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Physiological, Pharmacological, and Nutritional Regulation of Circulating Adiponectin Concentrations in Humans

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Abstract

Adiponectin is an adipocyte hormone that links visceral adiposity with insulin resistance and atherosclerosis. It is unique among adipocyte-derived hormones in that its circulating concentrations are inversely proportional to adiposity, and low adiponectin concentrations predict the development of type 2 diabetes and cardiovascular disease. Consequently, in the decade since its discovery, adiponectin has generated immense interest as a potential therapeutic target for the metabolic syndrome and diabetes.

This review summarizes current research regarding the regulation of circulating adiponectin concentrations by physiological, pharmacological, and nutritional factors, with an emphasis on human studies. In humans, plasma adiponectin concentrations are influenced by age and gender, and are inversely proportional to visceral adiposity. *In vitro* studies suggest that adiponectin production may be determined primarily by adipocyte size and insulin sensitivity, with larger, insulin-resistant adipocytes producing less adiponectin. While adiponectin concentrations are unchanged after meal ingestion, they are increased by significant weight loss, such as after bariatric surgery. In addition, adiponectin production is inhibited by a number of hormones, including testosterone, prolactin, glucocorticoids and growth hormone, and by inflammation and oxidative stress in adipose tissue. Smoking decreases, while moderate alcohol consumption increases, circulating adiponectin concentrations. Dietary fatty acid composition in rodents influences adiponectin production via ligand-activated nuclear receptors (PPARs); however, current evidence in humans is equivocal. In addition to PPAR agonists (such as thiazolidinediones and fibrates), a number of pharmacological agents (angiotensin receptor type 1 blockers, ACE inhibitors, and cannabinoid receptor antagonists) used in treatment of the metabolic syndrome also increase adiponectin concentrations in humans.

Introduction

ADIPOSE TISSUE IS NOW well recognized as an important source of hormones that influence body adiposity, glucose homeostasis, inflammation, and cardiovascular disease.^{1,2} Due to its involvement in each of these physiological processes, the adipocyte-derived hormone adiponectin (also referred to as Acrp30, AdipoQ, apM1, and GBP28 in initial reports)^{3–6} has been intensively studied. This review will focus on the physiological, pharmacological, and nutritional factors that influence circulating adiponectin concentrations, with an emphasis on studies conducted in humans.

Adiponectin is an Adipocyte-Specific Secreted Protein Dysregulated in Obesity, Type 2 Diabetes, and Cardiovascular Disease

Adiponectin mRNA is highly expressed in and is relatively specific for mature adipocytes.^{3,4} The human adiponectin gene encodes a 244 amino acid, 30 kDa secreted protein, which contains a putative signal sequence, a collagen-like domain, and a globular domain. Adiponectin shares structural similarity with collagens VIII and X, tumor necrosis factor alpha (TNF- α), and complement factor C1q.

In plasma, adiponectin circulates at very high concentrations for a hormone, usually in the range 3 to 30 $\mu\text{g}/\text{mL}$.

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Adiponectin concentrations are decreased in a variety of human metabolic and cardiovascular disease states, including obesity,⁷ type 2 diabetes mellitus,⁸ lipodystrophy,⁹ nonalcoholic hepatic steatosis,¹⁰ essential hypertension,¹¹ and coronary artery disease.¹² Low adiponectin levels precede the development of insulin resistance¹³ and myocardial infarction¹⁴ in humans. Interestingly, adiponectin concentrations increase with age¹⁵ and are elevated in type 1 diabetes.¹⁶ Adiponectin is detectable in cerebrospinal fluid (CSF), with CSF concentrations in humans typically 0.1% of corresponding plasma concentrations.^{17,18}

Adiponectin Action in Peripheral Tissues

Adiponectin has insulin-sensitizing actions in the liver, and lowers blood glucose levels in diabetic animals by improving insulin-mediated suppression of gluconeogenesis.¹⁹ In liver and skeletal muscle, adiponectin also improves glucose utilization and stimulates fatty acid oxidation via a pathway that involves AMP kinase (AMPK) and acetyl-CoA carboxylase (ACC).²⁰ Adiponectin also prevents TNF- α -stimulated expression of adhesion molecules in cultured human endothelial cells²¹ by inhibiting IKK β phosphorylation and NF- κ B activation,²² and inhibits the transformation of macrophages into foam cells.²³ Together, these effects have been shown to prevent plaque formation in apoE-deficient mice, a mouse model of atherosclerosis.^{24,25} Adiponectin may also prevent excessive cardiac remodeling following injury. In response to pressure overload, adiponectin-deficient mice exhibit an exaggerated hypertrophic response compared to wild-type mice.²⁶ This response is prevented by intravenous administration of an adenovirus expressing adiponectin prior to injury.²⁷

Adiponectin's diverse actions in these tissues are mediated by its receptors, AdipoR1 and AdipoR2.²⁸ In humans, AdipoR1 is ubiquitously expressed, with highest levels of expression in heart and skeletal muscle; while AdipoR2 expression is more restricted to skeletal muscle and liver.²⁸ Overexpression of each receptor in the livers of leptin-deficient mice revealed their divergent functions: overexpression of AdipoR1 increased AMPK phosphorylation and reduced the expression of genes involved in hepatic gluconeogenesis; while overexpression of AdipoR2 increased peroxisome proliferator-activated receptor alpha (PPAR- α) mRNA and reduced the expression of inflammatory cytokines and markers of oxidative stress.²⁹ In this model, overexpression of either receptor reduced hepatic triglyceride content. In addition to AdipoR1 and AdipoR2, adiponectin also binds to T-cadherin, a receptor localized on vascular endothelium and muscle cells.³⁰ This interaction may underlie some anti-atherogenic, vascular-protective actions of adiponectin.

Adiponectin may also have actions in the central nervous system (CNS) to influence the control of body weight, although its specific role is controversial.³¹ Adiponectin is detectable in CSF, and its receptors are abundantly expressed in hypothalamic areas that control food intake.¹⁸ In mice, although central administration of adiponectin was initially shown to reduce body weight by increasing energy expenditure,³² intravenous adiponectin treatment has been recently found to *increase* feeding in mice by activating AMP kinase in the hypothalamus.³³ Further studies are needed to better define the potential role of adiponectin in the CNS regulation of energy homeostasis.

Adiponectin Circulates as Multimers that Activate Differential Signaling Pathways

Adiponectin's biological effects depend upon the formation of multimeric complexes and may require proteolytic cleavage. The formation of higher-order structures in plasma is similar to other proteins with collagen-like domains, such as complement factor C1q.³⁴ Adiponectin's basic unit consists of a trimer, formed by interactions within the globular domain and stabilized by a collagenous coiled-coil structure.⁶ These trimers associate by disulfide bonds to form hexamers, dodecamers (12 subunits), and octadecamers (18 subunits).^{35,36} Trimeric, hexameric, and larger forms of adiponectin are referred to as low, medium, and high molecular weight (LMW, MMW, HMW), respectively.³⁷ Globular adiponectin, a fragment of human adiponectin that includes the C-terminal globular domain, has demonstrated biological activity in some studies, but is present at a much lower concentration than the other forms of adiponectin.³⁸

Growing evidence indicates that HMW adiponectin is the most active form with respect to insulin sensitivity. Type 2 diabetes is associated with a lower proportion of adiponectin in the HMW form, and this ratio (termed S_A) is improved by treatment with antidiabetic thiazolidinediones (TZDs).³⁹ Injection of HMW, but not MMW, adiponectin reduced blood glucose in adiponectin-deficient mice,³⁹ and mutations in the adiponectin gene that interfere with the assembly of HMW adiponectin are associated with insulin resistance and type 2 diabetes in humans.³⁷ Other forms of adiponectin may have oligomer-specific functions, as LMW and globular adiponectin, but not MMW or HMW, activate AMPK in rat skeletal muscle.^{40,41} In monocytes, only the LMW form inhibits NF κ B activity and proinflammatory cytokine release,⁴² while HMW and adiponectin may instead exert the opposite effect.⁴³

Adiponectin Synthesis and Secretion

Circulating adiponectin concentrations are the end result of a complex, highly regulated secretory pathway in adipocytes.⁴⁴ Adiponectin mRNA expression is enhanced by a variety of adipogenic transcription factors, including PPAR- γ ,⁴⁵ C/EBP α ,⁴⁶ C/EBP β ,⁴⁷ FOXO1,⁴⁸ and by Sp1, which is induced during adipogenesis.⁴⁹ Studies of humans with obesity, type 2 diabetes, or gestational diabetes have shown dysregulation of adiponectin mRNA in human adipose tissue,⁵⁰⁻⁵² however, changes in adiponectin mRNA expression do not always correspond to changes in plasma adiponectin concentrations.^{53,54} This latter observation supports the involvement of post-transcriptional and post-translational mechanisms in the regulation of adiponectin production.

Prior to secretion, adiponectin undergoes extensive post-translational modifications including hydroxylation of proline and lysine residues and glycosylation of hydroxylsines.⁵⁵ These modifications are necessary for HMW multimer formation^{56,57} and are therefore likely to determine HMW-induced activation of hepatic AMPK and its effects to stimulate fatty acid oxidation and reduce liver triglyceride deposition.⁵⁷ Type 2 diabetes is associated with reduced glycosylation of adiponectin as well as lower concentrations of HMW adiponectin in the circulation.⁵⁷

The assembly of hexameric and HMW adiponectin from trimers requires the formation of disulfide bonds, at Cys-36 of the human protein and Cys-39 in the murine equiva-

lent.^{35,37,40} These disulfide bonds are crucial for the release of intracellular adiponectin⁵⁸ via a process known as thiol-mediated protein retention.⁵⁹ This process involves two endoplasmic reticulum chaperones, ERp44 and Ero1- α . ERp44 retains adiponectin within the cell, and Ero1- α competes with adiponectin for binding to ERp44. Accordingly, increasing the amount of ERp44 in a heterologous system (cultured human embryonic kidney cells) dose-dependently reduced adiponectin secretion, while reducing ERp44 levels in adipocytes increased adiponectin secretion. The *in vivo* relationships between these chaperones and circulating adiponectin concentrations are likely to be complex, however, as levels of ERp44 protein in adipose tissue were greater in female mice relative to male mice, and higher in wild-type mice relative to *ob/ob* mice, both conditions under which ERp44 protein levels would be expected to be reduced.^{35,37} The specific mechanisms by which adiponectin is assembled and secreted are currently under investigation, and may yield new pharmacological targets to increase adiponectin production.

Adiponectin may also exert negative feedback inhibition of its own production, as adiponectin mRNA expression in cultured adipocytes is suppressed by treatment with physiological concentrations of adiponectin.⁶⁰ This is likely to be due to degradation of about half of the synthesized adiponectin prior to secretion.⁴⁵ In a similar manner, transgenic mice designed to overexpress adiponectin specifically in adipose tissue actually displayed lower circulating adiponectin levels relative to wild-type mice.⁶⁰ To circumvent this problem, it was necessary for Combs and colleagues⁴⁵ to use transgenic mice overexpressing a mutated form of adiponectin in order to elevate circulating adiponectin concentrations.

Circulating adiponectin concentrations may also be affected by renal clearance, as adiponectin levels are elevated in states characterized by impaired renal function, such as macroalbuminuria⁶¹ and end-stage kidney disease.^{62,63}

Role of Adipose Distribution and Adipocyte Size

Visceral adiposity is an important determinant of plasma adiponectin concentrations in humans. Direct assessments of visceral fat in humans have repeatedly shown an independent and inverse relationship between visceral adiposity and plasma adiponectin concentrations.^{15,64–66} While this relationship is not well supported by analyses of adiponectin mRNA expression,^{51,67,68} in one study of 36 morbidly obese nondiabetic subjects it was reported that adiponectin mRNA expression in visceral fat, but not in subcutaneous fat, was positively correlated with the serum adiponectin level.⁶⁹ This finding is supported by the results of *in vitro* experiments in which adiponectin secretion from omental, but not subcutaneous, adipocytes under basal conditions was found to be reduced in obesity.⁷ In another study, both insulin-stimulated and rosiglitazone-stimulated adiponectin secretion were found to be significantly higher in omental relative to subcutaneous adipocytes, although basal adiponectin secretion did not differ between the two depots.⁷⁰ Studies of cultured human adipose tissue also suggest that subcutaneous adipocytes do not make a major contribution (~10%) to interindividual variations in circulating adiponectin and insulin sensitivity.⁷¹ The importance of the visceral depot in determining circulating adiponectin concentrations is also supported by a recent study in mice.⁷²

Adiponectin production may also be determined by adipocyte size.⁷³ Larger adipocytes are more insulin-resistant,⁷⁴ and one mechanism by which TZDs improve insulin sensitivity is by increasing the number of small, insulin-sensitive adipocytes, at the expense of large, insulin-resistant ones.⁷⁵ TZDs also increase adiponectin secretion.⁷⁶ Our laboratory has reported data from *in vitro* experiments indicating a strong inverse relationship between adipocyte volume and adiponectin secretion from isolated rat adipocytes.⁷⁷ Although our results are not consistent with recent data obtained from human subcutaneous adipocytes,⁷⁸ due to their anatomical source, the contribution of subcutaneous adipocytes to circulating adiponectin concentrations appears likely to be minor compared with adipocytes in visceral depots.

Diurnal Variation of Circulating Adiponectin Concentrations and Effects of Meals, Glucose, and Insulin

Adiponectin concentrations in plasma are fairly stable throughout the day, exhibiting only a minor fluctuation (~20%) from the 24-hour mean, with levels declining modestly during the night to a nadir in the early morning.⁷⁹ This diurnal variation appears to be greater in females than in males,^{79,80} and may increase in amplitude following significant weight loss.^{80,81} Diurnal changes in adiponectin concentrations may be related to meals, as a study of 110 subjects found that adiponectin concentrations decreased by 6% two hours after a 75 g glucose load and by 8% five hours after a high-fat mixed meal.⁸² Other studies have reported little or no diurnal variation in adiponectin levels,^{8,83,84} and have indicated that adiponectin concentrations are unchanged after 72 hours of fasting,⁸⁵ however some of these studies may have been underpowered to detect such small effects. In one study, a four-fold postprandial increase in adiponectin in obese, but not in normal weight, subjects was reported.⁸⁶ In contrast, we have observed that plasma adiponectin concentrations do not change in either normal-weight or overweight/obese subjects over the course of a day during which 3 meals accompanied by glucose-sweetened beverages were consumed, despite large postprandial increases of glucose and insulin (unpublished observations). Consistent with these results, infusion of 200 mg/m²/min glucose for 48 hours in normal weight, insulin-sensitive humans produced moderate increases of plasma glucose, insulin, and leptin concentrations, but did not change circulating adiponectin concentrations at all.⁸⁷ Overall, the diurnal variation in circulating adiponectin concentrations is much less than that observed for leptin.⁸⁸

Although a consistent inverse relationship between plasma insulin and adiponectin concentrations has been shown in cross-sectional studies,^{8,89} the effects of insulin on adiponectin secretion and circulating adiponectin levels reported in both *in vivo* and *in vitro* studies are inconsistent. Short-term elevations in insulin, such as those measured during a hyperinsulinemic-euglycemic clamp, modestly lower circulating adiponectin concentrations, particularly the HMW form,⁹⁰ in human subjects.^{91–93} In type 1 diabetic patients, however, nearly two years of insulin replacement did not significantly increase adiponectin concentrations.¹⁶ Inconsistent effects of insulin on adiponectin synthesis have been observed in isolated

cells: pulse-chase studies of 3T3-L1 adipocytes have shown that supraphysiological concentrations of insulin (160 nM) roughly doubled adiponectin secretion over two hours.⁹⁴ This is supported by data from our laboratory indicating that adiponectin secretion from isolated rat adipocytes was increased by a 96-hour exposure to physiological insulin concentrations, and that both insulin-stimulated glucose utilization and adiponectin secretion were reduced in large adipocytes from obese animals compared with smaller, more insulin-sensitive adipocytes from nonobese rats.⁷⁷ The effects of insulin on adiponectin secretion may be cell- and time-dependent, however, as adiponectin secretion from cultured human subcutaneous and omental adipocytes was reportedly unaffected by 24 hours of 100 nM insulin treatment.⁷⁰

Effects of Caloric Restriction and Weight Loss on Circulating Adiponectin Concentrations

There is little consistent evidence to indicate that adiponectin concentrations in humans are regulated by short-term caloric restriction, prior to significant weight loss. In obese women, consumption of a very low calorie diet (550 kcal/day) for three weeks reduced weight by approximately 5% but did not change adiponectin concentrations.⁹⁵ In men, similarly, adiponectin levels were unchanged following consumption of an 800 kcal/day diet for four days.⁹⁶ We have observed a modest (~10%) but significant increase in serum adiponectin in normal-weight women following consumption of a calorie-restricted (600 kcal/day) diet for one week; interestingly, the opposite effect (an ~20% decrease of adiponectin) was observed in men restricted to 800 kcal/day.⁹⁷ One study of healthy normal-weight women restricted to 1000 to 1200 kcal/day for four weeks showed a significant reduction in adiponectin concentrations (16%), despite an average weight loss of 3.4 kg.⁹⁸ Analogously, exercise does not produce changes in circulating adiponectin concentrations independently of weight loss.^{99–101}

In contrast, longer-term caloric restriction producing significant weight loss (>8–9% of initial weight) has been repeatedly shown to increase adiponectin concentrations (reviewed recently in Imbeault¹⁰¹). Weight changes of this magnitude usually result from either long-term caloric restriction or various forms of weight loss surgery. In these studies, the increase in adiponectin concentration appears to be more related to the amount of weight lost than the method used.¹⁰² We and others have reported that increases in adiponectin following weight loss are strongly and negatively correlated with changes in body weight, body mass index (BMI) and fat mass.^{103–107} The failure of some adequately-powered studies to observe changes in adiponectin concentrations after significant weight loss may be attributable to a redistribution of adiponectin oligomers, towards the higher molecular weight forms, that is not apparent when the total adiponectin concentration is examined.^{108–110} We have observed that although total adiponectin concentrations were unchanged one month after Roux-en-Y gastric bypass surgery, absolute concentrations of HMW adiponectin and the proportion of HMW adiponectin were increased.¹⁰³ Notably, adiponectin levels are also elevated in patients with anorexia nervosa.^{111–112}

Regulation of Adiponectin by Peroxisome Proliferator-Activated Receptors

Peroxisome proliferator-activated receptors alpha, delta and gamma (PPAR- α , - δ and - γ) are ligand-activated nuclear receptors involved in the regulation of lipid and carbohydrate metabolism and adipogenesis.¹¹³ PPARs are thought to function as sensors for dietary fatty acids and their metabolic derivatives,¹¹⁴ and are also activated by synthetic ligands such as fibrates (PPAR- α), GW501516 (PPAR- δ) and TZDs (PPAR- γ). Both fibrates and TZDs increase adiponectin concentrations in humans^{115–117} through an induction of adiponectin mRNA in adipose tissue.^{76,118} These effects are mediated through a functional peroxisome proliferator response element in the proximal adiponectin promoter.¹¹⁹ Adipose-specific PPAR- γ knockout mice have reduced plasma adiponectin concentrations.¹²⁰

Of the dietary fatty acids, n-3 (or omega-3) polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have received a great deal of attention as prophylactic agents for cardiovascular disease and insulin resistance.¹²¹ DHA is a ligand for both PPAR- α and - γ ,¹²² and oxidized EPA is a potent regulator of PPAR- α .¹²³ n-3 fatty acids readily undergo oxidation at ambient temperatures, even in the absence of exogenous oxidizing reagents. In rats, the addition of high levels of EPA/DHA as part of a high-fat diet (15% of the 35% fat by weight) for five weeks increased adiponectin concentrations by approximately 20 to 30%.¹²⁴ In *ob/ob* mice, similarly, consumption of EPA at 5% of diet by weight for four weeks reduced adipocyte size and increased adiponectin concentrations.¹²⁵ Coculture experiments, involving both 3T3-L1 adipocytes and macrophages, have recently shown that the stimulatory effects of EPA on adiponectin concentrations are likely to involve inhibition of TNF- α secretion from neighboring macrophages rather than direct effects on adiponectin mRNA in adipocytes.¹²⁵ Interestingly, micromolar concentrations of EPA have also been shown to induce PPAR- γ 1 mRNA in isolated human subcutaneous adipocytes,¹²⁶ suggesting an additional mechanism by which EPA could increase adiponectin concentrations. In obese humans with the metabolic syndrome, Itoh et al.¹²⁵ recently found that consumption of 1.8g/day of highly-purified EPA for three months increased adiponectin concentrations by approximately 60%. The relationship between n-3 fatty acid intake and adiponectin concentrations is further supported by the observation that plasma DHA levels, which are indicative of dietary DHA intake, are proportional to adiponectin concentrations in humans.¹²⁷

Fish oil is rich in both EPA and DHA, and in rodents, dietary supplementation with fish oil improves insulin resistance with up to a two-fold increase of adiponectin concentrations.^{128,129} This effect likely involves PPAR- γ rather than PPAR- α , as fish oil-mediated increases in plasma adiponectin concentrations were prevented by pharmacological inhibition of PPAR- γ , and were still observed in PPAR- α -null mice.¹²⁹ In humans, while diets high in fish oil or n-3 PUFAs themselves are associated with a reduced risk of cardiovascular disease,^{130,131} studies have yet to conclusively demonstrate that they increase adiponectin concentrations¹³² independently of weight loss.⁸¹ The contrasting effects of EPA¹²⁵ and fish oil⁸¹ on adiponectin concentrations

in humans may be due to the use in the former study of highly-purified EPA preparations or subjects with preexisting metabolic syndrome components. However, the amounts of EPA administered were similar in both studies. Further investigation will be required to conclusively determine whether dietary supplementation with fish oil/EPA/DHA increases adiponectin concentrations in humans.

Another dietary fatty acid, conjugated linoleic acid (CLA), has been intensively studied for its effects to reduce fat mass,¹³³ especially in mice.¹³⁴ Dietary CLA is derived from dairy products and ruminant meats, such as beef and lamb, and when added to human diets, it has been shown to modestly reduce adiposity.¹³⁵ Studies in isolated rat adipocytes have shown that CLA inhibits adiponectin production, possibly via reductions in adipocyte glucose utilization and PPAR- γ mRNA expression.¹³⁶

Regulation of Adiponectin by Other Pharmacological Agents

Treatment of hypertension by inhibition of the renin-angiotensin system, using either angiotensin converting enzyme (ACE) inhibitors or angiotensin type 1 receptor (AT1R) blockers, concomitantly improves insulin sensitivity and reduces new-onset type 2 diabetes in humans.¹³⁷ The insulin-sensitizing effects of ACE inhibitors and AT1R blockers are likely to involve adiponectin, as the low adiponectin concentrations observed in hypertensive patients¹¹ are increased by treatment with these compounds.^{138,139} There are several potential mechanisms involved: angiotensin II inhibits differentiation of adipocytes, via the AT1 receptor,¹⁴⁰ and also inhibits key elements of the insulin signaling pathway in cultured smooth muscle cells.¹⁴¹ Accordingly, treatment of obese rats with AT1R blockers not only increases adipocyte differentiation but also reduces TNF- α expression in adipose tissue.¹⁴² AT1R blockers have also been shown to be partial agonists of PPAR- γ ,^{143,144} and their ability to increase adiponectin concentrations may be, at least partially PPAR- γ -dependent, as eprosartan, which does not activate PPAR- γ , had no effect on adiponectin secretion from 3T3-L1 adipocytes.¹⁴⁵ Interestingly, olmesartan, another AT1R blocker, prevented decreases in circulating adiponectin levels in genetically and diet-induced obese mice by reducing oxidative stress in adipose tissue.¹⁴⁶

Adiponectin secretion is also influenced by the endocannabinoid system. Receptors for endocannabinoids are present on human adipocytes,^{147,148} and treatment with the CB1 antagonist, rimonabant, increases adiponectin mRNA and protein in cultured mouse adipocytes.¹⁴⁷ In human patients, rimonabant treatment not only reduces body weight and waist circumference, but also increases adiponectin concentrations and HDL-cholesterol.¹⁴⁹ Notably, the increases in adiponectin concentrations are larger than would be expected from the magnitude of the reductions of body weight and adiposity. Although it has been approved and is used in treatment of the metabolic syndrome in 38 countries worldwide, rimonabant has not been approved for use in the U.S., due to concerns about psychiatric side effects (depression and suicidal thoughts) reported in some patients.

Adiponectin secretion in cultured adipocytes and in mice is inhibited by treatment with valproic acid, an anticonvulsant agent used therapeutically for the treatment of

epilepsy.¹⁵⁰ Common side effects of valproate treatment in humans include obesity¹⁵¹ and insulin resistance.¹⁵² Valproic acid inhibits adiponectin gene expression and decreases plasma adiponectin levels in mice by reducing the amount of C/EBP α ,¹⁵⁰ an adipogenic transcription factor which stimulates adiponectin transcription.^{46,153}

Endocrine Influences on Adiponectin Concentrations

Adiponectin concentrations in rodents and humans are sexually dimorphic, with higher concentrations observed in females compared with males. This appears to be due to a selective increase in the HMW oligomer of the hormone.³⁵ These differences develop during puberty and are a result of inhibition of adiponectin production by circulating androgens.¹⁵⁴ In mice, HMW adiponectin concentrations are increased by castration and are decreased by testosterone replacement,¹⁵⁵ and testosterone replacement therapy significantly reduces adiponectin concentrations in hypogonadal men.¹⁵⁶ Studies in 3T3-L1 adipocytes indicate that testosterone-mediated decreases in adiponectin secretion are due to enhanced intracellular retention of HMW adiponectin.¹⁵⁵

Adiponectin concentrations are stable throughout the menstrual cycle.¹⁵⁷ During pregnancy, however, both adiponectin mRNA expression and circulating adiponectin concentrations decline during the third trimester¹⁵⁸ and postpartum¹⁵⁹ when insulin sensitivity is reduced. This may be a mechanism to ensure greater nutrient availability for the developing fetus.¹⁶⁰ Reduced adiponectin concentrations during pregnancy do not appear to be attributable to central fat accumulation and weight gain,¹⁵⁹ rather, they are likely to result from inhibition by prolactin, which decreases adiponectin content and secretion in cultured human adipocytes and adipose tissue.^{159,161} Human adipocytes express prolactin receptors,^{159,162} and elevated prolactin levels in humans have been associated with insulin resistance.¹⁶³ Support for this inverse relationship has also been obtained in mice: female, but not male, transgenic mice overexpressing prolactin have reduced adiponectin levels.¹⁶¹ Interestingly, adiponectin concentrations are not increased in prolactin receptor-knockout mice,¹⁶¹ suggesting that this particular pathway may exist to favor the suppression of adiponectin, and thereby ensure fetal growth and development.

Adiponectin mRNA expression and secretion in human adipocytes are also inhibited by glucocorticoids.¹⁶⁴ In healthy subjects, similarly, acute intravenous administration of 25 mg hydrocortisone transiently decreased adiponectin by approximately 25% after one hour.¹⁶⁵ This effect may be dose-dependent, however, as no changes of adiponectin were observed in men treated for 5 days with 3 mg dexamethasone.¹⁶⁶ Excessive endogenous glucocorticoid production (Cushing disease) is associated with central obesity and insulin resistance, conditions under which adiponectin concentrations would already be expected to be reduced. However, at the present time, there are no convincing data to suggest that adiponectin levels are reduced in Cushing patients, independently of obesity.¹⁶⁵ In fact, Libè et al.¹⁶⁷ reported that there were no differences in adiponectin concentrations between normal-weight Cushing patients and BMI-matched control subjects with similar levels of insulin resistance, and adiponectin concentrations did not change after treatment of

the disease with transsphenoidal resection of the pituitary adenomas.

The discrepant effects of glucocorticoids on adiponectin observed between *in vivo* and *in vitro* studies might possibly be resolved by considering the effects of intracellular steroid metabolism, which appears to be an important determinant of glucocorticoid action. 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1) regulates intracellular glucocorticoid levels by converting inactive cortisone to active cortisol, and its activity is elevated in subcutaneous adipose tissue from obese subjects.¹⁶⁸ 11β HSD-1 may indirectly regulate adiponectin gene transcription, as adipose-specific overexpression of this enzyme in transgenic mice decreased adiponectin mRNA in mesenteric adipose tissue.¹⁶⁹ Conversely, knockout of 11β HSD-1 in all tissues was associated with increased adiponectin mRNA expression in epididymal fat, although not in visceral mesenteric fat.¹⁷⁰ Plasma adiponectin concentrations were not measured in either of these mouse studies, however, so the contribution of local glucocorticoid action in regulating circulating adiponectin concentrations remains to be determined.

Adiponectin may also be inhibited by growth hormone (GH). Adiponectin secretion in cultured explants of human adipose tissue is reduced by incubation with GH, and GH-overexpressing transgenic mice of both sexes have lower circulating adiponectin concentrations than wild-type littermates.¹⁶¹ This effect appears to be independent of energy balance and adiposity, as GH-overexpressing transgenic mice have reduced body fat and are resistant to diet-induced weight gain on a high-fat diet,¹⁷¹ conditions when circulating adiponectin concentrations would be expected to be elevated. The inverse relationship between GH and adiponectin in mice is further supported by the observation that GH receptor deficiency is associated with increased adiponectin concentrations in both sexes.¹⁶¹ The underlying mechanism has been recently shown to involve GH-mediated increases in the expression of the p85 subunit of phosphatidylinositol 3-kinase (PI3K), a negative regulator of insulin signaling, in adipose tissue.¹⁷² In humans, however, there is presently a lack of consensus on whether elevated GH levels (such as in acromegaly) are associated with reduced adiponectin concentrations.^{173–176} There is one positive report, however, of patients with acromegaly having low adiponectin levels that were reversed following GH-lowering therapy.¹⁷⁷ However, treatment of HIV-associated lipodystrophy patients with recombinant human GH increased circulating adiponectin by approximately 20% and the increase of adiponectin was correlated with increases of HDL cholesterol.¹⁷⁸

Adiponectin synthesis and secretion also appear to be inhibited by activation of the sympathetic nervous system. Adiponectin gene expression in human visceral adipose tissue is inhibited by β -adrenergic agonists.¹⁷⁹ Similarly, in both mouse adipose tissue explants and *in vivo*, β -adrenergic agonists reduce adiponectin mRNA, secretion and plasma concentrations, with β_3 -agonists having the greatest effect.¹⁷⁹ Consistent with these findings, six months of treatment with rilmenidine, which reduces the firing rate of sympathetic neurons, increased adiponectin concentrations by approximately 35% in hypertensive human subjects, independently of changes in weight or visceral adiposity.¹⁸⁰ In contrast, studies examining adiponectin concentrations in response to cold

exposure-mediated activation of the sympathetic nervous system have been much less consistent: one study in humans suggests that cold exposure at 10°C decreases adiponectin concentrations after 90 minutes,¹⁰¹ while studies in rodents have reported increases,¹⁸¹ decreases,¹⁸² and no change¹⁸³ in adiponectin mRNA or circulating concentrations in response to cold exposure (18–24 hours at 4–6°C). These discrepancies may reflect the different timepoints studied or species differences in responses to cold exposure.

Finally, a role for bone-derived hormones in the regulation of insulin sensitivity has been suggested by the recent observation that mice deficient in osteocalcin, a hormone secreted by osteoblasts, exhibit glucose intolerance and insulin resistance, likely due to reduced adiponectin concentrations.¹⁸⁴ The influence of such osteogenic factors on glucose homeostasis is likely to be an active area of future research.

Together, these observations indicate that during periods of growth, stress, reproduction (and male sexual development), a number of endocrine systems may act to decrease circulating adiponectin concentrations, potentially increasing nutrient availability via a transient reduction in insulin sensitivity. Prolonged suppression of adiponectin production, however, as occurs in response to visceral adipocyte hypertrophy associated with weight gain, may prove maladaptive and lead to the development of insulin resistance and type 2 diabetes in susceptible individuals.

Effects of Inflammation and Oxidative Stress

In humans and in laboratory animals, obesity is frequently characterized by macrophage infiltration into adipose tissue, resulting in chronic, low-grade inflammation.^{185–187} This inflammatory state, characterized by elevated adipose tissue TNF- α expression^{188–189} and circulating concentrations of C-reactive protein (CRP),¹⁹⁰ interleukin-6 (IL-6),¹⁹¹ and monocyte chemoattractant protein-1 (MCP-1),¹⁹² has been implicated in development of many of the complications of severe obesity, in particular, atherosclerosis, insulin resistance, and type 2 diabetes.¹⁹³ Cross-sectional studies have consistently demonstrated an inverse relationship between adiponectin concentrations and those of inflammatory markers such as CRP, TNF- α , and IL-6.^{194,195}

The inverse relationship between adiponectin and inflammation is well supported by *in vitro* data, as TNF- α ,^{164,196} IL-6,¹⁹⁷ and CRP,¹⁹⁸ inhibit adiponectin synthesis in human and murine adipocytes. These inflammatory factors have all been shown to interfere with insulin signaling in adipocytes, reinforcing the idea that adiponectin secretion is likely to be determined by adipocyte insulin sensitivity. TNF- α induces serine phosphorylation of insulin receptor substrate-1 (IRS-1), which inhibits insulin receptor kinase activity and downstream signaling via PI3K activation.¹⁹⁹ Inhibition of adiponectin mRNA by CRP is also at least partially dependent upon the PI3K pathway.¹⁹⁸ Both IL-6 and TNF- α reduce the expression of IRS-1, GLUT-4, and PPAR- γ in 3T3-L1 adipocytes.²⁰⁰ Furthermore, IL-6 induces the expression of suppressor of cytokine signaling (SOCS) proteins, which inhibit insulin signaling by binding to the insulin receptor and IRS-1.^{201,202} Lastly, interleukin-15, an anabolic cytokine produced by skeletal muscle, increases adiponectin secretion from 3T3-L1 adipocytes, suggesting the involvement of muscle-to-adipocyte endocrine signaling.²⁰³

There are abundant data from studies in mice to indicate that oxidative stress also regulates adiponectin secretion. Oxidative stress is defined as a persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen) and the capacity of antioxidant defense systems to inactivate or remove them.²⁰⁴ Oxidative stress is elevated in human obesity and insulin resistance.²⁰⁵ Results obtained from experiments in mice suggest that lipid accumulation in adipocytes, and a concomitant rise in ROS production, may be a key trigger for the development of insulin resistance via reduced adiponectin secretion.²⁰⁶ Exposure of cultured primary rat adipocytes to hyperglycemic conditions (15 mM glucose, 100 nM insulin) increases intracellular nutrient availability and ROS production, leading to a reduction in insulin sensitivity.²⁰⁷ Similarly, exposure of 3T3-L1 adipocytes to hydrogen peroxide, a powerful oxidizing agent, reduces adiponectin mRNA expression within 10 minutes.²⁰⁸ The mechanism(s) linking ROS production to

adiponectin secretion are currently under investigation, and studies in 3T3-L1 adipocytes have suggested roles for uncoupling protein-2 (UCP2), a protein which increases mitochondrial respiration, as well as the transcription factor CHOP-10, which interferes with the C/EBP-binding region in the promoter of the adiponectin gene.²⁰⁹

Cigarette smoking also reduces adiponectin concentrations.²¹⁰⁻²¹² Acute exposure to cigarette smoke significantly reduced adiponectin levels by 9% after 3 hours, and the maximum decrease (15%) was observed after 12 hours.²¹¹ There is some *in vitro* evidence to suggest that smoking suppresses adiponectin secretion, either via generation of ROS or by direct effects of nicotine on adipocytes,²¹¹ but this may also be due to smoking-related inflammation,²¹³ tissue hypoxia,²¹⁴ or possibly via activation of the sympathetic nervous system activity via nicotinic receptors in sympathetic ganglia.¹⁷⁹ The inhibitory effects of smoking on adiponectin contrast unfavorably with those of alcohol consumption, as several stud-

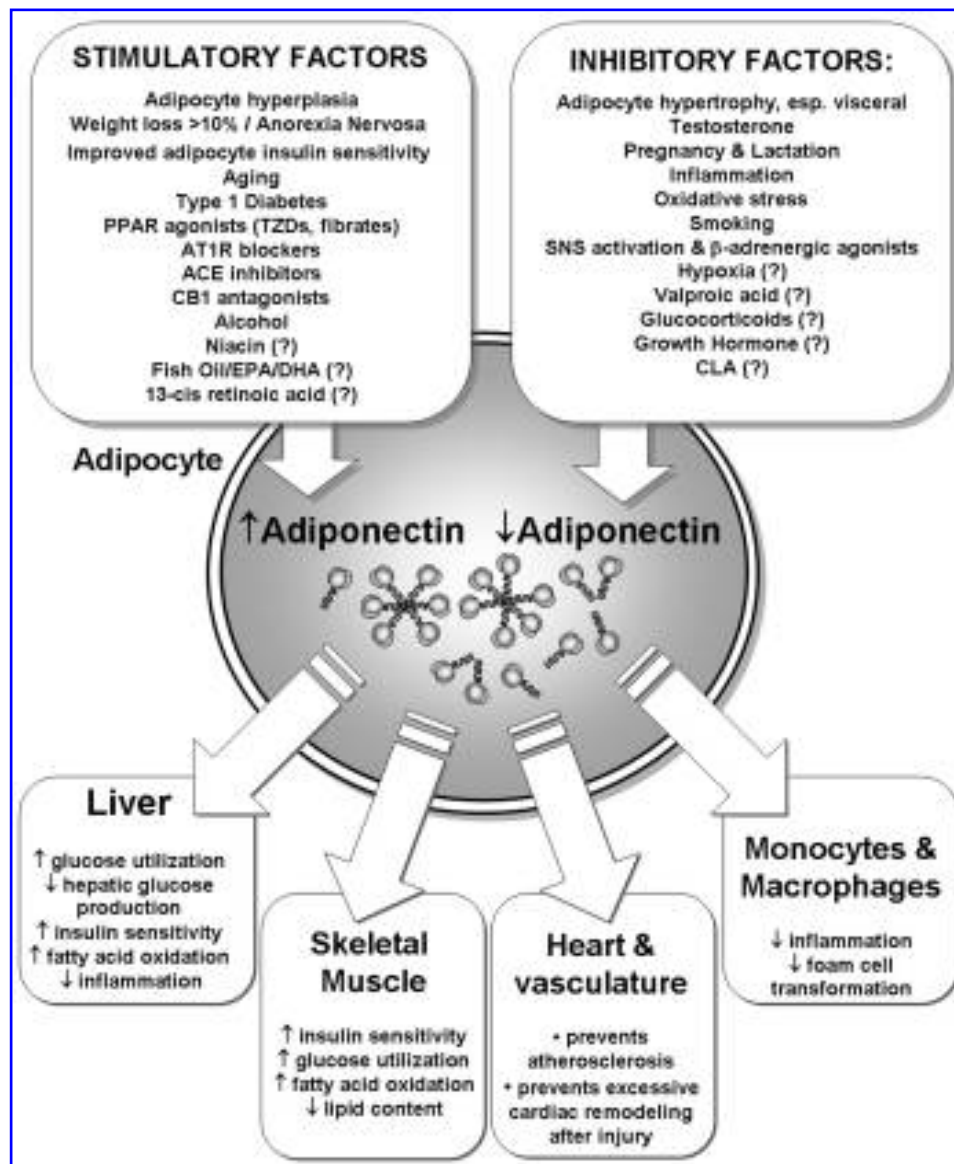


FIG. 1. Summary of factors that regulate adiponectin concentrations in humans. Factors with limited or conflicting data in humans (including extended-release niacin²²² and 13-cis-retinoic acid²²³) are indicated with a question mark.

ies have shown that adiponectin concentrations are increased by moderate alcohol consumption.^{215,217}

Conclusions

In the decade since its discovery, the adipocyte-derived hormone adiponectin has been revealed to be a key component in the relationships between excess adiposity, insulin resistance, inflammation and cardiovascular disease. Decreased adiponectin production by adipocytes, leading to reduced circulating adiponectin levels, is likely to be an important mechanism by which visceral adipose deposition and a number of other hormones promote insulin resistance in extra-adipose tissues, such as liver and skeletal muscle (Figure 1). Adiponectin concentrations are reduced in obesity, pregnancy, inflammation, and states of metabolic and oxidative stress, while adiponectin levels are increased following weight loss and in anorexia nervosa. Collectively, these observations can be drawn together by the recent proposal that increases of adiponectin may act as a systemic "starvation signal"²¹⁸ indicating the availability of excess storage capacity in adipocytes.²¹⁹ As discussed by Behre,²¹⁸ in starvation the presence of high adiponectin concentrations in concert with reduced insulin-stimulated glucose uptake.¹¹² would act to increase lipid oxidation in liver and muscle, limiting the use of amino acids as a source of energy and sparing carbohydrate (glucose) for use by the CNS. As a consequence of its actions to promote lipid metabolism as an energy source, adiponectin is able to prevent the ectopic deposition of triglyceride in liver and skeletal muscle, which can occur in obesity and is associated with the development of insulin resistance in these tissues.^{220,221} The "starvation signal" hypothesis is further supported by data indicating that adiponectin can stimulate food intake in mice by enhancing hypothalamic AMP kinase activity,³³ however the question of whether adiponectin has physiological actions within the CNS is still controversial. Nonetheless, strategies directed at increasing adiponectin production and its circulating concentrations, whether by lifestyle interventions (diet and weight loss), pharmacological therapy, or possibly with nutritional supplements, will likely be effective approaches for the prevention and treatment of insulin resistance/metabolic syndrome, type 2 diabetes, and cardiovascular disease, diseases that are rapidly increasing in prevalence worldwide.

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