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Regulation of Glucose and Lipid Homeostasis by Adiponectin: Effects on Hepatocytes, Pancreatic β Cells and Adipocytes

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Abstract

Adiponectin has received considerable attention for its potential anti-diabetic actions. The adipokine exerts control of glucose and lipid homeostasis via critical effects within the liver, adipose, and pancreas. By stimulating adipogenesis, opposing inflammation, and influencing rates of lipid oxidation and lipolysis, adiponectin critically governs lipid spillover into non-adipose tissues. Ceramide, a cytotoxic and insulin desensitizing lipid metabolite formed when peripheral tissues are exposed to excessive lipid deposition, is potently opposed by adiponectin. Via adiponectin receptors, AdipoR1 and AdipoR2, adiponectin stimulates the deacylation of ceramide-yielding sphingosine for conversion to sphingosine 1-phosphate (S1P) by sphingosine kinase. The resulting conversion from ceramide to S1P promotes survival of functional beta cell mass, allowing for insulin production to meet insulin demands. Alleviation of ceramide burden on the liver allows for improvements in hepatic insulin action. Here, we summarize how adiponectin-induced changes in these tissues lead to improvements in glucose metabolism, highlighting the sphingolipid signaling mechanisms linking adiponectin to each action.

Keywords

ceramide; insulin resistance; obesity

Introduction

Since the initial discovery in 1995, research on adiponectin has greatly shaped how we view adipose tissue and highlights the importance of adipose tissue as an endocrine organ (1, 2). Adiponectin was initially named Acrp30 as an adipocyte C1q-related protein of 30 kilodaltons. Adiponectin is an adipocyte-specific secretory protein with potent insulin sensitizing, glucose lowering, and lipid catabolizing functions on peripheral tissues. Though adiponectin receptors (AdipoRs) were originally described as having tissue-specific distributions with differing isoforms restricted to skeletal muscle (AdipoR1) and liver

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(AdipoR2) (3), both receptors are relatively ubiquitous. Tracer studies with infrared-labeled adiponectin reveal prominent sites of adiponectin targeting in the liver, heart, and kidney, with the endocrine pancreas also being evident as a prominent binding site for full-length adiponectin when visualized with immunofluorescence techniques (4, 5). Adiponectin is an excellent clinical marker for metabolic health (reviewed by Mather and Goldberg, in this issue). Consistent with the observed decreases in circulating adiponectin levels of obese individuals, numerous pre-clinical models have established roles for adiponectin in central and peripheral metabolic homeostasis (6–9). Here, we focus specifically on the beneficial actions of adiponectin to regulate glucose and lipid homeostasis via actions on the liver, adipose, and pancreas.

Adiponectin circulates in a combination of 3 forms: trimers, low molecular weight multimers, and high-molecular weight oligomers (HMW). Circulating adiponectin levels inversely correlate with adiposity, as inflammatory mediators impair adiponectin production and release. A number of treatments with beneficial anti-diabetic effects are known to influence circulating levels of adiponectin, including thiazolidinediones (TZDs- PPARγ agonists), fibroblast growth factor 21(FGF21), anti-inflammatory compounds, and weight loss (Table 1). Notably, adiponectin expression is essential for the complete glucose-lowering effects evoked by TZDs (10, 11) or FGF21 (12, 13). The HMW form of the protein is the best biomarker for clinical efficacy of TZDs (14) and is also markedly increased by FGF21 treatment (15). Additionally, diet and exercise, the first line of treatment for diabetes, can each elevate circulating adiponectin levels independently (16, 17). Exercise may additionally facilitate adiponectin action by upregulating expression of adiponectin receptors (18). Collectively, the literature suggests that targeting adiponectin production or adiponectin signaling are attractive targets for therapeutic interventions for the prevention or treatment of obesity-related derangements in metabolism.

Adiponectin improves hepatic lipid metabolism

The liver plays vital roles in metabolism of carbohydrates, lipids, amino acids and the synthesis of essential proteins. In the context of chronic over-nutrition, the liver is challenged by excess lipid deposition (steatosis) and a failure of insulin to suppress both the release and production of excess glucose. Liver disease can be caused by a spectrum of factors, including: genetics, ectopic lipid storage, and viral infection. Among all, fatty liver is the most frequently observed chronic liver condition. Nonalcoholic fatty liver disease (NAFLD), which currently effects about 1/3 of the population in industrialized countries, is characterized by the over-accumulation of triglycerides within lipid droplets of hepatocytes (19). Fatty liver disease has been classified into two categories depending on the contribution of alcohol to the excess accumulation of fat: NAFLD and alcoholic liver disease (ALD). Aside from alcohol intake and the differences in tendency toward progression to advanced liver disease, the two follow a similar disease spectrum and share several common features in pathology. A more symptomatic sub-class of NAFLD, non-alcoholic steatohepatitis (NASH), is additionally accompanied by inflammation, hepatocyte death, and fibrosis. In addition to impaired liver function, NASH leads to progressive formation of cirrhosis and hepatocellular carcinoma (20). NASH affects mortality and morbidity, with a ten-fold greater incidence of death from liver-related diseases (21).

Finding preventive and diagnostic measures for liver disease is therefore of utmost importance.

Adiponectin promotes numerous beneficial effects in liver, providing hope that compounds which harness adiponectin signaling capabilities may proof beneficial for metabolic health. Clinical data suggest that the development of NAFLD is associated with insulin resistance; most patients are overweight, obese, with dyslipidemia and hypertension. Even in lean subjects with normal glucose tolerance, this association between NAFLD and insulin resistance and hyperinsulinemia still correlates (22). However, causal links between the steatosis and insulin resistance are still controversial, particularly in some genetically prone populations (23). Obesity-linked down-regulation of adiponectin may mechanistically contribute to insulin resistance and diabetes. Clinically, adiponectin has been shown to inversely correlate with obesity and NAFLD, and a number of current treatments for hepatic steatosis raise adiponectin levels. Aside from its potent insulin sensitizing effects where adiponectin decreases hepatic glucose production, the adipokine also increases fatty acid oxidation in liver, decreases inflammation, promotes cell survival and diminishes fibrosis. As such, adiponectin mechanistically counters a number of processes involved in the progression of NASH. Not surprisingly, NAFLD patients have significantly lower plasma adiponectin levels and insulin resistance (24, 25).

Adiponectin opposes steatosis

Dietary lipids are metabolized primarily in the intestines, where they are broken down, rebuilt into triglycerides (TGs), and then repackaged with cholesterol and proteins into chylomicrons. Chylomicrons are intestinally secreted lipoprotein particles that function to transport exogenous lipids through the bloodstream primarily to the liver where lipids can be repackaged into lipoprotein particles. As lipoproteins reach target tissues, TGs are unloaded by lipoprotein lipase and undergo subsequent hydrolysis to release glycerol and free fatty acids (FFAs), which then enter the cell and function as an energy source, or building blocks for membrane lipid synthesis. Excess lipid can additionally be stored in target tissues by re-esterifying FFAs into TGs. Though adipose is the primary tissue for lipid storage, liver can also store lipid in a benign fashion, as steatosis fails to progress to NASH in most patients. Upon demand for energy, the stored TGs can be broken down into FFAs through lipolysis.

Hepatic steatosis is characterized by the accumulation of TG as lipid droplets within the cytoplasm of hepatocytes. The clinical definition for hepatic steatosis is a TG content >55mg/g of the liver or lipid droplets visible in > 5% of the hepatocyes (19). The liver TG pool comes from three major sources: exogenous lipid, as mentioned above, FFAs release from peripheral tissues, such as adipose tissue through lipolysis, and lastly, *de novo* lipogenesis from acetyl-CoA (19). High circulating FFAs from exogenous lipids and peripheral tissues signal to the liver to increase lipid uptake and decrease VLDL secretion. The lipid overload in hepatocytes can impair mitochondrial function in favor of *de novo* lipogenesis (26).

Preclinical models indicate roles for adiponectin in the maintenance of hepatic lipid metabolism. Adiponectin null mice develop fibrotic steatohepatitis and adenomas when maintained on high fat diets for 48 weeks (27) but not in response to shorter-term diet

administration (28, 29). Genetic ablation of adiponectin in leptin-deficient (*ob/ob*) mice further exacerbates hepatic triglyceride accumulation (12). Conversely, adiponectin overexpression prevents accumulation of triglycerides or the deleterious lipid metabolites diacylglycerols or ceramides (30, 31). Similar effects are seen in other transgenic mice which develop hyperadiponectinemia secondary to changes in adipose mitochondrial function, as they are also refractory to TG, diacylglycerol, or ceramide overaccumulation (32). Administration of recombinant adiponectin in rodents results in beneficial effects on lipid metabolism, such as enhancing lipid clearance and increasing fatty acid oxidation in muscle and liver (33, 34). Several groups have also demonstrated that circulating adiponectin concentrations decrease during chronic ethanol experiments in rodents (35–37). Adenoviral adiponectin overexpression can attenuate hepatomegaly, steatosis and liver injury in mice exposed to chronic ethanol exposure through admix to their high fat diet- this treatment lowers plasma adiponectin within 3 weeks as steatosis develops (36).

Adiponectin is anti-steatotic by decreasing free FFA influx into the liver and increased FFA oxidation and mitochondrial biogenesis (24). Studies with genetic manipulation of adiponectin receptors show similar trends as adiponectin itself, and human single nucleotide polymorphisms in either adiponectin receptor are significantly associated with liver triglyceride accumulation (38, 39) and even risk for cirrhosis (40). Though not consistently seen in either human or animal studies (41), some reports indicate downregulation of adiponectin receptor transcription may be seen in livers of NAFLD and NASH patients (42, 43). Decreased expression of AdipoR2 has also been observed in murine models of hepatic steatosis (44). Conversely direct manipulation of adiponectin receptor expression demonstrates a potential causal relationship between adiponectin signaling and steatosis (45). Adenoviral-mediated overexpression of either adiponectin receptor is sufficient to stimulate lipid oxidation and diminish hepatic triglyceride content (46). By contrast, mice lacking both isoforms of the adiponectin receptors display enhanced hepatic triglyceride accumulation. In sum, the combined effects of low plasma adiponectin and low AdipoR2 in liver may each contribute to the development of hepatic steatosis.

In the case of ALD, chronic ethanol exposure is thought to cause enhanced hepatic lipogenesis and impaired fatty acid oxidation by inhibiting transcriptional regulators such as AMP-mediated protein kinase (AMPK), sirtuin 1 (SIRT1), PPAR-gamma co-activator alpha (PGC-1α), peroxisome proliferator-activated receptor alpha (PPARα), and activating sterol regulatory element-binding protein 1 (SREBP-1) (35). Activation, of similar pathways can be instigated by adiponectin and its receptors, as its receptors were initially demonstrated to promote AMPK and PPARα (47). In turn, AMPK plays a critical role in regulating rates of lipid oxidation via phosphorylation of acetyl-CoA carboxylase and subsequent activation of carnitine palmitoyltransferase-1 (CPT-1) to facilitate uptake of fatty acids into the mitochondria, enhancing rates of beta oxidation. Additionally, AMPK and SIRT1 can increase PGC- 1α expression and decrease its acetylation to facilitate mitochondrial biogenesis, allowing for enhanced lipid oxidative capacity (48). Other anti-lipotoxic effects initiated by adiponectin appear to be regulated by the transcriptional effects of PPARα. These include reductions in lipid synthetic enzymes, increases in CPT-1, and enhanced ApoA synthesis for the production and secretion of HDL lipoproteins (49)

Adiponectin lowers hepatic ceramide accumulation and prevents apoptosis

Ceramides are a family of lipids composed of sphingosine backbone and a fatty acid (Figure 1). *De novo* ceramide synthesis starts with serine and palmitoyl Co-A to form an 18-carbon backbone. Through a series of enzymatic reactions, ceramide is formed. Ceramides can inhibit insulin action via diminished signaling of AKT, a central kinase involved in insulin signal transduction (50). As such, high levels of intracellular ceramides are associated with reduced nutrient uptake, decreased insulin sensitivity, and increased apoptosis. The deacylation of ceramide, characterized by the release of a sphingosine and free fatty acid, is carried out by an enzyme called ceramidase. Once free from ceramide, sphingosine can be phosphorylated by sphingosine kinase to form sphingosine-1-phosphate (S1P) (5, 50). S1P is known to exhibit opposite effect to ceramide, in which it can promote cell survival, improve insulin sensitivity, and reduce inflammation. Therefore, the relative ratios of ceramide and S1P are crucial for survival and insulin sensitivity of the cell. Hence, the modulation of ceramide metabolism is essential in maintaining metabolic homeostasis. Vastly overlapping beneficial metabolic functions between adiponectin and S1P are quite apparent. This therefore raised the interesting possibility that adiponectin may exert its activity through effects on the ceramide axis.

The association of sphingolipids and NAFLD was first revealed by non-biased bioinformatics screening by two independent groups. The Oresic group, using computational and lipidomic approaches applied to rodent models of obesity, identified parallel associations between hepatic triglycerides with ceramides and the ceramide biosynthetic pathways (51). Similarly, Yki-Jarvinen and colleagues identified ceramide signaling and metabolism genes as significantly altered from microarrays of human subjects with extreme steatosis without histological signs of inflammation (52). These were further supported by lipidomic data from livers of steatotic patients revealing significant correlations between liver triglycerides, ceramides and inverse correlations with adiponectin (53). Such correlations between hepatic steatosis and ceramides are not consistently observed, perhaps due to differences in the stage or severity of the disease (54).

The regulation of ceramide metabolism is tightly associated with lipid intake, increased by inflammatory mediators, and decreased by adiponectin (55). Accumulation of lipid metabolites appear following impairments in adiponectin-induced lipid oxidation (56). Using various adiponectin mouse models, the inverse correlations between genetic dosing of adiponectin and hepatic ceramide content have been measured after high fat diet challenge (57). Overexpression of either adiponectin receptor isoform is sufficient to diminish hepatic ceramide accumulation and enhance ceramidase activity. Using genetic gain or loss of adiponectin receptors in cell culture experiments further clarified the role of adiponectin in inducing a ceramidase activity mediated via its canonical receptors. This is supported through research showing a heterologous system connecting this class of receptors with ceramidase activity (58, 59). These receptors convey ceramidase activity that can be further enhanced by adiponectin, which results in simultaneous decreases in ceramide and increases in S1P. Collectively, these data suggest activation of AdipoR1and R2 induces up-regulation of ceramidase activity and ultimately favoring the production of S1P (50, 57). The resulting sphingosine and S1P produced in this process may be sufficient to activate PPARα and

AMPK, the downstream mediators of adiponectin signaling. S1P addition is sufficient to induce AMPK phosphorylation (5), and sphingosine has been reported as a ligand for PPARα (60). In the context of lipid oxidation, ceramide may contribute to impairments in lipid oxidation, as it promotes de-activation of AMPK via activation of protein phosphatase 2a (PP2A) (61, 62). This may be of particular relevance to fatty liver disease as alcohol impairs AMPK activity in cultured hepatocytes via ceramide-dependent mechanisms (61). Moreover ceramides have been consistently elevated in rodent models of ALD (63–66), and can be lowered by targeted disruption of ceramide formation with imipramine or fumonisin B1, inhibitors of sphingomyelinase or *de novo* derived ceramide generation, respectively (61).

This local and systemic increase in S1P likely conveys the anti-apoptotic effects of adiponectin, as S1P is sufficient to recapitulate the protective effects of adiponectin in cardiomyocytes and pancreatic β cells. In other words, adiponectin lowers ceramide content and prevent apoptosis through adiponectin-receptor mediated increase ceramidase activity, i.e. driving the ceramide: S1P rheostat toward S1P mediated survival and proliferation. Tissues are constantly in equilibrium between death, survival, and proliferation/renewal. Adiponectin is critical for cell survival and self-renewal for several tissues (5, 67). Adiponectin null mice also have impaired capacity to regenerate liver following partial hepatectomy (68), a model where S1P production is critical for the pro-mitotic actions during recovery (69).

Adiponectin is anti-fibrotic

Hepatic steatosis is considered a risk factor for advanced liver disease; however, only a fraction of the affected individuals continue to develop steatohepatitis. Similarly in rodent models; some mice never develop a fibrotic phenotype unless under extreme challenge (70). Steatohepatitis is characterized by immune infiltration and hepatocyte apoptosis. Depending on the degree of injury, fibrogenesis may be initiated. Steatohepatitis and fibrosis are the results of genetic, environmental, and behavioral factors.

Fibrogenesis is a complex wound-healing response involving multiple aspects, such as nuclear receptors, inflammatory cytokines, and growth factors. Prolonged fibrogenesis can ultimately lead to fibrosis and cirrhosis. Fibrosis, scarring tissue, is characterized by an accumulation of fibrillar collagen (collagen I and III) in the extracellular matrix (ECM). It has been shown that activation of hepatic stellate cells (HSCs) and Kupffer cells modulate the hepatic fibrogenic process in injured liver tissue. Not all, but most, of the fibrotic cells are derived from activated HSCs (71). Upon liver injury, quiescent HSCs lose partial structural integrity and their droplet function as they switch on collagen production and become more proliferative. Activated HSCs are fibrogenic and can feedback to active more HSCs via amplifying inflammatory responses (71).

Activated HSCs are functionally and phenotypically distinct from quiescent HSCs. The activated HSCs are proliferative and are capable of releasing paracrine factors and survival signals to promote expansion of progenitor cells, scarring, and hepatic regeneration. HSC activation can be broken down to two phases: initiation and perpetuation. The initiation phase refers to the early injury recognition events such as LPS/TLR 4 signaling activation,

sensing of oxidative stress, apoptotic hepatocytes, and paracrine stimuli from Kupffer cells. These early events are targeted at quiescent HSCs to induce collagen production and progressive changes of the ECM (71). The perpetuation phase is the functional change following the phenotypic changes of HSCs. Depending on the extrinsic stimuli, HSCs can be prompted to: 1) proliferate to recover the loss of cell body due to apoptotic hepatocytes; 2) contract to increase portal resistance; 3) migrate to site of injury; 4) work in synergy with TFG-β and other pro-fibrogenic signals to promote fibrogenesis; 5) enhance inflammatory signals. It is the differential functions of HSCs that give them the ability to contribute to the scar forming fibrogenesis, and also offer potential as therapeutic targets.

An additional observation in favor of adiponectin and its anti-fibrotic potential is that quiescent HSC display adipocyte-like properties, and they are able to secrete adiponectin. However, upon activation, instead of adiponectin, HSCs switch to leptin production. Based on these observations, several studies have demonstrated the potential of using adiponectin for regression of fibrogenesis (71, 72). Shafiei et.al reported that adiponectin overexpressing transgenic mice receiving thioacetamide were resistant to fibrosis. In contrast, adiponectin knockout animals developed severe fibrosis (72). Summarizing these observations and adiponectin's anti-apoptotic function, we hypothesize that adiponectin is anti-fibrotic agent by reinforcing HSCs to remain in the quiescent state to prevent activation and the release of pro-fibrotic and pro-inflammatory factors following the activation.

Adiponectin is anti-inflammatory

What exactly promotes the transition from simple steatosis to steatohepatitis in patients is still unclear. There may be a connection of this transition to lipotoxicity (73). Lipotoxicity describes the condition of cellular dysfunction or apoptosis as a consequence of lipid deposition in tissues other than adipose tissue (74, 75). When the net storage of TG in hepatocytes exceeds its limits, the accumulated lipid will impair regular cell function and promote apoptosis. Along with the loss of functional hepatocytes and apoptosis, inflammatory cytokines and various stress signals are also released; thus creating a toxic environment for the surrounding cells. This toxicity can trigger cell defense and repair mechanisms, which include fibrogenesis and apoptosis (76).

Toll-like receptor 4 (TLR-4) can be activated as a consequence of aberrant lipid homeostasis. Recent publications have indicated saturated fatty acid can indirectly activate TLR4 signaling initiate inflammatory response and production of ceramide biosynthetic enzymes (77). Direct and indirect activation of TLR-4 receptor activates the downstream NF-κB signaling pathway. This activation process will lead to increased pro-inflammatory cytokine production and up-regulation of ceramide production (78). Ceramide itself has also been implicated as an inducer of inflammatory signaling via activation of IKKβ and Jun N-terminal kinase (JNK) (79). In acute inflammation, pro-inflammatory cytokines have a short half-life, therefore limiting the duration of the inflammatory response. To tightly control the inflammatory response, anti-inflammatory cytokines can counter immune activation and attenuate the activation of pro-inflammatory cytokines. This regulation is further accompanied by macrophage-mediated removal of dead cells, thereby terminating the source of pro-inflammatory signals (80).

Using a macrophage-like cell line, Hung et. al reported that globular adiponectin can normalize TLR-4 mediated signaling (81). A similar set of experiments using primary Kupffer cells has also demonstrated a LPS-desensitizing, anti-inflammatory effect of adiponectin (82). Collectively, adiponectin is anti-inflammatory by attenuating activation of pro-inflammatory responses, NFκB signaling, and also decreasing ceramide accumulation in tissues.

Adiponectin enhances hepatic insulin sensitivity and decreases hepatic glucose production

Several laboratories have examined the effects of adiponectin on glucose and lipid metabolism. Berg et al. reported a two- to five-fold elevation in circulating adiponectin levels can reduce plasma glucose levels in wild-type and diabetic mice (83). In addition, adiponectin knockout mice display glucose intolerance and severe hepatic, but not muscle insulin resistance upon high fat diet challenge (84). Injection of purified recombinant adiponectin during hyperinsulinemic-euglycemic clamp studies also leads to improved insulin action (5, 85).The effect of adiponectin on *in vivo* glucose metabolism in the clamped state was attributed to a 65% reduction in the rate of glucose production in either *wt* or *ob/ob* backgrounds. Adiponectin did not affect the rates of glucose uptake, glycolysis, or glycogen synthesis. Instead, an acute increase in circulating adiponectin levels lowers hepatic glucose production without affecting muscle glucose uptake. This is further evidenced by hepatic expression of the gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), whose mRNAs was reduced by more than 50% following adiponectin infusion, suggests a moderate rise in circulating levels of the adiponectin can inhibit both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production. However, these glucose lowering effects observed did not coincide with a rise in insulin, suggesting that the effects were primarily on insulin sensitivity. Consistent with these rodent studies, fasting adiponectin levels strongly correlate with insulin sensitivity in humans (86).

The mechanism by which adiponectin enhances insulin sensitivity was long thought to involve receptor-mediated activation of AMPK pathway to stimulated glucose utilization and fatty-acid oxidation (10, 87). However, recent reports also reveal mechanisms independent of AMPK (57, 88). Following inducible reductions in LKB1/AMPK signaling in the liver, adiponectin still potently evokes improvements in glucose homeostasis. Receptor mediated ceramidase activity is a primary signaling mechanism by which adiponectin elicits broad spectrum of effects in the liver and elsewhere. Although ceramidase can promote AMPK activation, AMP Kinase signaling is not required for adiponectin to promote ceramidase activation or ceramide-lowering effects (57). Miller and colleagues nicely demonstrated that, in the absence of LKB1/AMPK signaling, adiponectin can still reduce gluconeogenic gene expression and facilitate insulin-induced suppression of hepatic glucose efflux during hyperinsulinemic-euglycemic clamps (88).

Exposure to excess circulating saturated lipids (31, 77), glucocorticoids (31, 89), dietary fats (90, 91), or overconsumption of nutrients in general (due to leptin deficiencies) can increase hepatic ceramide accumulation in rodent models and is associated with hepatic insulin

resistance (5, 12, 31, 92). Notably, targeted inhibition of *de novo* ceramide synthesis can normalize hepatic ceramide and restores insulin's ability to suppress hepatic glucose output in each of these models. The kinetics of adiponectin-mediated improvements in hepatic insulin action overlap with the time required for adiponectin to normalize ceramide levels in the livers of *ob/ob* mice (5). Although ceramides have been shown to accumulate in the livers of obese insulin resistant humans (53), the specific role of ceramides in hepatic insulin resistance in humans as either a marker or a cause of insulin resistance, remains under debate (93).

Epidemiologically, adiponectin and insulin sensitivity share a strong correlation, as both are tightly linked to adiposity (94). The requirements for large quantities of protein production to clinically replenish a relatively abundant serum protein have largely deterred clinical pursuits of adiponectin itself, and have also limited the direct evaluation of adiponectin in human subjects. Several genetic polymorphisms have been identified in adiponectin and its receptors which are associated with insulin resistance. One such SNP that is very intriguing in relation to sphingolipids, which require saturated fats for their production, is a polymorphism in AdipoR1 which is highly responsive to differences in saturated fatty acids to evoke insulin resistance (95).

Enhancements in circulating adiponectin also strongly correlate with clinical efficacy of insulin sensitizers. Most notably, PPARγ agonists (TZDs) are strongly linked with adiponectin induction. In preclinical models, adiponectin is essential for TZDs to promote efficient improvements in glycemia, particularly at low doses (10, 11). In humans, TZD-induced improvements in gluconeogenesis strongly correlate with increases in circulating adiponectin (96). The high molecular weight form of adiponectin is the best predictor for improvements in glucose homeostasis evoked by TZDs (97), and this circulating form is also a better correlate for insulin sensitivity in general than total adiponectin (98). These correlations also extend for other effects of TZDs, particularly TZD induced decreases in hepatic steatosis, fibrosis, and inflammation seen in NASH patients (99). Another promising insulin sensitizer, FGF21, has also recently emerged as a potential therapeutic capable of improving insulin resistance. FGF21 is a target of PPARα (in liver) or PPARγ (in adipose), and elicits robust increases in plasma adiponectin in rodents (100, 101) and humans (15), and requires adiponectin for a majority of its antidiabetic effects (12, 13).

Adiponectin promotes the maintenance of functional β-cell mass

In a normal pancreas, a subpopulation of endocrine cells known as β-cells constitute the predominant type of cell in clusters called islets of Langerhans. These cells are responsible for the secretion of the peptide hormone insulin, which promotes the uptake of carbohydrates and nutrients in skeletal muscle and fat while suppressing glucose efflux from the liver and lipolysis from adipose. While the majority of metabolic studies evaluating adiponectin effects on glucose homeostasis have evaluated insulin resistance, several lines of evidence suggest that adiponectin may additionally promote β–cell survival. Compounds such as sulfatides and TZDs known to prevent diabetes in non-obese diabetic (NOD) mice or genetically predisposed humans, increase circulating levels of adiponectin (102, 103). Adiponectin prevents lipid, ceramide or cytokine (interleukin-1β+interferon-γ)-induced

apoptosis in cultured INS-1 β–cells (5, 104). A 3–4 fold overexpression of full-length adiponectin maintains β–cell mass and glucose homeostasis in *ob/ob* mice and a model of type 1 diabetes (5, 30). Adiponectin null mice are more susceptible to caspase-8-induced β–cell apoptosis, and cells from adiponectin receptor deficient animals are highly prone to lipoapoptosis (5). Additionally, in terms of β–cell function, adiponectin maintains glucose stimulated insulin secretion when the β cell is challenged with lipid or cytokine (104), but it does not consistently affect insulin secretion in the absence of such insults.

The cytoprotective effects of adiponectin are highly relevant to the β–cell. Sphingolipids, such as ceramide and glucosylceramides, are an important class of bioactive lipids. The levels of these lipids change as a function of adipose tissue mass and functionality, and are partially driven by cellular availability of palmitoyl-CoA. Aberrant accumulation of ceramide has been strongly implicated in lipotoxic β–cell failure by Unger and colleagues (105–108). In stark opposition to ceramides, the phosphorylated sphingoid base Sphingosine 1-phosphate (S1P) is a potent inducer of proliferation and inhibitor of apoptosis (109). The conversion of ceramide to S1P consists of deacylation of ceramide by ceramidase enzymes, and a subsequent phosphorylation of sphingosine by one of two sphingosine kinase isoforms (110). The opposing nature and simple 2-step conversion process separating these lipids has led to speculation that the dynamic ratio of ceramide:S1P may constitute a physiological rheostat regulating in numerous cellular processes (109).

Adiponectin targets the endocrine pancreas (but not the exocrine pancreas) and protects β–cells from apoptosis (5). Using the rat insulin promoter, the Scherer group generated a model of inducible β–cell apoptosis by expressing a transgenic cassette encoding an FKBP-caspase-8 fusion protein specifically in β–cells (111). Through injection of a chemical dimerizer (AP20187), the caspase-8 fusion protein can be triggered to dimerize and apoptosis can be induced at any age, resulting in an “acute” model of β–cell decompensation, the PANIC-ATTAC mouse (*Pan*creatic *I*slet *C*ell *A*poptosis *T*hrough *T*argeted *A*ctivation of *C*aspase 8). A low concentration of dimerizer triggers only modest hyperglycemia in PANIC-ATTAC mice on a wild-type background. In contrast, after the same treatment conditions, mice that overexpress adiponectin (3–4 fold increase in circulating levels) are completely euglycemic and maintain larger islet area. While changes in adiponectin expression have no significant effects on islet size or insulin content in the absence of the PANIC-ATTAC transgene, the combination of ATTAC expression and adiponectin ablation results in substantially smaller islets and lower pancreatic insulin content in male mice even in the absence of dimerizer. Wild-type female PANIC-ATTAC mice are more resistant to apoptosis than male mice. Nevertheless, adiponectin ablation does enable dimerizer-induced hyperglycemia following moderately aggressive dosing regimens. AP20187 administration resulted in enhanced loss of pancreatic insulin content and led to smaller islets in adiponectin null mice (5), suggesting an increased susceptibility to apoptosis. Combined, these results highlight the potent cytoprotective effects that adiponectin exerts on β–cells *in vivo*.

S1P signaling promotes cell survival and proliferation

The generation of S1P from sphingosine requires phosphorylation by one of two sphingosine kinase (SK) isoforms. Sphingosine kinases have been studied extensively in the context of cancer for their critical roles in cell survival and proliferation. Relatively few studies have evaluated sphingosine kinases in the context of diabetes or metabolism, but the existing reports suggest that driving the phosphorylation of sphingosine is beneficial for β–cell survival, glucose stimulated insulin secretion, and insulin action on peripheral tissues. SK1 is implicated for the majority of these effects, and SK1 ablation is sufficient to promote β–cell failure and frank diabetes in diet-induced obese mice (112). Extracellular signal-related kinases Erk1/2 plays a pivotal role in activation of both SK1 (113) and SK2 (114). Although several studies from other cell types have implicated SK2 in apoptosis rather than survival (109), studies analyzing SK2 within the β–cell suggest it is beneficial for survival and function. SK2 knockout mice actually display elevations in circulating S1P which may benefit β–cell survival *in vivo*. However, SK2 may have important roles in the β–cell by driving S1P production and enhancing glucose stimulated insulin secretion (GSIS)(115).

The best known effects of S1P result via activation of a family of G-protein linked receptors (S1P1,2,3,4,5, formerly EDG1, 3, 5, 6 and 8), which regulate cell growth and survival by promoting mitogen activated protein kinase (MAPK) and PI3-kinase-Akt/PKB signaling pathways (116). In addition to serving as an extracellular agonist of S1P receptors, S1P may also function as an intracellular messenger. For example, the overexpression of sphingosine kinase, which produces S1P from sphingosine, stimulates cell proliferation and survival of S1P-receptor null fibroblasts (117).

High-glucose conditions acutely increase expression of the S1PR1 isoform in freshly isolated islets (e.g. after a two hour treatment), while chronic glucose diminishes S1PR1 expression (e.g. after 7 days of treatment) (118). Interestingly, mice selectively lacking a S1P receptor in β–cells become glucose intolerant within 1 month of age and display a marked reduction in β–cell number (118). Moreover, administration of phosphorylatable sphingosine analog (FTY720) prevents β–cell destruction and diabetic onset in a mouse model of autoimmune diabetes (NOD mice), though this may primarily be a product of the drug's effectiveness as an immune modulator. Studies in cultured β–cells or isolated islets revealed that S1P may directly stimulate insulin secretion (119).

Addition of adiponectin to INS-1 cells attenuated palmitate-, ceramide-, or cytokine-induced cell death while preventing ceramide accumulation and promoting ceramide catabolism(5). Lipidomic analysis revealed that adiponectin increased concentrations of the cytoprotective lipid S1P – the product of sphingosine kinase action. Pharmacological treatment with S1P potently prevented ceramide-induced apoptosis, and also prevents palmitate (5) or cytokine (120) induced apoptosis in INS-1 cells. Consistent with an S1P-mediated cytoprotective role for adiponectin, AdipoR1/R2 double knockout murine embryonic fibroblasts (MEFs) displayed much lower levels of S1P and higher levels of ceramide. Palmitate exposure exacerbated these differences, and produced far more cell death in double knockout MEFs as compared to wildtype cells. Similar trends were seen *in vivo*, as adiponectin null animals displayed lower levels of S1P in the heart and adiponectin transgenic mice had higher

circulating levels of S1P (5). Use of the sphingosine kinase 1 inhibitor SKi-178 prevented adiponectin from enhancing survival of INS1 cells, suggesting a likely role for SK1 in adiponectin action. Though in a different tissue, it is noteworthy that the Walsh group has indicated roles for SK1 in the cardioprotective effects of adiponectin using this same inhibitor and siRNA knockdowns in cardiomyocytes (121).

Adiponectin facilitates lipid sequestering by adipose

Adiponectin additionally alters lipid and glucose metabolism via its effects on adipose tissue. Adiponectin enhances the storage capacity of lipid within adipose, decreases lipolysis, and enhances lipid oxidation to minimize ectopic lipid deposition in non-adipose tissues. Healthy adipose tissue acts like a sponge to absorb extra nutrients and store them in inert triglyceride droplets for subsequent release during energy-deplete conditions. Adiponectin promotes this metabolic flexibility by facilitating adipose expansion, preventing adipose inflammation and fibrosis, and maintaining adipose health (122).

Adiponectin can enhance healthy adipose tissue expansion. The Scherer group has demonstrated roles for adiponectin in adipose expansion in two distinct animal models. Conversely, adiponectin knockout mice are more sensitive to lipolysis (123). Kim et al reported that AP2-driven (adipose restricted) adiponectin overproduction in leptin deficient *ob/ob* mice results in pronounced expansion of healthy adipose tissue, consisting of smaller adipocytes and less macrophage infiltration (30). Despite being far more obese than their obese *ob/ob* littermates, these adiponectin transgenic *ob/ ob* mice display normal glucose tolerance, decreased hepatic steatosis, and normal islet architecture. Marked lowering of serum triglycerides, enhanced triglyceride clearance, improved HDL:LDL profiles, and lower FFA levels were all noted. These improvements in lipid profiles appear largely driven by enhanced lipoprotein lipase activity in adipose and subsequent increases in adipose lipid uptake. These fat pads were highly effective at limiting lipid spillover to other tissues and diminished formation of lipid metabolites in liver. Increases in whole-body energy expenditure were also evident with enhanced mitochondrial proliferation in white adipose (30).

Similar improvements in glucose homeostasis have also been noted in mice with overabundant adiponectin occurring secondary to altered expression of a mitochondrial outer-membrane protein termed mitoNEET (32). These AP2-driven mitoNEET-overexpressing mice offer remarkable similarities to adiponectin transgenic mice, though they have impaired lipid oxidation due to overexpression of this mitochondrial protein. Despite record-setting obesity, they are completely glucose tolerant with remarkable hepatic insulin sensitivity, even on leptin deficient backgrounds. Like adiponectin transgenic mice, mitoNEET transgenic mice have enhanced adipose LPL activity and additionally show enhanced expression of fatty acid transport proteins. These offer a remarkable capacity to clear triglycerides from the bloodstream and store them in adipocytes, without developing adipose fibrosis or inflammation. This let to decreased accumulation of TG and lipid metabolites in the liver, and maintained islet architecture. Thus, adiponectin overexpression or hypersecretion in response to metabolic perturbations profoundly enhances adipose tissue expansion and function, sparing non-adipocytes from ectopic lipid.

Summary

The adipose-derived protein adiponectin has helped to dispel the notion that the adipocyte is simply a storage site for excess lipid. Adiponectin exerts effects directly on hepatocytes, pancreatic islets, and within the adipocyte to promote glucose and lipid homeostasis. Adiponectin's effects within adipose tissue facilitate the ability of adipose to store excess lipid by promoting healthy adipose expansion, facilitating lipid uptake, and opposing lipolysis. This spares non-adipose tissues such as the pancreas and liver from ectopic lipid deposition. Additionally, adiponectin can protect against the harmful effects of ectopic lipid deposition by promoting lipid oxidation and triggering the deacylation of the lipid metabolite ceramide. The adipokine exerts beneficial metabolic effects in liver resulting in enhanced insulin sensitivity and decreased gluconeogenesis, steatosis, fibrosis, cell death and inflammation which collectively can protect against the development of NAFLD and advanced liver diseases. Adiponectin also offers potent cytoprotective effects to β-cells, where it may additionally maintain islet function during metabolically challenged states. Thus, by maintaining insulin production and insulin action in the liver, adiponectin offers potent anti-diabetic effects.

Due to the abundant nature of adiponectin in the serum, it would require substantial production and delivery efforts to supply adiponectin for use in humans. As such other therapeutic strategies which are known to enhance adiponectin production, and novel compounds to mimic adiponectin or its actions will likely be required to fully harness the therapeutic potential of this adipokine.

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Abbreviations

AdipoR	adiponectin receptor
HMW	high-molecular weight
TZD	thiazolidinedione
FGF21	fibroblast growth factor 21
PPAR	peroxisome proliferator-activated receptor
PGC-1α	PPARγ coactivator 1-alpha
TG	Triglyceride
SK	sphingosine kinase
S1P	sphingosine 1-phosphate
AMPK	AMP-mediated protein kinase
SIRT1	sirtuin 1

NALFL	non-alcoholic fatty liver disease
NASH	non-alcoholic steato-hepatitis
ALD	alcoholic liver disease
SREBP	sterol regulatory element-binding protein 1
CPT1	carnitine palmitoyltransferase 1
ECM	extracellular matrix
HSC	hepatic stellate cell
TLR4	toll-like receptor 4
LPS	lipopolysaccharide
FFA	free fatty acid
PP2A	protein phosphatase 2A.

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Practice Points

- Adiponectin promotes glucose homeostasis by improving hepatic insulin sensitivity and maintaining functional beta cell mass
- Adiponectin facilitates adipose expansion and benign storage of lipid and improves serum lipid profiles
- Adiponectin opposes inflammation, fibrosis, steatosis, and apoptosis
- Adiponectin promotes lipid oxidation and degradation of the cytotoxic lipid ceramide

Research Agenda

- Harnessing adiponectin's therapeutic potential could provide treatments for NAFLD and diabetes
- Understanding the mechanisms of adiponectin action will provide new drug targets to recapitulate the protective effects of adiponectin.
- Understanding the regulatory processes gating adiponectin production secretion may offer new strategies to raise adiponectin levels with future drugs.

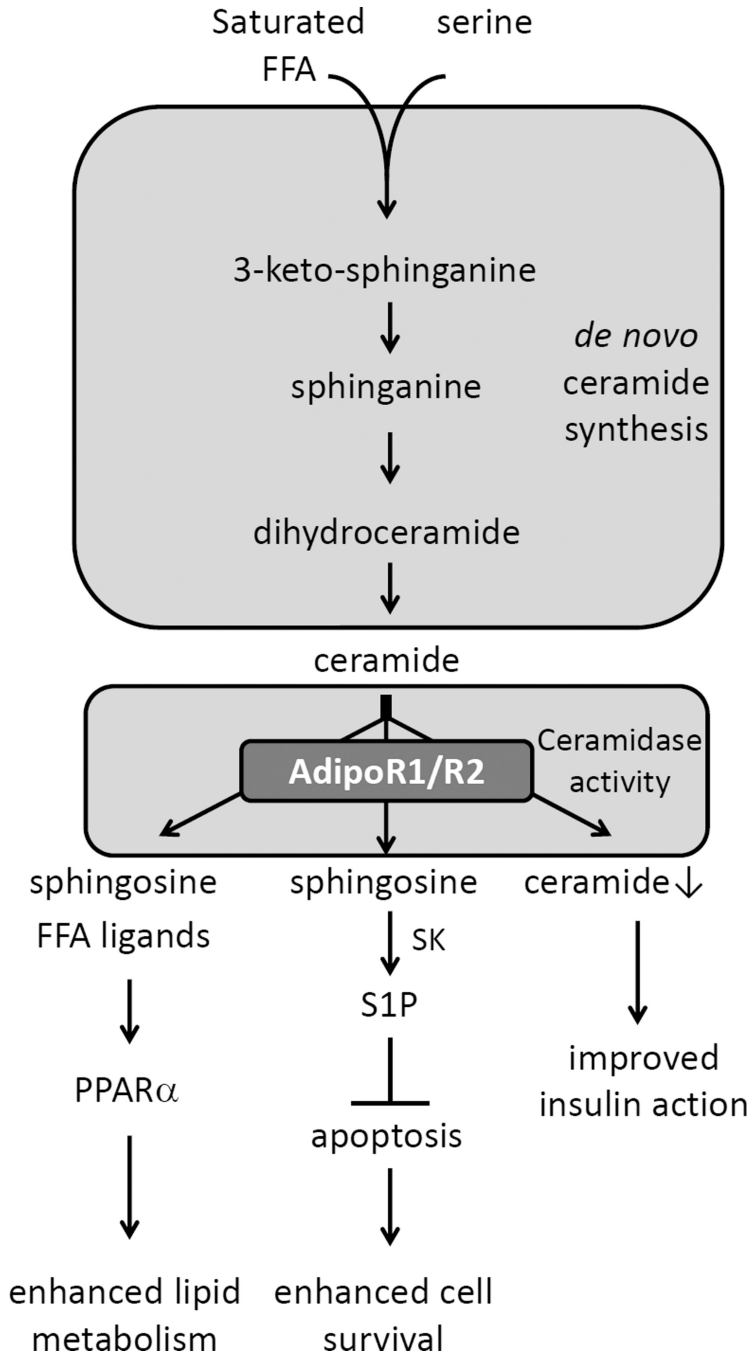

Figure 1.

A schematic diagram of *de novo* ceramide synthesis and its deacylation by ceramidase is drawn. *De novo* ceramide synthesis is strongly driven by inflammation and the availability of saturated fats to promote the condensation of serine and palmitate and the commitment to ceramide generation. The deacylation of ceramide by adiponectin receptors can promote 3 key effects driven by adiponectin: 1) sphingosine and free fatty acids are known ligands for PPARα, explaining how adiponectin and its receptors promote the activation of this nuclear receptor; 2) sphingosine is made available as a substrate for sphingosine kinase, yielding

production of S1P and subsequent activation of AMPK and Akt signaling pathways to promote cell survival; 3) depletion of ceramide restores insulin signaling, as ceramide prevents Akt activation by insulin.

Table 1

Therapeutic interventions shown to enhance circulating adiponectin concentrations

Many therapeutic interventions provide benefits in insulin sensitivity, which are associated with increases in circulating adiponectin. The drug class, drugs, and mechanism of drugs shown to alter adiponectin levels are summarized.

Class	Agent/s	Mechanism of Adiponectin Effect
Statins(124, 125)	Pravastatin, Simvastatin, Atorvastatin,	Inhibition of HMG-CoA reductase
Angiotensin-Converting Enzyme Inhibitors (126, 127)	Ramipril, Telmisartan, Captopril, Valsartan	Angiotensin blockade, also triggers activation of RAR/RXR-PPAR signaling
Thiazolidinediones(96–98, 128, 129)	Rosiglitazone, Pioglitazone	PPARγ activation
Non-Steroidal Anti-Inflammatory	Amlexanox(130)	IKKε inhibitor
	Salsalate(131, 132)	IKKβ inhibitor