whether adiponectin is capable of acting centrally, we showed that adiponectin immunoreactivity increased in cerebrospinal after intravenous injection of recombinant adiponectin in mice (63). In contrast to leptin, injection of mammalian adiponectin into the lateral cerebral ventricle increased energy expenditure but did not affect feeding (63). The full-length, globular, and a mutant adiponectin unable to form hexamers all increased energy expenditure and reduced glucose after intraperitoneal or intracerebroventricular injection, whereas the collagenous domain was not effective (63). *Lep*$^{ob/ob}$ mice were especially sensitive to CNS and systemic adiponectin treatment, which increased thermogenesis and reduced body fat, glucose, and lipids (63). Adiponectin potentiated the central effects of leptin to increase thermogenesis and fatty acid oxidation and reduce glucose and lipids in *Lep*$^{ob/ob}$ mice (63). In contrast, dominant agouti (A^y/a) mice failed to respond to both leptin and adiponectin, implying a common involvement of melanocortin receptors (63).

Whether adiponectin enters the brain is controversial (64,65). Iodinated globular adiponectin does not cross the BBB in mice (64). Nonetheless, murine cerebral microvessels express AdipoR1 and R2, which are up-regulated during fasting (64). Globular adiponectin reduced the release of IL-6 from brain endothelial cells, providing a potential mechanism of action (64). Adiponectin, in particular the trimeric form, has been shown in human cerebrospinal fluid using gel filtration chromatography and is closely related to plasma adiponectin (P. Schereer, unpublished observations). Direct application of adiponectin protects human neuroblastoma SH-SY5Y cells from apoptosis induced by the mitochondrial complex I inhibitor, 1-methyl-4-phenylpyridinium (66). The antioxidative and antiapoptotic activities of adiponectin in this model were attributed to induction of superoxide dismutase and catalase and differential regulation of Bcl-2 and Bax expression (66). Furthermore, adiponectin depolarizes neurons in the area postrema and PVN (A. Ferguson and K. Sharkey, unpublished observations), raising the possibility that adiponectin gains access to the CNS through the circumventricular organs. How adiponectin is transported, what molecular forms of adiponectin mediate its biological effects, and what role, if any, AdipoR1 and R2 play in the diverse actions of this adipokine remain to be resolved.

Conclusion

Adipose tissue has complex interactions with the brain and peripheral organs. The discovery of leptin marked a major milestone in our understanding the endocrine role of adipose tissue. The critical roles of leptin in energy homeostasis, glucose and lipid metabolism, and immune and neuroendocrine function have been shown in humans and rodents with congenital or acquired leptin deficiency (e.g., fasting and lipodystrophy). In contrast, the biology of leptin in normal individuals and whether and leptin is indeed involved in obesity-related diseases are still uncertain. How leptin reaches its targets in the brain and peripheral organs, what receptors and downstream molecules specifically mediate leptin's effects on feeding, energy expenditure, glucose and lipid metabolism, and hormonal regulation and growth, and whether "leptin resistance" is the cause or consequence of obesity are yet to be clarified. Characterization of the biology of leptin provides a framework for understanding how adiponectin, resistin, cytokines, complement, procoagulant, and vasoactive peptides secreted by adipose tissue function under normal and pathological conditions. Insights into the signaling mechanisms involved in

the central and peripheral actions of adipokines will greatly benefit the pathophysiology and treatment of obesity and various metabolic diseases.

Acknowledgments

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