Section IV: Lipid Modulators of Islet Function

Update on Adipocyte Hormones

Regulation of Energy Balance and Carbohydrate/Lipid Metabolism

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Hormones produced by adipose tissue play a critical role in the regulation of energy intake, energy expenditure, and lipid and carbohydrate metabolism. This review will address the biology, actions, and regulation of three adipocyte hormones—leptin, acylation stimulating protein (ASP), and adiponectin—with an emphasis on the most recent literature. The main biological role of leptin appears to be adaptation to reduced energy availability rather than prevention of obesity. In addition to the well-known consequences of absolute leptin deficiency, subjects with heterozygous leptin gene mutations have low circulating leptin levels and increased body adiposity. Leptin treatment dramatically improves metabolic abnormalities (insulin resistance and hyperlipidemia) in patients with relative leptin deficiency due to lipoatrophy. Leptin production is primarily regulated by insulin-induced changes of adipocyte metabolism. Dietary fat and fructose, which do not increase insulin secretion, lead to reduced leptin production, suggesting a mechanism for high-fat/high-sugar diets to increase energy intake and weight gain. ASP increases the efficiency of triacylglycerol synthesis in adipocytes leading to enhanced postprandial lipid clearance. In mice, ASP deficiency results in reduced body fat, obesity resistance, and improved insulin sensitivity. Adiponectin production is stimulated by thiazolidinedione agonists of peroxisome proliferator-activated receptor-γ and may contribute to increased insulin sensitivity. Adiponectin and leptin cotreatment normalizes insulin action in lipoatrophic insulin-resistant animals. These effects may be mediated by AMP kinase–induced fat oxidation, leading to reduced intramyocellular and liver triglyceride content. The production of all three hormones is influenced by nutritional status. These hormones, the pathways controlling their production, and their receptors are promising targets for managing obesity, hyperlipidemia, and insulin resistance. *Diabetes* 53 (Suppl. 1): S143–S151, 2004

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apo, apolipoprotein; ASP, acylation stimulating protein; CNS, central nervous system; DGAT, diacylglycerol acyltransferase; TNF, tumor necrosis factor; TZD, thiazolidinedione.

Adipose tissue plays a crucial role in the regulation of energy homeostasis, insulin sensitivity, and lipid/carbohydrate metabolism. These actions are mediated by both the actions of a number of nonsecreted proteins and hormones produced in adipocytes. A recent example of the importance of adipocyte function to have profound systemic effects is provided by the report that mice specifically lacking insulin signaling in adipocytes (FIRKO mouse) are not only lean, leptin sensitive, and obesity resistant (1), but live almost 20% longer than wild-type control animals (2). Adipocytes produce a number of hormones that have wide-ranging effects on energy intake, energy expenditure, and carbohydrate and lipid metabolism, including nutrient partitioning and fuel selection. Work in our laboratory has primarily focused on the biology and regulation of three key adipocyte hormones: leptin, acylation-stimulating protein, and adiponectin. A review examining the role of these three hormones in regulating energy homeostasis and insulin action was published in early 2002. The purpose of the present review is to summarize the most important aspects of the biology, actions, and regulation of these hormones and to serve as an update of new information published during the past ~18 months.

LEPTIN

Because the biology of leptin, including its role in energy balance and the regulation of its production, has been reviewed in detail (3,4), this section will primarily concentrate on more recent findings not covered in previous reviews. Importantly, recent data indicate that the effects of leptin to inhibit food intake are mediated by signaling through phosphatidylinositol 3-kinase (5), which is shared by the insulin signal transduction pathway. This pathway is therefore likely to mediate common actions of insulin and leptin as peripheral signals to the central nervous system (CNS) in the hypothalamic regulation in eating behavior and metabolic homeostasis (3,6,7). Another study implicated inhibition of liver steroyl CoA desaturase as a mechanism mediating some of the metabolic effects of leptin, particularly with regard to hepatic lipid metabolism (8).

Leptin deficiency and leptin treatment. It is now apparent that the primary importance of leptin in the

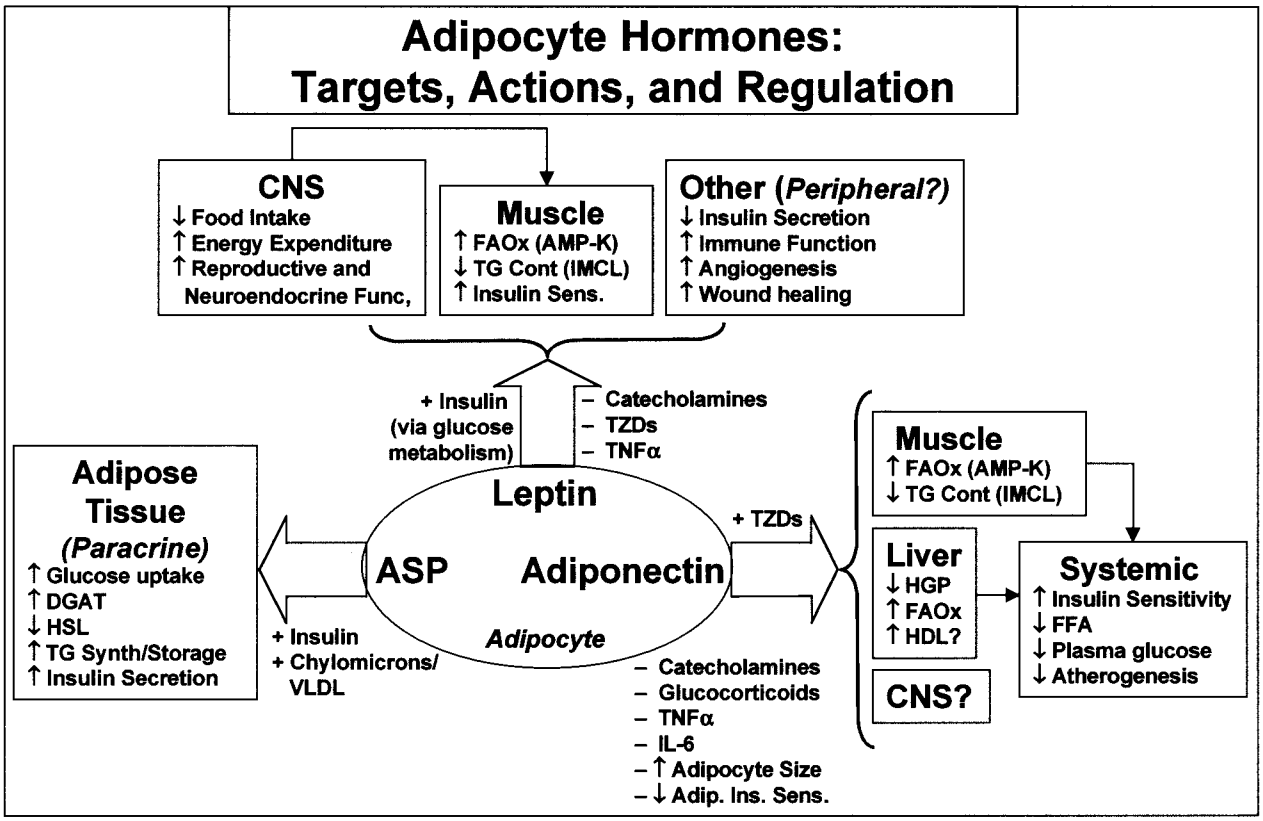

FIG. 1. Leptin acts within the CNS to inhibit food intake and increase energy expenditure, perhaps via its effects to activate the sympathetic nervous system. Leptin also influences reproductive and neuroendocrine function. Leptin can increase insulin sensitivity, and this action appears to be mediated by direct and indirect (CNS) effects to activate AMP kinase (AMP-K) and increase muscle fatty acid oxidation (FAOx), leading to decreased intramyocellular lipid (IMCL) content. In addition to the CNS, leptin receptors are also found in numerous peripheral tissues where the hormone exerts diverse effects. Leptin secretion is primarily mediated by changes of adipocyte glucose metabolism driven by increases or decreases of meal-induced insulin secretion. Catecholamines and TZDs have been reported to inhibit leptin production; however, the physiological role of these mechanisms has not been definitively established. ASP has anabolic effects to increase triglyceride (TG) synthesis by increasing adipocyte glucose uptake, activating DGAT, and inhibiting hormone-sensitive lipase (HSL). ASP has recently been shown to stimulate insulin secretion. ASP deficiency results in obesity resistance and increased insulin sensitivity. ASP production is stimulated by insulin and by the presence of chylomicrons/VLDL after meals. Adiponectin increases insulin sensitivity, decreases hepatic glucose production (HGP), and lowers glucose plasma levels. The insulin-sensitizing effects of adiponectin appear to be mediated by activation of AMP-K, resulting in increased FAOx, and a lowering of hepatic triglyceride and IMCL content. TZD agonists of via peroxisome proliferator-activated receptor-γ may increase insulin sensitivity by stimulating adiponectin production. Adiponectin expression and secretion are inhibited by catecholamines, glucocorticoids, TNF-α, interleukin-6 (IL-6), increased adipocyte size, and possibly decreased adipocyte insulin sensitivity. FFA, free fatty acid.

regulation of energy homeostasis is for reduced leptin production to function as a signal of negative energy balance and low energy reserves, rather than as an indicator of positive energy balance and increased energy reserves in the prevention of obesity. Accordingly, the physiological effects of decreased leptin concentrations are notably more pronounced than when leptin levels are increased above the normal physiological range. Thus, the dose response to increasing leptin concentrations appears to be near maximal at physiological levels. As in rodents, genetic mutations in the leptin gene (9,10) or defects in the leptin receptor (11) in humans result in extreme hyperphagia and obesity. Treatment with recombinant leptin reduces the marked hyperphagia and produces weight loss in leptin-deficient subjects (12). Leptin administration corrects many of the neuroendocrine, reproductive, metabolic, and immune system deficits associated with leptin deficiency (13) (Fig. 1). Heterozygous mutations of the leptin gene result in a partial deficiency syndrome characterized by increased body adiposity (14). Physiological leptin replacement prevents the onset of hyperphagia in untreated insulin-deficient diabetes (15) and the increase of food-seeking behavior in energy-restricted rats (16). Increased sensations of hunger during dieting are related to the magnitude of decreases of leptin (17), and in one study, reduced appetite was reported in humans treated with leptin (18). In addition, it was recently demonstrated that the normal compensatory decreases of energy expenditure and thyroid axis function in response to consuming an energy-restricted diet in humans were prevented by low-dose leptin replacement (19). Together, these data suggest that decreases of leptin during weight loss could contribute to hunger, a lowered metabolic rate, and weight regain. New studies are needed to determine whether leptin replacement, or the use of strategies to increase endogenous leptin production to prevent the fall of leptin during dieting and weight loss, will help prevent weight regain in weight-reduced subjects.

The marked insulin resistance and hyperlipidemia in leptin-deficient rodent models of lipoatrophy is largely reversed by leptin administration (20,21). Low-dose leptin treatment has dramatic effects to ameliorate insulin resistance and hyperlipidemia in patients with low leptin levels resulting from congenital or acquired lipodystrophy (22).

The beneficial metabolic effects were associated with reduced triglyceride deposition in liver and intramyocellular lipid content in skeletal muscle (23,24). Leptin also improved pituitary, reproductive, and thyroid axis function in lipoatrophic patients (25). Plasma leptin concentrations are also decreased (along with adiponectin) in some patients with lipodystrophy associated with human immunodeficiency virus infection and antiretroviral treatment (26,27). It is possible that leptin replacement therapy would be beneficial in managing some of the metabolic abnormalities (hepatic steatosis, hyperlipidemia, and insulin resistance) in those patients with low leptin levels. Leptin-induced decreases of muscle lipid accumulation and improvements of insulin resistance appear to be mediated via direct and indirect neural activation of skeletal muscle AMP kinase (28,29). Together, the available data support a critical role for leptin in the regulation of energy balance in humans (4,30). In addition, a number of recent studies provide evidence of a role for leptin in the regulation of insulin action and lipid metabolism (4).

Regulation of leptin production. Insulin responses to meals are the primary mediator of changes of leptin production observed during fasting/energy restriction and refeeding and of the diurnal variation of circulating leptin levels (3). Data from experiments in isolated adipocytes (31) and from clinical studies in human subjects (32) support the idea that insulin increases leptin production indirectly via its effects to increase glucose utilization and oxidative glucose metabolism in adipocytes (33) at the transcriptional level (34) (Fig. 1). The region of the leptin gene involved in the activation of the leptin promoter by insulin-mediated glucose metabolism appears to be located between −135 and −95 bp (35), a region that includes the binding site for the transcription factor Sp1 (36). The 24-h diurnal leptin concentrations are reduced on a day when three high-fat meals are consumed when compared with high-carbohydrate/low-fat meals, which induce larger postprandial glucose excursions and greater insulin secretion (37). In a study comparing the effects of consuming glucose- and fructose-sweetened beverages with meals, postprandial insulin responses were markedly reduced and 24-h circulating leptin concentrations were reduced by 35% (38). Consumption of high-glucose meals suppressed plasma levels of the orexigenic gastric hormone ghrelin (39,40), whereas this response was attenuated after high-fructose meals. In addition, fructose consumption induced a rapid and sustained increase of postprandial triglyceride levels, consistent with increased hepatic metabolism of fructose to lipid precursors (41). The endocrine effects of dietary fat and fructose, resulting in decreased insulin secretion and leptin production, and reduced postprandial suppression of ghrelin suggest a mechanism by which consumption of diets high in energy derived from fat and fructose could lead to overconsumption of calories, weight gain, and obesity.

Leptin and insulin secretion. There is a large body of evidence demonstrating that leptin has direct effects on insulin secretion with the large majority of studies reporting that leptin inhibits insulin gene transcription (42–44) and insulin secretion (45,46). Briefly, the long form of the leptin receptor is expressed in pancreatic β-cells (47). Leptin can inhibit insulin secretion by activating with ATP-dependent potassium channels or via interactions with the cAMP protein kinase A signaling pathway (48), perhaps by activating phosphodiesterase B3 (49). Physiological levels of leptin have been demonstrated to inhibit insulin secretion in rats in vivo (50); however, this effect may be indirectly mediated via actions in the CNS (51).

ACYLATION STIMULATING PROTEIN

The acylation stimulating protein (ASP) is a unique hormone produced from complement factor C via an interaction requiring factor B and adipsin (factor D), resulting in the formation of the C3 derivative, C3a-des-Arg, which is also known as ASP. Plasma ASP and C3 levels are highly correlated in normal subjects and in patients with elevated ASP levels associated with the nephrotic syndrome (52). An orphan G protein–coupled receptor (C5L2) that is coupled with Gi (53) has recently been shown to bind ASP (54). The receptor is expressed in 3T3-L1 cells, human fibroblasts, and human adipose tissue and has been proposed to be the receptor responsible for the metabolic actions of ASP in adipose tissue (54). ASP has a primary role in the regulation of lipid metabolism in adipocytes. However, these actions in adipose tissue result in profound effects on whole-body energy homeostasis and insulin sensitivity.

ASP and lipid metabolism. ASP acts locally in adipose tissue, where it stimulates glucose uptake, increases the activity of diacylglycerol acyltransferase (DGAT), and inhibits hormone-sensitive lipase activity (Fig. 1). These actions of ASP increase the efficiency of triglyceride synthesis and storage in adipocytes (55,56). C3 knockout mice, with an inability to produce ASP, exhibit delayed postprandial lipid clearance in mice (57). Intraperitoneal administration of exogenous ASP to mice accelerates the clearance of free fatty acids and triglycerides from the circulation after oral fat administration (58,59). Results from a genetic study demonstrating that plasma ASP levels are related to genes controlling total cholesterol, LDL, and triglyceride levels (60) support a role for ASP in the regulation of lipid metabolism in humans. In addition, patients with combined familial hyperlipidemia have a delayed postprandial increase of plasma C3 concentrations, suggesting a potential link between the ASP precursor and impaired free fatty acid clearance and VLDL overproduction (61). Lastly, a recent study of patients experiencing marked weight loss after gastric bypass surgery reported that the decrease of the atherogenic apolipoprotein (apo)-B is closely related to the decrease of plasma ASP levels (62).

ASP and energy balance/carbohydrate metabolism. ASP action is a determinant of energy homeostasis and insulin action. C3 knockout mice, which are unable to produce ASP, consume ~30% more food than wild-type mice, yet have reduced adipose mass and are resistant to weight gain induced by being fed a high-fat diet (63). The C3/ASP-deficient animals have increased energy expenditure as assessed by 24-h oxygen consumption, which is elevated both at rest (light cycle) and during the active phase (dark cycle) (64). Cross-breeding of C3/ASP knockout animals with leptin-deficient *ob*/*ob* mice results in mice with reduced adiposity and increased energy expenditure (65). ASP/C3 knockout animals also have reduced fasting

insulin levels and improved glucose clearance after intraperitoneal glucose administration (58,63). It is of interest that mice with genetic knockout of the DGAT enzyme, which is regulated by ASP, exhibit a similar lean insulin-sensitive obesity-resistant phenotype as C3/ASP knockout animals, as well as increased sensitivity to the effects of leptin to suppress food intake (66,67).

In addition to its known anabolic paracrine actions in adipocytes, direct effects of ASP on insulin secretion have recently been reported. ASP directly stimulated insulin secretion by INS-1 cells and isolated mouse islets. The stimulatory action appears to depend on glucose phosphorylation, calcium influx, and protein kinase C. Furthermore, ASP administration acutely increased first-phase glucose-stimulated insulin secretion in mice in vivo, resulting in enhanced glucose disposal (68).

Regulation of ASP production. Adiposity is an important determinant of circulating ASP levels, which are elevated in obese subjects in proportion to body adiposity (69,70). Plasma ASP concentrations decrease during fasting and after weight loss (71), including after marked weight loss resulting from gastric bypass surgery (62). In humans, plasma ASP concentrations do not increase in response fat ingestion (72). ASP release into venous plasma from subcutaneous adipose tissue can be measured 4–5 h after meals (73). ASP secretion by adipocytes in vitro is increased by insulin (74), suggesting that insulin could mediate the decrease of ASP production during energy restriction and the increase of ASP production after meals. However, circulating lipids are also likely to stimulate ASP production after fat ingestion because chylomicrons potently increase ASP secretion from cultured human adipocytes in vitro (74,75) (Fig. 1). Clearly, additional experiments are required to better understand the nutritional regulation of ASP production. However, because ASP enhances triglyceride storage, whereas interfering with ASP production reduces body fat and protects against diet-induced obesity and insulin resistance, reducing the production of ASP and ASP receptor antagonists represents potential approaches for treating obesity and type 2 diabetes.

ADIPONECTIN

Adiponectin—also known as complement-related protein 30 (ACRP30), adipose most abundant gene transcript (apM1), adiponectin, and adipoQ—was identified in by several laboratories (76–78). Adiponectin is a large (30-kDa) protein produced by adipocytes. It has been reported that adiponectin is present in the circulation as a dimer-trimer and as larger higher-order complexes and that the state of these oligomers influences the biological activity of the protein (79). Identification of the receptor(s) mediating the biological actions of adiponectin in liver and skeletal muscle has not yet been reported. Low circulating levels of adiponectin have been linked to several components of the metabolic (insulin resistance) syndrome, including intra-abdominal body fat distribution, hyperlipidemia, low HDL levels, and insulin resistance/type 2 diabetes.

Adiponectin and lipid metabolism. There is a growing body of evidence that adiponectin is involved in the regulation of both lipid and carbohydrate metabolism. Adiponectin also appears to have direct and indirect actions that would be considered to protect against cardiovascular disease (4,80). It has been hypothesized that reduced adiponectin concentrations observed in obese subjects (81) are involved in the development of atherosclerosis and cardiovascular disease (82,83). Decreased adiponectin levels have been linked to small dense LDL and high apoB and triglyceride levels (84). Several studies have shown that adiponectin has direct actions on vascular endothelium that would protect against cardiovascular disease (85,86). Recent reports that adiponectin knockout mice exhibit an increase in inflammatory response to vascular injury (87) and that adiponectin administration prevents atherosclerosis in apoE-deficient mice (88,89) provide further support to the idea that adiponectin protects against cardiovascular disease. With respect to circulating lipids, several genes linked to circulating adiponectin levels have pleiotropic genetic effects on serum HDL and triglyceride levels (60). In addition, data from two large cross-sectional studies indicate that after adjusting for both sex and body adiposity, circulating adiponectin concentrations are negatively correlated with triglyceride levels and strongly positively correlated with plasma HDL concentrations (90,91).

Adiponectin and insulin action/carbohydrate metabolism. Adiponectin administration enhances insulin action in animals (4) and low levels of adiponectin have been proposed to contribute to insulin resistance associated with obesity (92). Adiponectin gene expression (93) and circulating adiponectin levels (94) are lower in patients with type 2 diabetes than in nondiabetic individuals. Independent of body adiposity, circulating adiponectin levels are positively correlated with insulin sensitivity as assessed by fasting insulin levels, homeostasis analysis, hyperinsulinemic-euglycemic clamp, or frequently sampled intravenous glucose tolerance test (90,91,95,96). Circulating adiponectin levels are decreased in aging obese rhesus monkeys at the time the animals begin to exhibit insulin resistance and develop type 2 diabetes (97). Decreased tyrosine phosphorylation of muscle insulin receptors is related to lower plasma adiponectin concentrations, and the low levels are predictive of the subsequent development of diabetes (98), although not of future weight gain (99) in Pima Indians. Markers of insulin resistance are linked to a quantitative trait locus on chromosome 3 in the region containing the adiponectin gene (100). Further evidence that adiponectin production is required for normal insulin action is provided by reports that heterozygous and homozygous adiponectin knockout mice are insulin resistant with a gene dose effect (87) or develop diet-induced insulin resistance (101). However, it is possible that insulin resistance resulting from adiponectin deficiency may be compensated by genetic background (i.e., differences in mouse strain), because other investigators have reported normal insulin action in an adiponectin knockout mouse model (102).

Administration of adiponectin lowers circulating glucose levels without stimulating insulin secretion in both normal mice and in mouse models of diabetes (103). Adiponectin may act directly on the liver because adiponectin lowers hepatic glucose production in mice (104) and enhances the effects of insulin to decrease glucose production by isolated hepatocytes (105). Adiponectin administration also reduces insulin resistance and im-

proves glucose tolerance in mice with low adiponectin levels resulting from lipoatrophy- or obesity-induced insulin resistance (105). In these studies, plasma glucose levels in mice with lipoatrophic diabetes were normalized when leptin was co-administered with adiponectin (105). Furthermore, the amelioration of insulin resistance was associated with decreased triglyceride deposition in liver and in skeletal muscle, the expression of genes involved in lipid transport and use, and increased fat oxidation in muscle (105). Circulating adiponectin levels are also decreased in patients with congenital (106) or human immunodeficiency virus–associated lipodystrophy (107–111). Therefore, adiponectin treatment may be of benefit in controlling the multiple metabolic disturbances, including hepatic steatosis, insulin resistance, and dyslipidemia present in these patients.

In one study, adiponectin treatment was reported to induce weight loss without decreasing food intake in mice consuming a high-fat high-sucrose diet—an effect associated with increased muscle fat oxidation and lowered circulating fatty acid concentrations (112). There is evidence that the insulin-sensitizing effects of adiponectin in muscle, like those of leptin, also involve activation of the AMP kinase (113,114). Therefore, it appears that adiponectin can increase insulin action via direct effects on hepatic glucose production and by reducing ectopic fat deposition in liver and muscle via increases of fat oxidation (115,116) (Fig. 1). Accordingly, low adiponectin concentrations in obese adolescent subjects are associated with increased intramyocellular lipid deposition and impaired insulin action (117). At this time, there are no published reports of direct effects of adiponectin on insulin secretion.

Regulation of adiponectin production. Circulating concentrations of most hormones produced by adipose tissue, including leptin, tumor necrosis factor (TNF)-α, plasma activator inhibitor 1, and ASP, are positively related to body adiposity. In contrast, circulating adiponectin concentrations are reduced in obese animals (105,118) and humans (82,90,95). In a cross-sectional study including obese and lean men and women, the negative relationship between plasma adiponectin and visceral fat (measured by computed tomography scan) was significantly stronger than that with subcutaneous fat (119). One explanation is that adiponectin is primarily produced by visceral adipose tissue, but that large triglyceride-filled visceral adipocytes produce less adiponectin. It has been reported that omental adipocytes secrete more adiponectin than adipocytes isolated from subcutaneous fat (120). The known insulin-sensitizing actions of adiponectin suggest that reduced adiponectin production may contribute to the well-known relationship between visceral fat deposition and insulin resistance (121). Like leptin (122,123), plasma adiponectin levels are increased in women (90). Differences in adipocyte size and body composition could contribute to the sex difference in adiponectin levels because women with a gynoid body fat distribution are known to have smaller and more numerous adipocytes than women with android fat distribution (124). Circulating adiponectin levels increase after weight loss in humans (94). The low plasma adiponectin concentrations in morbidly obese subjects are normalized after weight loss induced by gastric bypass surgery (62,125,126). Furthermore, in patients with stable weights, those subjects with the lowest presurgical adiponectin levels lost the most weight after surgery (62) and the subjects exhibiting the largest increases of plasma adiponectin were the most insulin sensitive after surgery-induced weight loss (62,125). Again, a possible explanation for the paradoxical reduction of adiponectin in obese subjects and the increase after weight loss is that adiponectin may be primarily produced by visceral fat, as suggested by one study of human adipocytes in vitro (120), but that large visceral adipocytes with greater triglyceride stores produce less adiponectin than small adipocytes. Because large adipocytes are less insulin sensitive, it is possible that the insulin sensitivity of adipocytes is also a determinant of adiponectin production, as has been suggested by our unpublished data and that of other investigators (127) (Fig. 1).

Humans with severe insulin-resistant diabetes due to dominant-negative mutations that inactivate peroxisome proliferator-activated receptor-γ (128) have very low circulating adiponectin levels (129). Thiazolidinedione (TZD) agonists of peroxisome proliferator-activated receptor-γ increase adiponectin expression and circulating levels in rodents (105,108,129–131) and plasma adiponectin levels in nondiabetic subjects (132) and in patients with type 2 diabetes (132–134). In contrast, plasma adiponectin was unchanged in response to metformin (134). In addition, the improvement of insulin sensitivity during TZD treatment was related to the increase of circulating adiponectin (134). It is possible the effects of TZDs to increase whole-body insulin sensitivity (135) and to protect against cardiovascular disease (136) could be mediated by increased adiponectin production. Adiponectin gene expression is reduced by TNF-α (130,137–139), interleukin-6 (139,140), β-adrenergic agonists (141–143), or glucocorticoids (13,144). Adrenalectomy increases adiponectin gene expression and circulating adiponectin levels, along with insulin sensitivity in *ob*/*ob* mice (145). The effects of cytokines, catecholamines, and glucocorticoids to induce insulin resistance could be mediated, in part, by their effects to decrease adiponectin production (Fig. 1).

The role of insulin in the regulation of adiponectin production is not yet clear. There are reports that insulin can either stimulate (144,146) or inhibit (138) adiponectin gene expression or secretion in cultured adipocytes. A modest decrease of plasma adiponectin was observed during a 5-h hyperinsulinemic-euglycemic clamp (132). However, plasma adiponectin levels increase in patients with type 2 diabetes during sulfonylurea treatment, which stimulates insulin secretion (147). In contrast to the marked decline of circulating leptin concentrations in response to acute energy restriction (148), the increase of adiponectin during acute energy restriction in humans, with little change in body fat, is relatively small and depends on sex (149). Circulating adiponectin concentrations are increased by exercise training when body fat content is reduced (150,151), but they do not change if body composition is unaltered (152). A recent study reported a diurnal pattern of circulating adiponectin concentrations in six normal-weight male subjects, with a nocturnal decrease of ~20% below 24-h mean levels (153). However, this diurnal pattern of adiponectin concentrations was not apparent over a 24-h period in six female

subjects consuming three high-carbohydrate meals that induce large postprandial insulin responses, suggesting another potential sex difference (K. Teff, P.J.H., unpublished data). Available data suggest that infusion of fatty acids (Intralipid) (154), insulin and glucose administration (132), insulin responses to meals, and acute energy restriction (149) have, at most, modest effects on plasma adiponectin concentrations.

CONCLUSIONS

A large number of proteins produced by adipose tissue, both intracellular and secreted, function, in concert with the CNS, liver, and muscle, in the coordination of energy homeostasis and fuel metabolism. Among these proteins, alterations in the production of the hormones, leptin, ASP, and adiponectin appear to have substantial effects on body adiposity and insulin sensitivity. The processes involved in regulating energy homeostasis and intermediary lipid and carbohydrate metabolism are inextricably linked by common neuroendocrine mediators, including, leptin, ASP, and adiponectin. The production of all three adipocyte hormones appears to be regulated by nutritional status, i.e., feeding, fasting, and/or weight loss. A more complete understanding of the molecular and biochemical pathways regulating the biosynthesis of these hormones and their precise mechanisms of action is likely to lead to new approaches for managing obesity, dyslipidemia, and insulin resistance/type 2 diabetes (4).

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