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ADIPONECTIN SIGNALING IN THE LIVER

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Abstract

High glucose production contributes to fed and fasted hyperglycemia in Type 1 Diabetes (**T1D**) and Type 2 Diabetes (**T2D**). The breakdown of the adiponectin signaling pathway in **T1D** and the reduction of circulating adiponectin in **T2D** contribute to this abnormal increase in glucose production. Sufficient amounts of insulin could compensate for the loss of adiponectin signaling in T1D and T2D and reduce hyperglycemia. However, the combination of low adiponectin signaling and high insulin resembles an insulin resistance state associated with cardiovascular disease and decreased life expectancy. Future development of medications that correct the deficiency of adiponectin signaling in the liver could restore the metabolic balance in T1D and T2D and reduce the need for insulin. This article reviews the adiponectin signaling pathway in the liver through T-cadherin, AdipoR1, AdipoR2, AMPK, ceramidase activity, APPL1 and the recently discovered Suppressor Of Glucose from Autophagy (**SOGA**).

1. Liver contribution to circulating glucose

The liver releases glucose ensuring sufficient amounts of this essential fuel are always available in the circulation for other tissues. Endocrine and neural mechanisms stimulate the liver during fasting, exercise and pregnancy to meet the increased demand for glucose. In addition to ensuring the availability of glucose, the liver plays a major role in preventing hyperglycemia. Hyperglycemia causes increased osmolarity, oxidative damage, glycation end products and other changes that contribute to the life threatening complications of diabetes. Liver glucose production is lowered through **(a)** the inhibition of gluconeogenesis, glycogenolysis, proteolysis and lipolysis and **(b)** the stimulation of glycolysis and the synthesis of glycogen, protein and lipids.

2. Adiponectin suppression of liver glucose production

Adiponectin (30 kDa) is a hormone produced by adipocytes that was discovered in 1995 by subtractive hybridization studies aimed at identifying adipocyte differentiation genes [1]. The idea that adipocytes secrete an insulin sensitizing protein was inconceivable before the reduction of adiponectin mRNA in the obese state was reported in 1996 [2]. Computed tomography (**CT**) scans that showed omental fat expansion is associated with the reduction

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of circulating adiponectin in 1999 suggested that adiponectin could raise liver insulin sensitivity [3].

Human adiponectin consists of 244 amino acids that generate a collagenous N-terminal domain and a globular C-terminal domain [4]. About 90% of the circulating adiponectin in humans is bound in (a) a high molecular weight (**HMW**) structure (360–540 kDa) comprised of either 12 or 18 adiponectin molecules or (b) a low molecular weight (**LMW**) structure (180 kDa) comprised of 6 adiponectin molecules. At 5 μg/ml, the molar concentration of HMW and LMW adiponectin in human plasma is approximately 3 nM [5]. The remaining 10% of the circulating adiponectin in humans is bound in a structure (90 kDa) called the full-length adiponectin trimer comprised of 3 adiponectin molecules.

HMW, LMW adiponectin and full-length trimers are stable in solution, meaning that a decrease in one isoform does not enable the remaining isoforms to restore the balance [6]. However, under reducing conditions (low pH) that result in disulfide bond cleavage *in vitro*, HMW and LMW adiponectin produce full-length trimers and globular domain trimers that lack the collagenous N-terminal domain [1, 7, 8]. The reduction and proteolytic processing of HMW and LMW adiponectin is reviewed below in the context of receptor binding.

Intraperitoneal injection of HMW and LMW adiponectin lowers plasma glucose in healthy mice as well as mice with Type 1 Diabetes (**T1D**) and Type 2 Diabetes (**T2D**) [9]. High doses of adiponectin do not cause hypoglycemia. Insulin lowers plasma glucose by lowering glucose production and raising glucose disposal. Insulin injection does not cause hypoglycemia when its ability to stimulate glucose uptake is eliminated [10]. The absence of hypoglycemia in mice injected with high doses of HMW and LMW adiponectin suggests the glucose lowering effect of adiponectin is primarily mediated through the inhibition of glucose production.

Euglycemic clamp studies using tracers could distinguish whether the reduction of plasma glucose is mediated by a decrease in glucose production, an increase in glucose disposal or both. Intravenous infusion of HMW and LMW adiponectin in mice, causing a 3-fold elevation in circulating adiponectin, lowers glucose production by 65% without any effect on glucose disposal or glycolysis [11]. Targeted genetic modifications in mice, causing a 3-fold elevation or a complete absence of HMW and LMW adiponectin, have effects solely on glucose production as well [12–14].

Cultured liver cells release glucose into the media, but short exposure to HMW and LMW adiponectin inhibits glucose production by 20–40% [9, 15]. Similar exposure to full-length adiponectin trimers, derived by disulfide bond cleavage of HMW and LMW adiponectin, lowers glucose production by 90% [8].

3. Clinical Correlation: Low adiponectin and Type 2 Diabetes

Low circulating adiponectin in the obese and lipodystrophic states can cause an elevation in glucose production that causes an increase in beta cell insulin secretion [16, 17]. Frank diabetes can be avoided as long as the beta cell could compensate for the reduction of circulating adiponectin. However, when the beta cell cannot keep glucose production under

control, the decrease in circulating adiponectin could raise glucose production, contributing to the appearance of T2D.

Interest in the therapeutic properties of adiponectin peaked amid reports that a class of highly effective oral diabetes medications cause a 2- to 3-fold elevation in circulating adiponectin [18]. Thiazolinedione (**TZD**) drugs are amphipathic compounds that interact with the ligand binding domain of peroxisome proliferator-activated receptor-gamma (**PPAR-γ**), a member of the steroid receptor family of transcription factors and dominant promoter of adipocyte differentiation. Studies in T2D patients, adiponectin transgenic and knockout mice suggest the therapeutic effects of TZD drugs are at least partly mediated by the elevation of adiponectin followed by decreases in liver glucose production, circulating glucose and insulin [8, 12, 13, 18].

TZD drugs restore circulating levels of adiponectin in people with T2D, sparing the beta cell from having to overproduce insulin and reducing the unwanted effects of hyperinsulinemia [19]. When prescribed alone, TZDs lower glucose without the risk of hypoglycemia; however, concerns about their side effects have shifted the focus on adiponectin-based therapeutics away from the elevation of circulating adiponectin [20]. The sheer abundance of circulating adiponectin, its complex structures and short half-life (150 minutes) make the activation of the adiponectin signaling pathway a more promising target in the clinical treatment of T2D than the elevation of circulating adiponectin [21].

4. Liver cell surface receptors

The reduction of Cys-Cys bonds and proteolytic processing of HMW and LMW adiponectin into full-length and globular adiponectin trimers suggests that circulating adiponectin mediates its effects through a cell surface receptor system that depends on multiple proteins. Accordingly, three cell surface receptors were identified between 2003 and 2004. HMW and LMW adiponectin ligands led to the identification of T-cadherin whereas full-length and globular adiponectin trimers led to the identification of adiponectin receptor-1 and -2 (**AdipoR1 and AdipoR2**) (Figure 1).

Adiponectin binding to T-cadherin (90 kDa) is evident using N-Flag-tagged HMW and LMW murine adiponectin, anti-Flag linked magnetic beads, retroviral transduced murine bone marrow Ba/F3 cells expressing a murine C2C12 myoblast undifferentiated cDNA library and, finally, PCR amplification of isolated clones. T-cadherin-adiponectin binding is also evident by co-immunoprecipitation, ELISA and FACS based binding assays [22]. The half-maximal binding concentration of HMW and LMW adiponectin to stable transfected C-GFP-tagged T-cadherin in Chinese hamster ovary (**CHO**) cells is 25 nM (trimer equivalents). T-cadherin does not bind to full-length adiponectin trimers or globular adiponectin trimers.

T-cadherin was discovered in the nervous system, but it has widespread tissue distribution including the liver [23]. It belongs to a family of cell surface proteins involved in Ca^{2+} mediated cell-cell interactions [24]. The globular domain of adiponectin contains a Ca^{2+} binding site, dependent on Asp 288, that plays a role in T-cadherin binding [6]. Ca^{2+} chelators like EDTA block T-cadherin binding in Ba/F3 cells suggesting a potential role of a

divalent cation such as Ca^{2+} in hormone-receptor interactions [22]. T-cadherin gene ablation produces a 10-fold elevation in circulating adiponectin due to the release of adiponectin that is normally sequestered to the cell surface [25].

T-cadherin is not an integral membrane protein. It is retained on the extracellular membrane by a glycosylphosphatidylinositol (**GPI**) anchor that localizes to caveolin-rich microdomains called lipid rafts [26]. The mechanism of T-cadherin mediated signaling may be similar to other GPI-anchored signal-transducing receptors capable of recruiting additional proteins upon ligand binding. The absence of an intracellular domain, the lipid raft link and the absence of full-length or globular adiponectin trimer binding to T-cadherin suggest the adiponectin signaling pathway depends on additional co-receptors.

Adiponectin binding to AdipoR1 (42 kDa) is evident using fluorescent labeled globular adiponectin trimers, retroviral transduced Ba/F3 cells expressing a human skeletal muscle cDNA library and clone selection by fluorescence-activated cell sorting (**FACS**) [27]. AdipoR1-globular adiponectin trimer binding is also evident by yeast two-hybrid screening of human fetal brain cDNA [28].

AdipoR1 has 7 transmembrane domains, like G-protein coupled receptors, but an inverse topology [27]. Yeast two-hybrid screening shows that the globular adiponectin trimer interacts with C-terminal domain of AdipoR1 (aa 311–375) [28]. AdipoR1 is not a tyrosine kinase receptor like the insulin receptor. *In vivo* labeling studies reveal little tyrosine phosphorylation of AdipoR1 under basal or adiponectin-stimulated conditions [28].

AdipoR2 (34 kDa), identified on the basis of its homology to AdipoR1, is highly liver specific [27]. Full-length adiponectin trimer has a higher binding affinity to liver membrane fractions than globular adiponectin trimers [29]. In C2C12 myocytes, the globular adiponectin trimer binds with greater affinity to AdipoR1 (K_d = 1.14 nM) than AdipoR2 (K_d = 14.4 nM). Scatchard plot analysis shows siRNA mediated suppression of AdipoR1 decreases globular adiponectin trimer binding without affecting full-length adiponectin trimer binding and *vice versa*. T-cadherin, AdipoR1 and AdipoR2 do not bind to C1q, a structural homologue of adiponectin that attaches to immunoglobulin for complement fixation [22, 27].

5. A shield against lipotoxicity

Adiponectin is not an “insulin mimetic” (Figure 2). Increasing circulating levels of insulin to compensate for the loss of adiponectin signaling in T1D and T2D promotes lipid storage which causes an even greater need for insulin. The detrimental effects of high insulin and low adiponectin signaling in humans can be seen in fatty liver and cardiovascular disease [19, 30]. The development of therapies that restore adiponectin signaling in T1D and T2D provides a way to avoid lipotoxicity.

Adiponectin lowers intracellular lipid content by two mechanisms. Adiponectin inhibition of liver glucose production lowers circulating levels of insulin which decreases insulin mediated lipogenesis and insulin mediated inhibition of fatty acid (**FA**) oxidation (Figure 2). Adiponectin also stimulates FA oxidation directly. The half-maximal doses for FA oxidation

through AdipoR1 and AdipoR2 in C2C12 myocytes are 0.5 nM and 6 nM, respectively [27]. Studies in mice and human hepatoma (HepG2) cells suggest that adiponectin does not affect liver triacylglycerol (**TAG**) secretion [31].

Acute exposure to HMW and LMW adiponectin activates AMP-activated kinase (**AMPK**) in rat hepatoma McArdle 7777 cells [32]. AMPK is a serine/threonine kinase that inhibits acetyl CoA carboxylase (**ACC**), a rate limiting enzyme in *de novo* lipogenesis [33]. AMPK suppression of ACC lowers malonyl-CoA production thereby increasing the oxidation of long chain FAs and circumventing insulin mediated lipid synthesis (Figure 3). Adiponectin activates AMPK through two independent pathways involving liver kinase B1 (**LKB1**) and Ca^{2+}/calmodulin-dependent protein kinase kinase (**CaMKK**).

LKB1 is a serine/threonine protein kinase that activates AMPK upon translocating to the cytosol. Adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1 (**APPL1**) is a 100 kDa endosomal protein expressed in mouse hepatocytes and other cells that binds to the N-terminal domains of AdipoR1 and AdipoR2 [34]. Yeast two-hybrid screens using a human fetal brain cDNA library show the phosphotyrosine binding (**PTB**) domain on the C-terminal end of APPL1 (aa 455–693) interacts with the intracellular N-terminal domains of AdipoR1 (aa 4–136) and AdipoR2 (aa 4–142) [28]. APPL1:APPL1 homodimerization is required for AdipoR1 and AdipoR2 binding [35]. In muscle, adiponectin signaling is suppressed by APPL2, an APPL1 homologue that forms an APPL1:APPL2 heterodimer. As such, increased APPL2 expression blocks receptor binding.

CaMKK is an alternate upstream kinase of AMPK that shares significant sequence and structural homology with LKB1 [36]. Both purified HMW adiponectin and recombinant globular adiponectin trimers activate CaMKK [37–39]. AdipoR1 mediated Ca^{2+} release in C2C12 myotubes activates CaMKK [38, 39]. Intracellular Ca^{2+} release involves phospholipase C (**PLC**) production of inositol triphosphate (**IP_3**). Adiponectin receptor mediated activation of PLC is independent of APPL1, but may involve G-proteins used by GPCRs. Besides APPL1, other proteins can bind to the intracellular domain of AdipoR1, including endoplasmic reticulum protein 46 (**ERp46**), activated protein kinase C1 (**RACK1**) and protein kinase CK2β subunit (**CK2β**) [40].

Adiponectin does not stimulate FA oxidation by increasing intracellular AMP concentrations or diacylglycerol (**DAG**) levels in the plasma membrane. While causing a transient change in adenosine nucleotide levels, the energy status is rapidly restored by the rise in FA oxidation and the drop in lipogenesis and gluconeogenesis, a process referred to as substrate switching [41]. Adrenergic hormones also stimulate lipolysis and FA oxidation. However, adiponectin does not affect membrane DAG content, a second messenger in G-protein coupled receptor signaling and activator of protein kinase C (**PKC**), in hepatocytes and liver samples from leptin deficient (**ob/ob**) or high fat diet (**HFD**) induced obese mice.

6. Adiponectin mediated ceramidase activity

In addition to the accumulation of intracellular lipid droplets, lipotoxicity can be linked to the abundance of specific lipids. Ceramides are bioactive sphingolipids produced by the

liver that interfere with insulin signaling. Insulin activation of phosphatidylinositol-3 kinase (**PI3K**) causes a transient increase of phosphatidylinositol-3,4,5-phosphate **(PIP_3)** in cell membranes that binds to Akt, also known as protein kinase B (**PKB**). Ceramide activation of PKCζ interferes with PIP_3 binding to Akt/PKB in L6 muscle cells [42]. Ceramide also impairs insulin signaling by PP2A and PKC epsilon (**PKCε**) activation in human embryonic kidney 293 cells (**HEK 293**) and cancer cells [43, 44]. In contrast, the metabolism of ceramides into phosphorylated sphingoid bases, such as sphingosine-1-phosphate (**S1P**), reduces insulin resistance [45–47].

Adiponectin lowers liver ceramide content [48, 49]. In agreement with euglycemic clamp results in other mice, adiponectin infusion in ob/ob mice lowers liver ceramide content and glucose production concurrently [11–14]. Notably, it has no effect on glucose disposal. Adiponectin decreases all ceramide and dihydroceramide species regardless of saturation or acyl chain length [14]. It stimulates deacylation of ceramides at neutral pH in a dose-dependent manner producing sphingosine, S1P and dihydrosphingosine-1-phosphate.

AdipoR1 and AdipoR2 belong to the family of progesterone/adiponectin/adipoQ receptors (**PAQR**) that stimulate intracellular ceramidase activity [50]. Both contain a series of histidine residues that are conserved among ceramidases. Substituting these histidines for arginines lowers the ceramidase activity of AdipoR1 and AdipoR2 [14]. Adenoviral vectors that double liver AdipoR1 and AdipoR2 expression increase ceramidase activity, lowering the ceramide content of the liver while improving insulin sensitivity in HFD-induced insulin resistant mice [14].

Mouse embryonic fibroblasts (**MEFs**) derived from fetal livers cannot produce glucose, but they demonstrate the synergy between T-cadherin, AdipoR1 and AdipoR2. HMW and LMW adiponectin triggered increases in ceramidase activity are blocked in AdipoR1/AdipoR2 −/− (double-knockout) MEFs [14]. Adiponectin mediated increases in ceramidase activity may lower hepatic glucose production by altering the lipid composition of the plasma membrane. The ceramide content of lipid rafts is higher in AdipoR1 and AdipoR2 deficient MEFs [14].

Catabolic conditions stimulate liver glucose production by cell autonomous mechanisms retained in tissue culture. Nutrient deficient media induce a marked increase in hepatocyte glucose production before triggering apoptosis. However, the addition of HMW and LMW adiponectin increases MEF survival [14]. S1P, a potent stimulator of cell growth, rescues AdipoR1 and AdipoR2 deficient MEFs from cell death [45, 51]. Despite its antiapoptotic effects, adiponectin is associated with tumor suppression in the liver and other tissues [23, 52].

7. Suppression of gluconeogenic enzymes

Tracer studies using deuterated water show that adiponectin lowers glucose production in rat hepatoma (McArdle 7777) cells by suppressing both glycogenolysis and gluconeogenesis [32]. Suppression of glucose-6-phosphatase (**G6Pase**) and phosphoenolpyruvate carboxy kinase (**PEPCK**) inhibits glycogenolysis and gluconeogenesis. HMW, LMW and full-length adiponectin trimer lower liver G6Pase and PEPCK mRNA expression in lab rodents [11, 29, 53–55].

Adiponectin inhibition of glucose production can be blocked by **(a)** the expression of a dominant negative AMPK mutant in hepatoma cells and **(b)** gene ablation of AMPK in mice [29, 32, 56]. How is it possible for AMPK to exert such a dominant effect on plasma glucose when the reduction of intracellular lipids by itself is insufficient in the clinical treatment of diabetes [18]? The answer is that, in addition to inhibiting ACC and decreasing intracellular lipid stores, AMPK lowers liver G6Pase and PEPCK mRNA expression.

Gluconeogenic hormones such as glucagon stimulate G6Pase and PEPCK mRNA expression by activating the cAMP-responsive element-binding (**CREB**) (Figure 4). CREB stimulation of G6Pase and PEPCK mRNA expression depends on binding to the CREB-regulated transcription coactivator (**CRTC2**), also called transducer of regulated cAMP response element–binding protein 2 (**TORC2**), which drives the expression of PPARγ cofactor-1 alpha (**PGC1α**). PGC1α binds to the nuclear hormone receptors hepatic nuclear factor-4 α (**HNF4α**) and the forkhead family member Foxo1 driving G6Pase and PEPCK mRNA expression [57]. Adenoviral small hairpin RNA (**shRNA**) for TORC2 lowers glucagon-stimulated PGC-1α expression [58]. Glucagon stimulation dephosphorylates TORC2 allowing TORC2 translocation to the nucleus where it enhances CREB-dependent transcription of PGC1α, G6Pase and PEPCK mRNA expression.

Adiponectin activation of AMPK blocks G6Pase and PEPCK mRNA expression by promoting TORC2 phosphorylation and blocking its translocation to the nucleus (Figure 4). Liver specific knockout of LKB1 through adenovirus bearing CMV-Cre causes TORC2 dephorphorylation and increased PGC1α, PEPCK and G6Pase mRNA expression [58, 59]. AMPK mediated induction of the immediate early transcription factor Early Growth Response 1 (**EGR1**) and Dual Specificity Phosphatase **(DUSP4)** also lowers G6Pase and PEPCK expression and glucose production in Fao rat hepatoma cell lines [60]. Other relevant AMPK targets in hepatocytes include glycogen synthase, insulin response substrate 1 and -2 (**IRS-1 and IRS-2**) [61–63].

Adiponectin mediated suppression of G6Pase and PEPCK mRNA expression in mouse hepatocytes may also occur independently of LKB1, AMPK and TORC2 (Figure 4). Adiponectin mediated decreases in glucogenic gene expression, hepatic glucose production and plasma glucose is partly preserved after liver LKB1 deletion by viral expression of CRE recombinase [54]. LKB1 and AMPK null hepatocytes exhibit a lack of correlation between TORC2 electrophoretic mobility and adiponectin suppression of PEPCK and G6Pase expression. Adiponectin and AMPK do not suppress glucagon and cAMP induced PKA phosphorylation of target proteins. However, hepatocytes from TORC2-null mice demonstrate robust adiponectin-induced repression of PGC1α, a target gene of protein kinase A (**PKA**).

Adiponectin mediated decreases in G6Pase and PEPCK expression can be triggered independent of AMPK through convergence of the adiponectin and insulin signaling pathways through APPL1. Insulin lowers PEPCK and G6Pase expression through PI3K (Figure 4) [64]. PI3K production of PIP_3 promotes Akt/PKB translocation to the nucleus wherein Akt/PKB phosphorylates Foxo1, a member of the Forkhead/winged helix family of transcription factors [65]. Tribble-3 (**TRB3**) prevents Akt/PKB translocation to the plasma

membrane. [66, 67]. APPL1 interferes with TRB3 binding increasing insulin-stimulated Akt/PKB phosphorylation [68]. APPL1 reduces Akt/PKB-TRB3 binding in the liver of leptin receptor deficient (**db/db**) mice. APPL1 overexpression also increases the phosphorylation of mitogen-activated protein kinase (**p38 MAPK**) in mouse hepatocytes, but it does not affect every aspect of insulin signaling. APPL1 does not affect insulin stimulated MAP kinase (**p42/44 Erk**) phosphorylation.

NFκB can also inhibit glucose production by stimulating the production of nitric oxide NO (Figure 4) [69]. Adiponectin stimulation of APPL1 prevents obesity-induced vascular insulin resistance and endothelial dysfunction by modulating the endothelial production of nitric oxide (**NO**) [70]. In C2C12 myocytes, adiponectin phosphorylates **IκB** which activates **NFκB**, a heterodimer of two DNA-binding subunits, p50 and p65 [71]. IκB retains NFκB in the cytoplasm under basal conditions. IκB phosphorylation allows the translocation of NFκB to the nucleus where it can regulate gene expression. However, NFκB also increases NO production in hepatocytes by stimulating inducible NO synthase (**iNOS**) expression [72]. NFκB inhibits glucocorticoid and glucagon induction of glucose production [73]. TLR4, IL1-R and TNFα–R suppress the gene expression of G6Pase and PEPCK through NFκB [74, 75]. Adiponectin activation of NFκB in macrophages occurs independent of AdipoR1 and AdipoR2 [63]. NFκB targeting must be hepatocyte specific as the liver's resident macrophages, Kupffer cells, could elicit an innate immune response [76].

8. Suppression of gluconeogenic substrate availability

Besides the regulation of rate limiting enzymes, such as G6Pase and PEPCK, glucose production can be suppressed by decreasing the availability of energy, reducing equivalents and substrates [77–79]. Adiponectin stimulation of FA oxidation generates energy and reducing equivalents making the reduction of substrate availability a potential target for the inhibition of glucose production (Figure 5).

The hydrolysis of peptide bonds through proteasomal and autophagic mechanisms is associated with the presumed elevation of gluconeogenic amino acid availability and the appearance of hyperglycemia [80, 81]. Food withdrawal, streptozotocin induced diabetes, glucagon, epinephrine and glucocorticoids increase autophagy in the liver [82–85]. Adiponectin mediated increases in ceramidase activity may contribute to an inhibition of autophagy; however, the possibility that adiponectin lowers autophagy through AMPK is ruled out as AMPK stimulation of Ulk1 and AMPK inhibition of the mammalian target of rapamycin (**mTOR**) increase autophagy [86–88].

The search for an inhibitor of autophagy in the adiponectin signaling pathway led to the discovery of a previously unknown protein called the Suppressor of Glucose from Autophagy (**SOGA**) (Figure 5) [89]. Proteomic analysis shows that HMW and LMW adiponectin upregulate SOGA in hepatoma and hepatocyte cultures. siRNA knockdown of SOGA stimulates autophagy and proteolysis in hepatocytes blocking adiponectin inhibition of glucose production. AICAR, an AMP analogue that stimulates AMPK and glycogenolysis, lowers SOGA in primary hepatocytes [90, 91]. LY294002, which blocks the ATP binding site in PI3K, also lowers SOGA [92].

The elevation of protein turnover suggests that substrate availability is linked to the increase in gluconeogenesis and glucose production in T2D [93, 94]. As such, the loss of adiponectin signaling could lower SOGA in the liver and muscle contributing to the appearance of hyperglycemia. Proteolytic cleavage of SOGA yields a C-terminal fragment that is secreted into the extracellular space and further processed in the circulation (Figure 6) [89]. The circulating SOGA fragment provides a surrogate marker for changes in the intracellular levels of SOGA. TZD treatment and calorie restriction, interventions that increase circulating adiponectin and restore glucose homeostasis, raise SOGA and lower glucose in ob/ob and wild-type mice.

9. Clinical Correlation: Low Adiponectin Signaling and Type 1 Diabetes

The marked increase of circulating adiponectin with little benefit in people with T1D indicates a breakdown of the adiponectin signaling pathway [95]. In nonobese diabetic (**NOD**) mice, an autoimmune model of T1D, the loss of adiponectin signaling in the liver is evident from the reduction of SOGA [89]. Insulin injection eliminates hyperglycemia in NOD mice without correcting the deficiency of SOGA. TZD drugs prescribed for the treatment of insulin resistance in T1D may work by stimulating the production of SOGA through adiponectin. However, considering the breakdown of the adiponectin signaling pathway in T1D, the development of medications that stimulate the production of SOGA directly could restore the metabolic balance, diminish the insulin requirement and improve clinical outcomes.

10. Restoring the activity of the adiponectin signaling pathway in the liver

Adiponectin is a hormone that slows down the liver's production of glucose. The loss of adiponectin signaling in the liver contributes to the elevation of glucose in T1D and T2D. Insulin does not fully compensate for the loss of adiponectin signaling in T1D and T2D. The adiponectin signaling pathway within liver cells provides molecular and phenotypic targets for the development of drugs that can restore the body to the nondiabetic state.

The loss of adiponectin signaling in T1D is due to a breakdown of the adiponectin signaling pathway. The loss of adiponectin signaling in T2D is due to low circulating adiponectin. Chronic calorie restriction and TZD drugs raise circulating levels of adiponectin. The elevation of circulating adiponectin is beneficial in the treatment of T2D, when the adiponectin signaling pathway is intact. The development of "adiponectin sensitizers", drugs that activate the intermediates in the adiponectin signaling pathway directly, is necessary to restore adiponectin signaling in T1D.

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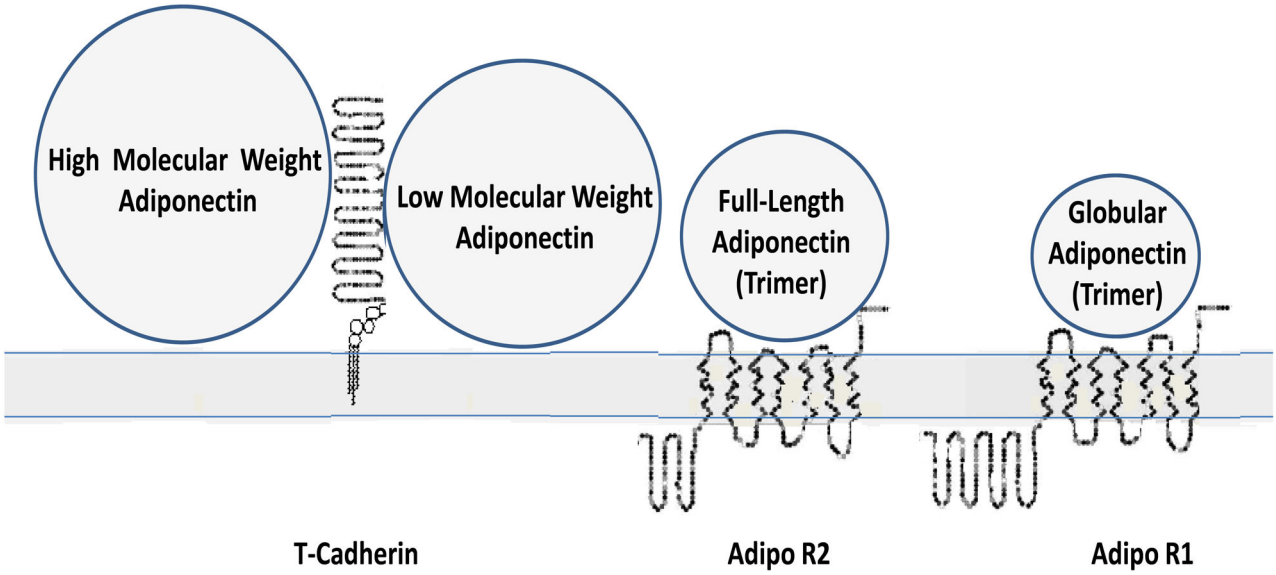

Figure 1. Synergy Model of Adiponectin Receptors

HMW and LMW adiponectin binding to T-cadherin leads to **(a)** disulfide bond cleavage producing “full-length adiponectin trimers” that bind to AdipoR2 and **(b)** proteolytic cleavage producing “globular adiponectin trimers” that bind to AdipoR1. T-Cadherin, AdipoR1 and AdipoR2 expression is not limited to hepatocytes.

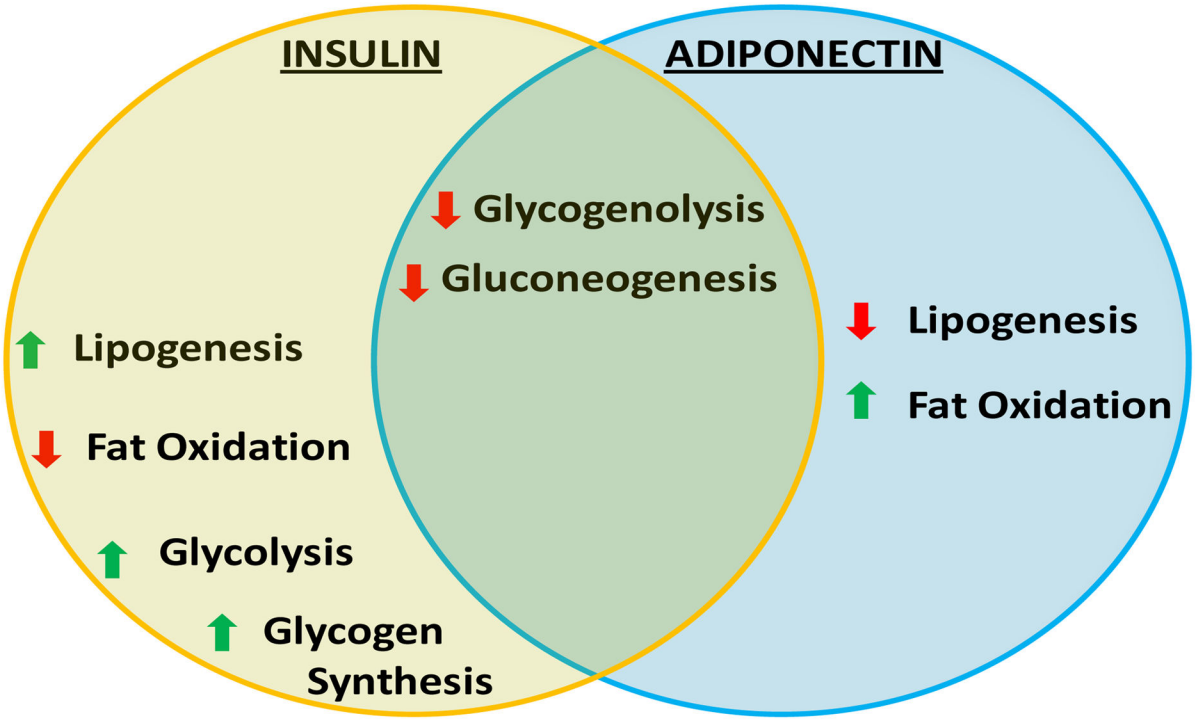

Figure 2. Similarities and Differences between Adiponectin and Insulin Effects in the Liver

Adiponectin and insulin reduce circulating lipids by different mechanisms. Insulin stimulation of lipogenesis in the liver converts excess glucose into fatty acids that are incorporated into triglyceride molecules that are packed in lipoprotein particles and secreted. Adiponectin increases fatty acid and triglyceride clearance by stimulating fatty acid oxidation in the liver [12].

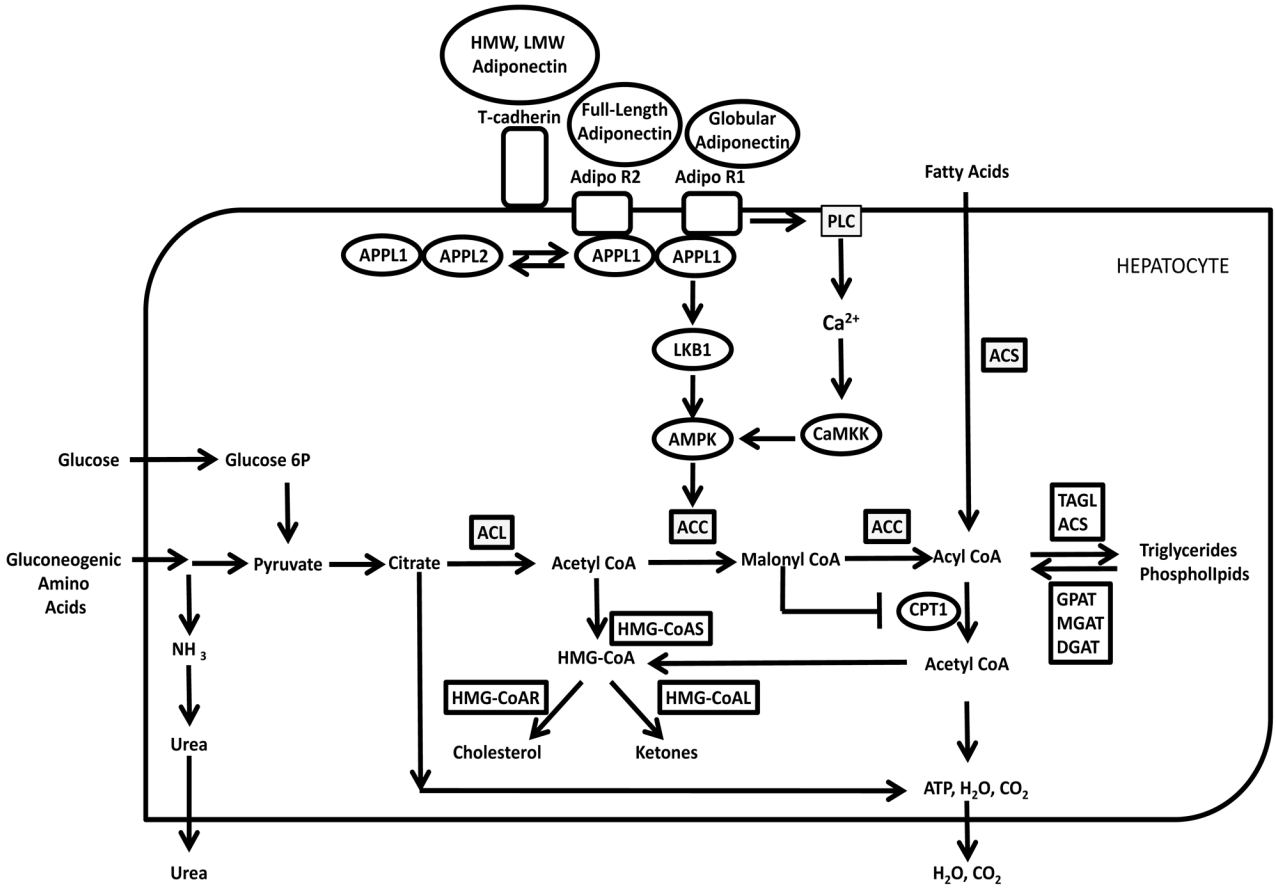

Figure 3. Adiponectin Regulation of Lipid Metabolism

Adiponectin activation of AMPK by Ca^{2+} dependent and Ca^{2+} independent pathways, involving LKB1 and CaMKK, increases FA oxidation decreasing intracellular lipid stores and insulin resistance.

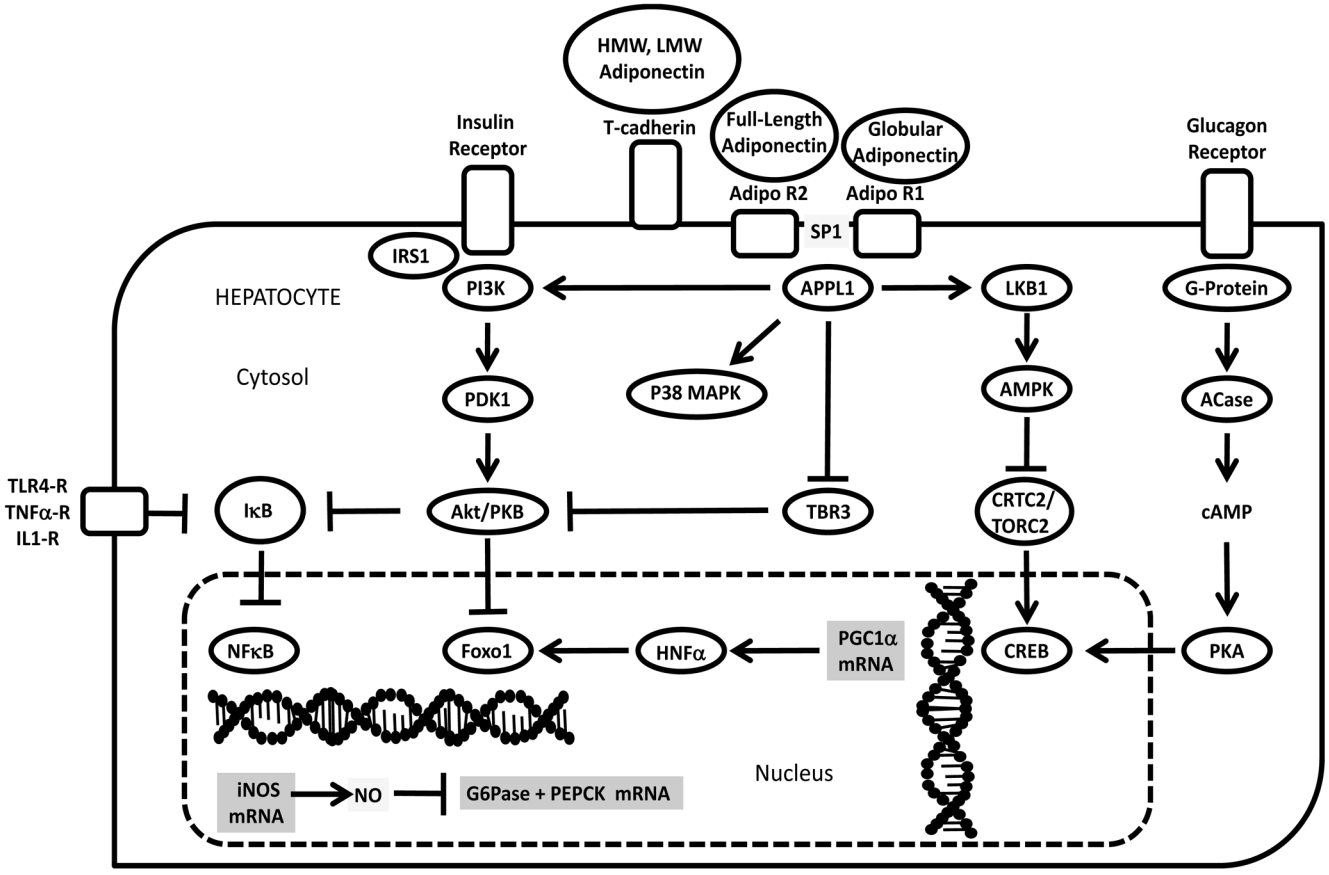

Figure 4. Adiponectin Regulation of G6Pase and PEPCK Expression in Hepatocytes in Relation to Insulin Receptor and Glucagon Receptor Action

The catalytic activity of G6Pase and PEPCK is regulated at the level of gene expression. Adiponectin regulation of PGC1α and iNOS mRNA can play a role the suppression of G6Pase and PEPCK mRNA.

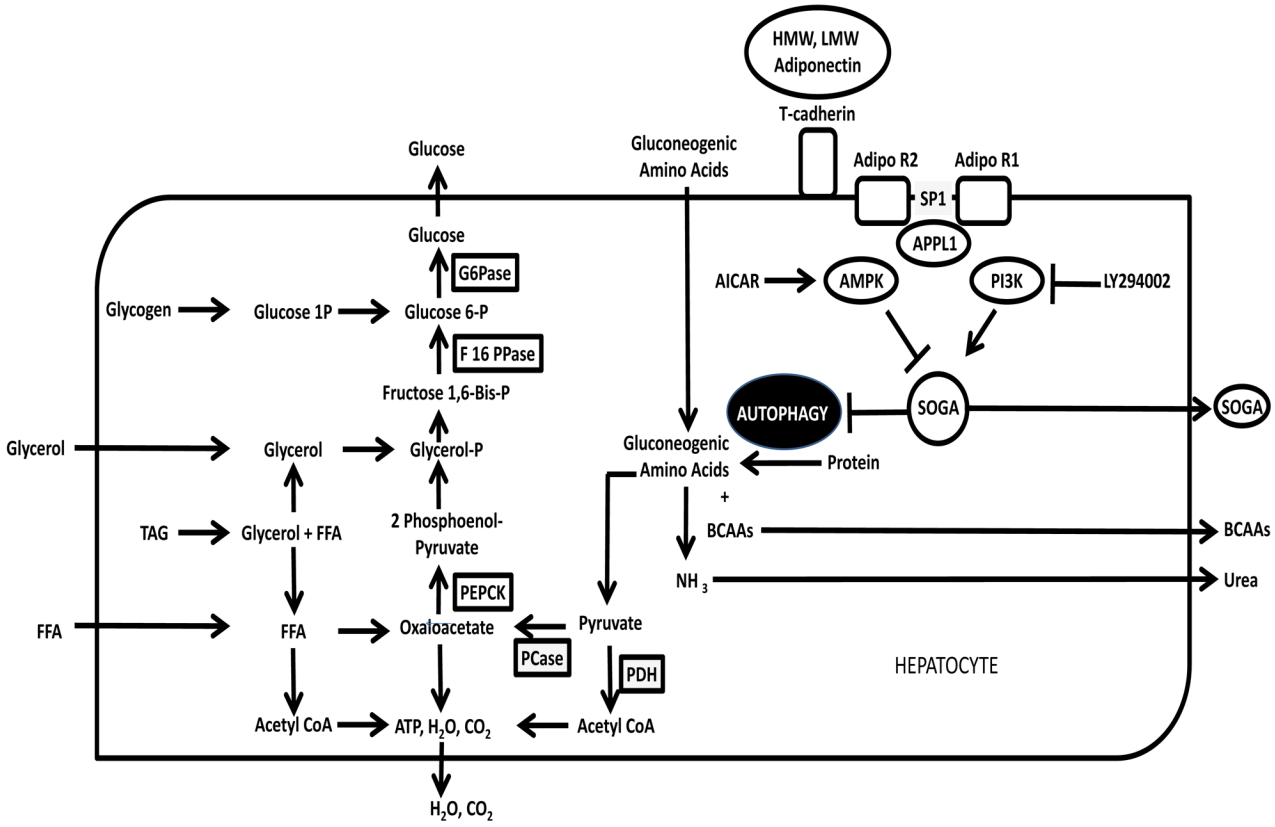

Figure 5. Rate Limiting Enzymes and Biochemical Substrates needed for Liver Glucose Production *via* Gluconeogenesis and Glycogenolysis

Liver cell glucose production can be lowered by decreasing the catalytic activity of pyruvate carboxylase (**PCase**), PEPCK, fructose-1,6-bisphosphatase (**F16PPase**) and glucose-6-phosphatase (**G6Pase**) and increasing the catalytic activity of pyruvate dehydrogenase (**PDH**). Liver cells cannot synthesize or metabolize branched chain amino acids (**BCAAs**). Adiponectin upregulation of SOGA inhibits autophagy lowering the availability of gluconeogenic amino acids for the synthesis of glucose.

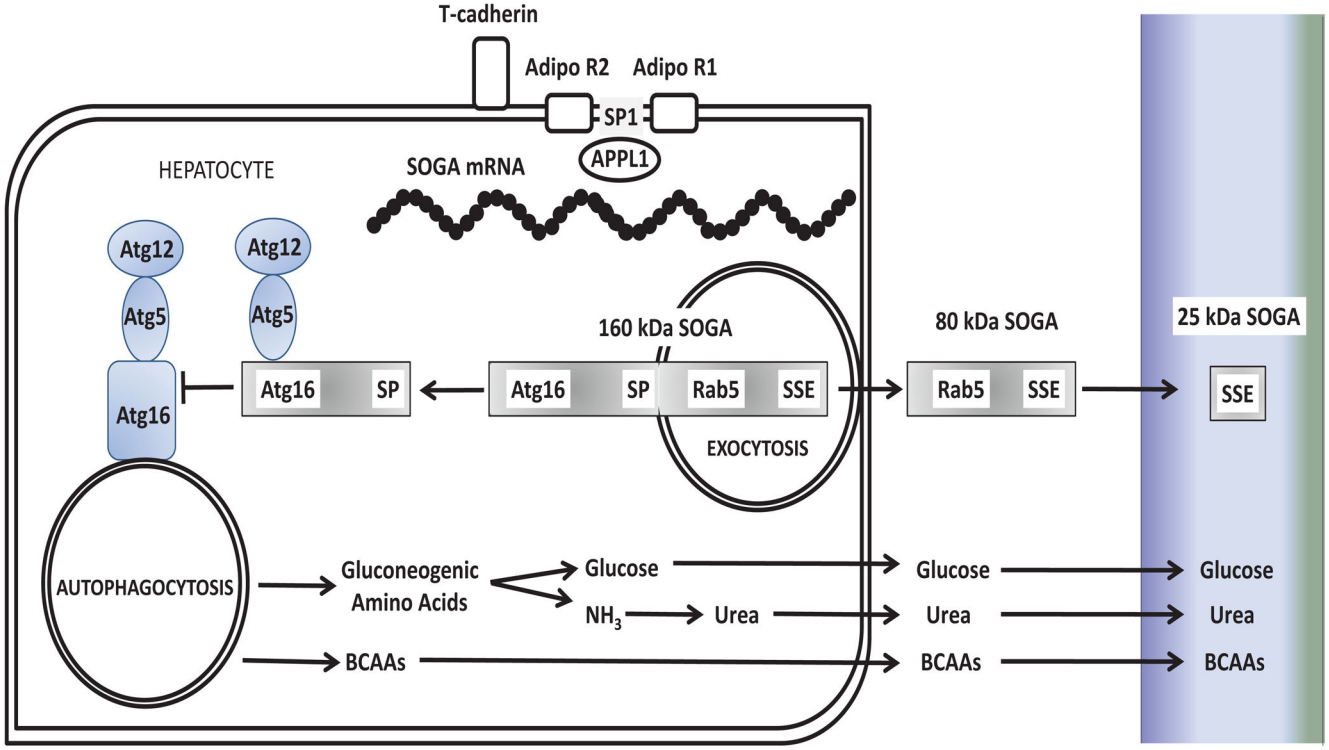

Figure 6. Proteolytic Processing of SOGA and Potential Mechanism of Action

Full-length SOGA contains Atg16 and Rab5-binding motifs, an internal signal peptide (SP) and a C-terminal species specific antigenic epitope (SSE). Autophagy involves the encapsulation of protein in membrane bound vacuoles that fuse with lysosomes and the release of free amino acids. This model shows **(a)** the proteolytic processing of full-length SOGA at the internal signal site, **(b)** the N-terminal fragment of SOGA interfering with the formation of the Atg12-Atg5-Atg16 complex required for the initiation of autophagy, **(c)** the secretion of the C-terminal fragment of SOGA and **(d)** further processing of the C-terminal fragment to produce the circulating 25 kDa C-terminal fragment of SOGA.