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MINIREVIEW

Adipokines and the Peripheral and Neural Control of Energy Balance

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Adipokines are secreted by adipose tissue and control various physiological systems. Low leptin levels during fasting stimulate feeding, reduce energy expenditure, and modulate neuroendocrine and immune function to conserve energy stores. On the other hand, rising leptin levels in the overfed state prevent weight gain by inhibiting food intake and increasing energy expenditure. These actions are mediated by neuronal circuits in the hypothalamus and brainstem. Leptin also controls glucose and lipid metabolism by targeting enzymes such as AMP-activated protein kinase and stearoyl-coenzyme A desaturase-1 in liver and muscle. Likewise, adiponectin and resistin control energy balance and insulin sensitivity via central and peripheral targets. As highlighted in this review, there are distinct as well as common signaling pathways for adipokines. Understanding adipokine signaling in the brain and other organs will provide insights into the pathogenesis and treatment of obesity, diabetes and various metabolic disorders. (*Molecular Endocrinology* 22: 1023–1031, 2008)

ADIPOKINES

THE WORLDWIDE INCREASE in obesity, diabetes, and related diseases has focused attention on the biology of adipose tissue. Adipose tissue secretes polypeptide hormones, *e.g*. leptin, adiponectin, and resistin (in rodents), proinflammatory cytokines, complement and coagulation factors, and vasoactive peptides (Table 1) (1, 2). Adipose tissue also produces enzymes that control the biosynthesis and activities of steroid hormones. Adipose tissue-derived aromatase and 17β-hydroxysteroid dehydrogenase catalyze the interconversion of sex steroids, whereas 11β-hydroxysteroid dehydrogenase type 1 mediates the conversion of cortisone to cortisol in humans and 11-dehydrocorticosterone to corticosterone in mice (3, 4). Collectively, adipose tissue-secreted factors called "adipokines" are involved in energy homeostasis and regulation of glucose and lipid metabolism, immunity, and neuroendocrine systems (Table 1). This review will focus on how leptin, adiponectin, and resistin affect energy homeostasis and glucose and lipid metabolism, and how dysregulation of the central and peripheral actions of these adipokines may underlie the pathogenesis of obesity, diabetes, and lipid disorders.

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Abbreviations: ACC, Acetyl-CoA carboxylase; AGRP, agouti-related protein; AMPK, AMP-activated protein kinase; AP, area postrema; CoA, coenzyme A; CPT-1, carnitine palmityl transferase 1; CSF, cerebrospinal fluid; GIP, gastric inhibitory polypeptide; JAK, Janus family of tyrosine kinases; LPL, lipoprotein lipase; LR, leptin receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription.

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LEPTIN

Leptin is mainly expressed by adipocytes but low levels are produced in the stomach, intestine, mammary epithelium, placenta, skeletal muscle, and possibly the brain (5). The concentrations of leptin in adipose tissue and plasma closely parallel the mass of adipose tissue and adipocyte size and triglyceride content. Thus, leptin increases in obesity and falls with weight loss (5). These changes are dependent on insulin and glucose. Leptin is also higher in women, partly due to higher production by sc adipose tissue, stimulation by estrogens, and inhibition by androgens. Moreover, leptin is increased by chronic glucocorticoid exposure and inflammatory cytokines. In contrast, cold exposure and adrenergic stimulation decrease leptin (1, 5).

Leptin reaches neuronal targets via the circumventricular organs and a saturable transport mechanism across the blood-brain barrier (1). Five leptin receptor isoforms, LRa–LRe, derived from alternate splicing of *lepr* mRNA have been identified (1, 5, 6). The most

Table 1. Actions of Adipokines

Adipokine	Source and Nutritional Regulation	Energy, Glucose, and Lipid Metabolism
Leptin	Mainly adipose tissue; low levels in gastric fundus, intestine, and muscle. *Obesity*: adipose mRNA and protein ↑ ↑; plasma ↑ ↑. *Fasting*: adipose mRNA and protein ↓; plasma ↓. *Refeeding*: adipose mRNA and protein ↑; plasma ↓	Inhibits feeding and increases energy expenditure; insulin sensitizer; stimulates fatty acid oxidation
Adiponectin	Adipose tissue. *Obesity*: adipose mRNA and protein ↓; plasma ↓. *Fasting*: adipose mRNA and protein ↑; plasma ↑. *Refeeding*: adipose mRNA and protein ↓; plasma ↓	Insulin sensitizer; stimulates fatty acid oxidation; may increase or decrease adiposity
Resistin	Adipose tissue in rodents and macrophages in human. *Obesity*: rodent adipose mRNA ↓ and protein ↑; plasma ↑. *Fasting*: rodent adipose mRNA and protein ↓; plasma ↓. *Refeeding*: rodent adipose mRNA and protein ↑; plasma ↑	Induces insulin resistance in rodents
TNFα	Adipose tissue and immune cells. *Obesity*: adipose and plasma protein ↑	Inhibits feeding, induces cachexia, and inhibits insulin sensitivity
IL-6	Adipose tissue, immune cells and muscle. *Obesity*: adipose and plasma protein ↑	Inhibits feeding, increases energy expenditure, and induces insulin resistance
Adipsin; complement factor D	Adipose tissue. *Obesity*: adipose mRNA and protein ↓ in rodents; ↑ in humans; adipsin levels are linked to acylation stimulating protein (ASP)	ASP promotes fatty acid and glucose uptake by adipocytes and stimulates insulin secretion
Plasminogen-activator inhibitor-1	Adipose tissue and liver. *Obesity*: adipose and plasma protein ↑; suppressed by thiazolidinediones	Increases adiposity and insulin resistance in rodents
Renin-angiotensin system	Adipose tissue, kidney, and vasculature	Angiotensin II increases adipogenesis and reduces insulin sensitivity
Retinol binding protein-4	Adipose tissue and liver. *Obesity*: adipose and plasma protein ↑ in rodents; not consistently elevated in humans	Enhances insulin action in rodents
Fasting-induced adipose factor; angiopoeitin-like protein 4	Expressed in adipose tissue, liver, and intestinal epithelium. mRNA and protein ↑ by calorie restriction, PPAR-α ,and fenofibrate	Increases triglycerides by inhibiting lipoprotein lipase; stimulates cholesterol synthesis; implicated in obesity and insulin resistance induced by gut bacteria
Visfatin; pre-B cell colony-enhancing factor 1; extracellular nicotinamide phosphoribosyltransferase	Adipose tissue, liver, and various tissues. *Obesity*: adipose and plasma protein ↑	Not an insulin mimetic as originally proposed
Vaspin	Adipose tissue and liver. *Obesity*: adipose and plasma protein ↑	Insulin sensitizer in rodents

↑, Increased; ↓, decreased.

abundant short leptin receptor, LRa, lacks the cytoplasmic domain necessary for Janus family of tyrosine kinases (JAK)-signal transducer and activator of transcription (STAT) signaling. LRa is abundantly expressed in brain capillary endothelium and peripheral organs and proposed to mediate leptin transport (1). The long leptin receptor, LRb, is restricted to the hypothalamus, brainstem, and key regions of the brain that control feeding, metabolism, and neuroendocrine systems (1, 5, 6). Binding of leptin to LRb leads to

association with JAK2, autophosphorylation of JAK2, phosphorylation of tyrosine residues 985 and 1138 on LRb, and activation of STAT3 (6) (Fig. 1). This cascade of events culminates in translocation of STAT3 to the nucleus and transcription of neuropeptides (6) (Fig. 1). Phosphorylated Tyr^{985} of LRb binds Src homology 2 (SH2)-containing tyrosine phosphatase-2, which activates ERK. Additionally, Tyr^{985} binds the suppressor of cytokine signaling (SOCS)3, leading to the termination of LRb signaling (6). Studies have also demonstrated that leptin stimulates the phosphorylation of Tyr^{1077} on LRb and activates STAT5 (Fig. 1) and ribosomal protein S6 kinase (7). Tyr^{1138} has a secondary role in the acute phosphorylation of STAT5. Moreover, Tyr^{1138} and STAT3 attenuate STAT5-dependent transcription (7). Protein-tyrosine phosphatase 1B activity is also stimulated by leptin and inactivates JAK2 and leptin signaling (6, 8). Studies have also demonstrated an interaction between the signaling pathways for leptin and insulin signaling in the hypothalamus (9). Both hormones inhibit food intake through activation of insulin receptor substrate-2, MAPK, ERK, Akt, and phosphatidylinositol 3-kinase (9).

LRb and downstream leptin signaling molecules have been localized in the hypothalamus and brain regions that control energy balance, hormone levels, and glucose metabolism (5). Leptin directly inhibits neurons in the arcuate nucleus of the hypothalamus expressing neuropeptide Y (NPY) and agouti-related protein (AGRP) (5) (Fig. 2). Conversely, leptin induces proopiomelanocortin (POMC), precursor of MSH, and cocaine- and amphetamine-regulated transcript in the arcuate nucleus (Fig. 2). These neurons project to the paraventricular nucleus and perifornical, dorsomedial, and lateral hypothalamic areas to suppress feeding, stimulate thermogenesis, and enhance lipid oxidation and insulin sensitivity in peripheral organs. Neurons in the paraventricular nucleus expressing melanocortin-4 receptor, CRH, TRH, and vasopressin, have been implicated as critical mediators of central leptin action (1, 5) (Fig. 2). Leptin also indirectly controls expression of melanin-concentrating hormone and orexins in the lateral hypothalamus as well as mesolimbic dopaminergic circuits (10, 11). Deficiency of leptin, LRb, and STAT3 specifically in POMC neurons induces hyperphagia and impairs thermogenesis leading to morbid obesity (5, 12–15). In contrast, the loss of orexigenic peptides, *e.g*. NPY and melanin-concentrating hormone, attenuates obesity in leptin-deficient $Lep^{ob/ob}$ mice (16, 17). SOCS3 and PTP1B deficiency ameliorates obesity by enhancing leptin sensitivity (18–21).

Apart from activating JAK-STAT signaling, leptin has rapid effects on neurotransmission and neuropeptide secretion and also modulates neuronal plasticity. Leptin inhibits NPY secretion by the hypothalamus, depolarizes POMC neurons by decreasing the inhibitory tone of γ-aminobutyric acid released from NPY terminals in the arcuate nucleus, and hyperpolarizes NPY neurons (22–24). Congenital leptin deficiency has been associated with a decrease in brain size, impaired myelination, and reduction in expression of neuronal and glial proteins in mice (25). Moreover, gray matter

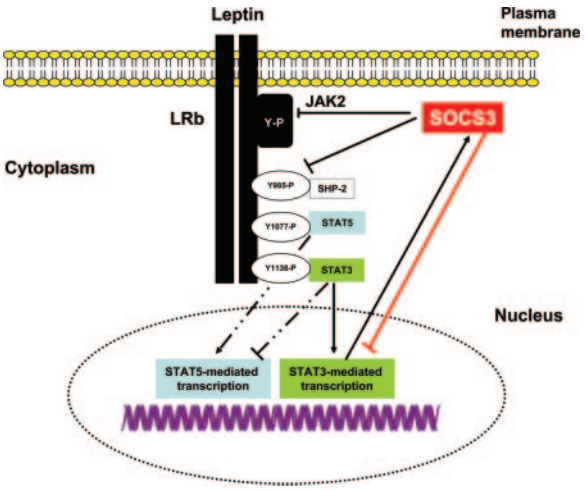

Fig. 1. Intracellular Signaling Pathways Regulated by LRb

Binding of leptin to the extracellular domain of LRb activates JAK2 tyrosine kinase leading to autophosphorylation of tyrosine residues on JAK2 and phosphorylation of Tyr ^{985}, Tyr^{1077}, and Tyr^{1138} on LRb. Phosphorylation of Tyr^{1138} mediates the activation and nuclear translocation of STAT3, which induces the transcription neuropeptides in the hypothalamus as well as SOCS3, which terminates leptin signaling. Tyr^{985} also promotes interaction of SOCS3 with LRb-JAK2, thereby attenuating leptin signaling. Tyr^{1077} plays a dominant role in the transcriptional activation of STAT5, and this action is inhibited by Tyr^{1138}-STAT3. SHP2, Src homology 2-containing tyrosine phosphatase-2.

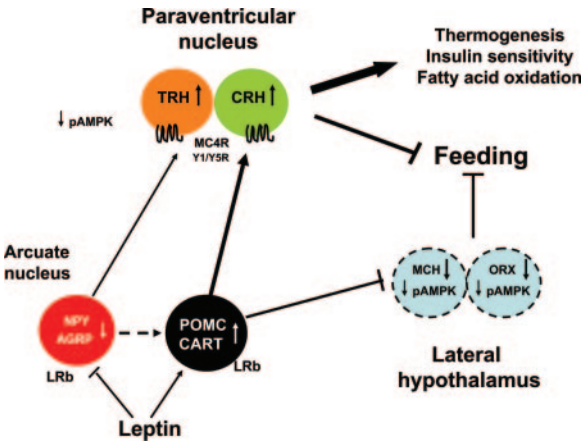

Fig. 2. Leptin Signaling in the Hypothalamus

Leptin binds to LRb on NPY/AGRP and POMC/cocaine- and amphetamine-regulated transcript (CART) neurons in the arcuate nucleus, leading to inhibition of feeding, and stimulation of thermogenesis, fatty acid oxidation, and enhancement of peripheral insulin sensitivity. Leptin-sensitive neurons in the arcuate nucleus project to the paraventricular nucleus to increase CRH and TRH, and lateral hypothalamic area to suppress melanin-concentrating hormone (MCH) and orexins (ORX). Leptin also inhibits AMPK phosphorylation.

defects have been demonstrated in the anterior cingulate gyrus, inferior parietal lobule, and cerebellum in patients with congenital leptin deficiency (26). These abnormalities are partially reversed by leptin treatment (25, 26). Leptin stimulates the development of axonal projections from the arcuate nucleus to paraventricular nucleus and has been shown to increase inhibitory synapses and reduce excitatory synapses in the hypothalamus (27, 28).

Leptin is a critical signal for alterations in energy stores in adipose tissue. An extreme manifestation of leptin's role as a starvation hormone is seen in patients and mice with congenital leptin deficiency, which develop voracious appetite, morbid obesity, immunosuppression, and hypothalamic hypogonadism (1, 5, 11). Acquired leptin deficiency due to fasting or lipodystrophy also stimulates feeding and suppresses immunity, sympathetic nervous activity, and sex and thyroid hormones (29–35). In contrast, the ability of leptin to signal excess energy storage is less robust (1, 5, 6). A majority of obese individuals have high levels of leptin but do not respond to rising endogenous leptin levels suggesting leptin resistance (1, 6). Studies have shown that leptin resistance in obese rodents is associated with impairment of leptin transport across the blood-brain barrier, reduction of leptin-mediated JAK-STAT signaling, and induction of SOCS3 (6, 36). Attenuation of leptin sensitivity in the brain leads to excess triglyceride accumulation in adipose tissue as well as muscle, liver, and pancreas (37).

Leptin plays an important role in preventing triglyceride storage outside adipose tissue (37). In lean healthy individuals, leptin is proposed to act indirectly on muscle and liver to stimulate the phosphorylation and activity of a critical energy sensor, AMP-activated protein kinase (AMPK) (38). Activated AMPK phosphorylates acetyl-coenzyme A (CoA) carboxylase (ACC) and malonyl-CoA decarboxylase, resulting in inhibition of ACC and activation of malonyl-CoA decarboxylase. ACC catalyzes the formation of malonyl-CoA, the first step in fatty acid synthesis, and malonyl-CoA inhibits carnitine palmityl transferase 1 (CPT-1), which controls fatty acid transport into mitochondria. Leptin limits accumulation of triglyceride in liver and muscle by activating AMPK, inhibiting ACC, reducing malonyl-CoA, increasing CPT-1 activity, and stimulating fatty acid oxidation (38). Leptin also acts via the brain to inhibit the activity of stearoyl-CoA desaturase-1, an enzyme that catalyzes the synthesis of monounsaturated fatty acids (mainly oleate and palmitoleate) (39). Leptin resistance in obesity promotes extraadipose lipid storage (steatosis) by diminishing AMPK activity, increasing activities of ACC, fatty acid synthase and stearoyl-CoA desaturase 1, and reducing CPT-1 activity in liver and muscle. Steatosis leads to formation of ceramide and various lipid metabolites that impair insulin sensitivity in liver and muscle as well as insulin secretion (37).

Leptin directly regulates insulin sensitivity and pancreatic β-cell function. Deletion of *lepr* in the brain induces insulin resistance and diabetes, whereas restoration of leptin signaling in the arcuate nucleus decreases insulin and normalizes glucose levels (40). Administration of leptin in the hypothalamus attenuates hepatic insulin resistance and glucose production in rodents on a high-fat diet, partly through activation of melanocortin signaling (41, 42). Importantly, deletion of *lepr* in the pancreas limits islet growth and insulin secretion in diet-induced obese mice, thus providing a link between leptin signaling in islets and obesity-associated diabetes (43).

ADIPONECTIN

Adiponectin is produced exclusively by adipocytes and circulates at high concentrations (μg/ml) in plasma (44). Native adiponectin exists as homotrimers that form low-molecular weight hexamers and high-molecular weight (HMW) complexes. Plasma concentrations of total and HMW adiponectin are higher in women than men, partly due to suppression of adiponectin by testosterone. Unlike leptin, adiponectin is reduced in obesity, increased in response to fasting, and decreased by refeeding (44). Adiponectin deficiency induces insulin resistance, glucose intolerance, and hyperlipidemia and increases susceptibility to vascular injury and atherosclerosis (44–46). Adiponectin reverses these abnormalities by stimulating fatty acid oxidation, suppressing gluconeogenesis, and inhibiting inflammation (44–46). The levels of HMW adiponectin are highly predictive of insulin sensitivity (47). Insulin-sensitizing thiazolidinediones increase HMW adiponectin in humans and rodents, and mice lacking adiponectin do not respond to thiazolidinedione treatment (48). Thus, adiponectin plays an essential role in mediating the antidiabetic effect of thiazolidinediones.

The actions of adiponectin in suppressing gluconeogenesis and enhancing lipid oxidation are related to activation of AMPK and inhibition of ACC in liver and muscle, whereas the antiinflammatory effect of adiponectin is associated with suppression of nuclear factor-κB and vascular adhesion molecules (44). Adiponectin is proposed to signal through two seven-transmembrane domain-containing proteins, AdipoR1 and AdipoR2, which are widely expressed and induce AMPK phosphorylation and activity (44) (Fig. 3). APPL1 (adaptor protein containing pleckstrin homology domain phosphotyrosine binding domain and leucine zipper motif) binds to adiponectin receptors and has been linked to the insulin-sensitizing action of adiponectin *in vitro* (49). The expression of AdipoR1 and AdipoR2 was found to be diminished in livers of obese mice, and this was related to attenuation of AMPK activity and insulin resistance (50). These defects were reversed by adenovirus-mediated expression of AdipoR1 and -R2. Ablation of AdipoR1 prevented the ability of adiponectin to activate AMPK, whereas AdipoR2 deficiency decreased peroxisome

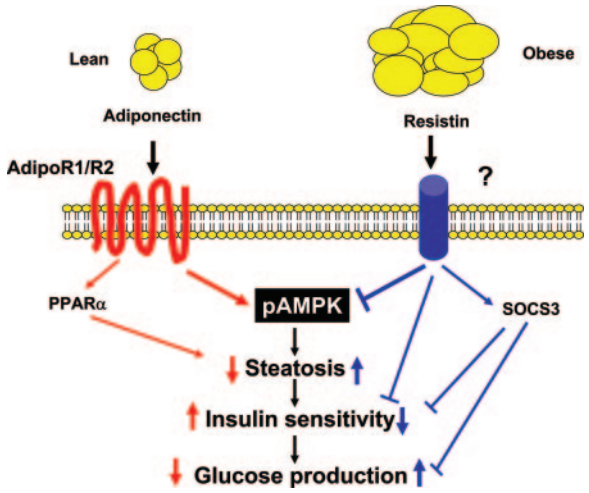

Fig. 3. Adiponectin and Resistin Signaling in the Liver

High adiponectin levels in lean individuals bind to AdipoR1 and -R2 in the liver, leading to phosphorylation and activation of AMPK and increased PPARα activity. Adiponectin stimulates fatty acid oxidation, prevents steatosis, enhances insulin signaling, and suppresses hepatic glucose production. Resistin is increased in obesity, inhibits AMPK activity, increases SOCS3, and induces insulin resistance.

proliferator-activated receptor-α (PPARα) signaling. Deficiency of AdipoR1 and R2 prevented adiponectin binding and induced steatosis, inflammation, oxidative stress, and insulin resistance, demonstrating important roles in glucose and lipid metabolism and immune function (50). AdipoR2 deletion in another study decreased lipid levels and improved insulin sensitivity in diet-induced obese mice, yet diabetes ensued because of pancreatic β-cell failure (51). Furthermore, AdipoR1 and AdipoR2 appeared to have opposing metabolic roles (52). AdipoR1 deficiency increased decreased energy expenditure, increased body fat, and induced insulin resistance. On the other hand, AdipoR2 deficiency led to higher energy expenditure, a leaner phenotype, reduced plasma cholesterol, and improved glucose levels (52).

Adiponectin receptors are widely distributed in the brain, but questions have been raised about a central action because adiponectin did not cross the blood-brain barrier in mice (53, 54). Nonetheless, several lines of evidence support the notion that adiponectin affects energy and glucose metabolism by targeting the brain (55). Trimeric and low molecular weight adiponectin are present in cerebrospinal fluid (CSF) in humans and rodents (56–58). The concentration of adiponectin in CSF increases after iv injection of adiponectin, suggesting blood-to-brain transport of adiponectin (55, 58). We have reported that intracerebroventricular administration of adiponectin potently increased energy expenditure and fatty acid oxidation and reduced body weight (55). Adiponectin and leptin both acted in the brain to stimulate energy expenditure and decrease glucose and lipids, showed similar patterns of signaling by increasing CRH expression and inducing Fos immunoreactivity in the paraventricular nucleus, and were inactive in agouti (A^y/a) mice lacking melanocortin signaling (55).

An antiobesity action of adiponectin is also supported by the ability of systemic administration of adiponectin to decrease body weight and fat via fatty acid oxidation (59, 60). However, other studies suggest an opposite effect of adiponectin on energy metabolism (61, 62). Transgenic overexpression of adiponectin in wild-type and *Lep*$^{ob/ob}$ mice resulted in obesity (61, 62). In *Lep*$^{ob/ob}$ mice, elevation of adiponectin decreased food intake and energy expenditure (62). Remarkably, insulin resistance and inflammation of adipose tissue were attenuated in these extremely obese mice (62). Kubota *et al.* (58) have reported that peripheral injection of adiponectin increased AMPK activity in the arcuate nucleus via AdipoR1, and this resulted in stimulation of food intake, reduction in energy expenditure, and weight gain. Conversely, hypothalamic AMPK activation was attenuated in adiponectin-deficient mice and was related to reduction of food intake, increased energy expenditure, and lean phenotype. Furthermore, adiponectin concentration in CSF increased after fasting and decreased after refeeding (58). Together, these data suggest that adiponectin acts as a starvation signal (58).

Electrophysiology of adiponectin has been studied in rat brainstem and hypothalamus (63, 64). Adiponectin depolarized area postrema (AP) neurons expressing both AdipoR1 and -R2, whereas AP neurons expressing only one subtype of receptor were insensitive (63). In the paraventricular nucleus, adiponectin hyperpolarized oxytocin neurons in contrast to induction of mixed depolarization-hyperpolarization responses in vasopressin neurons (64). Further analysis revealed that adiponectin-responsive oxytocin neurons expressed both AdipoR1 and R2, whereas vasopressin neurons expressed both receptors or one receptor. These results indicate different roles of adiponectin in controlling excitability of neurons in circumventricular areas such as AP that allow free access of large molecules into the brain *vs.* the paraventricular nucleus, which is protected by a blood-brain barrier (63, 64). Further work is needed to elucidate what molecular forms of adiponectin produce specific actions, how adiponectin-mediated electrical activity is coupled to energy balance, and whether AMPK and various cellular mediators are linked to electrical activity of adiponectin.

RESISTIN

Resistin belongs to a family of cystine-rich peptides called resistin-like molecules (65). Resistin is expressed and secreted by adipocytes in rodents and was named for its ability to induce insulin resistance (65). Resistin serum levels increase in diet-induced and genetic models of obesity (65, 67), although adi-

pose tissue mRNA levels are reduced (67, 68). Multimeric complexes of resistin and resistin-like molecule-β have been identified (66). Each promoter consists of a COOH-terminal disulfide-rich β-sandwich head and an NH_2-terminal α-helical tail, and the latter associates to form three-stranded coils, linked by interchain disulfide linkages to form tail-to-tail hexamers. As with leptin, resistin levels are higher in women, fall during fasting, and increase after refeeding (67). These changes are controlled partly by insulin and glucose (68). Very recently, resistin has been linked to incretin hormones and lipoprotein lipase (LPL) activity (69, 70). Resistin failed to increase when mice lacking receptors for glucagon-like peptide 1 and gastric inhibitory polypeptide (GIP) were fed a high-fat diet (69). This was associated with resistance to diet-induced obesity and preservation of pancreatic islet function (69). Chronic elevation of GIP levels increased plasma resistin levels in Zucker rats (70). Furthermore, treatment of 3T3-L1 adipocytes with resistin or GIP inhibited activities of AMPK and LPL (70). RNA interference-mediated suppression of resistin attenuated the effect of GIP on AMPK and LPL pathways in 3T3-L1 adipocytes, suggesting resistin acted downstream of GIP (70).

Systemic treatment or transgenic overexpression of resistin in rodents decreases the ability of insulin to suppress hepatic glucose production (71, 72). Conversely, ablation of the *retn* gene or reduction in resistin protein through antisense oligonucleotide treatment improves insulin sensitivity through AMPK activation (73, 74). Resistin inhibits adipogenesis, whereas the loss of resistin function increases body weight and fat and enhances insulin sensitivity (75, 76). Thus, resistin has significant roles in energy and glucose homeostasis. In agreement, we found that loss of resistin in leptin-deficient *Lep*$^{ob/ob}$ mice increased body weight and fat by decreasing energy expenditure (77). Insulin sensitivity improved in *Lep*$^{ob/ob}$ lacking resistin and was reversed by resistin treatment (77). The resistin receptor is not known but the effect of resistin to induce insulin resistance is associated with attenuation of AMPK phosphorylation and increased SOCS3 expression (72–74, 77) (Fig. 3). Thus, resistin may act at similar targets as leptin and adiponectin to affect glucose metabolism (Figs. 1–3).

Muse *et al.* (78) have reported that infusion of either resistin or an active cysteine mutant in the mediobasal hypothalamus stimulated glucose production, whereas antagonism of resistin action in the hypothalamus prevented the ability of plasma resistin to increase glucose production. Central resistin induced insulin resistance in liver, and this was related to induction of TNF-α, IL-6, and SOCS-3 (78). We have extended these findings by showing that intracerebroventricular resistin treatment induces hepatic insulin resistance and inflammatory markers by increasing expression of NPY and AGRP in the hypothalamus (79). The ability of resistin to increase glucose production and TNF-α, IL-6, and SOCS3 was attenuated in NPY-deficient mice as well as pharmacological blockade of NPY-Y1 receptor (79). These findings provide a framework for further investigation into the connection between resistin and inflammation and glucose metabolism.

Human resistin is made and secreted by macrophages (80, 81). Plasma resistin levels and single-nucleotide polymorphisms have been linked to obesity and lipid and glucose abnormalities in some studies (82–85), although others have failed to establish such a relationship (85, 86). Resistin has been associated with inflammation and atherosclerosis (88, 89). Resistin is strongly related to the levels of soluble TNFα receptor-2, IL-6- and lipoprotein-associated phospholipase A2, and severity of coronary artery calcification (90). The connection between resistin and inflammation was examined by injecting a low dose of lipopolysaccharide in humans (91). Lipopolysaccharide induced fever and increased adipose TNFα and IL-6 levels in parallel with insulin resistance. These effects were associated with increases in resistin and leptin, suggesting a link between inflammation, adipokines, and glucose metabolism (91). We also examined the link between inflammation and adipokines by treating patients with etanercept for 4 wk to neutralize TNFα (92). Etanercept increased the level of total adiponectin but not HMW adiponectin, and increased resistin. Etanercept decreased muscle fat content but did not enhance insulin sensitivity (91, 92). Longer studies are needed to establish whether the changes in proinflammatory cytokines and adipokines are indeed linked to glucose metabolism (91, 92).

CONCLUSION

This review highlights the effects of adipokines on energy homeostasis. Knowledge of specific signaling pathways will benefit the diagnosis and treatment of diabetes, lipid disorders, and various metabolic diseases related to obesity. As the list of adipokines continues to grow, it has become apparent that factors that control the production of adipokines vary according to the species under study. Adipokines may affect energy homeostasis via hormonal, paracrine, or autocrine mechanisms in the brain and peripheral organs. Future research requires systematic approaches in animal models and especially humans to elucidate the biology of adipokines and how this impacts diseases.

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