Protective roles of adiponectin in obesity-related fatty liver diseases: mechanisms and therapeutic implications

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ABSTRACT

Adiponectin is an insulin-sensitizing adipokine possessing multiple beneficial effects on obesity-related medical complications. This adipokine is secreted from adipocytes into the circulation as three oligomeric isoforms, including trimer, hexamer and the high molecular weight (HMW) oligomeric complex. Each oligomeric isoform of adiponectin possesses distinct biological properties and activates different signaling pathways in various target tissues. The hepato-protective activities have been demonstrated by many clinical and experimental studies. The decreased level of serum adiponectin represents an independent risk factor for nonalcoholic fatty liver disease (NAFLD) and liver dysfunctions in humans. In animals, elevation of circulating adiponectin by either pharmacological or genetic approaches leads to a significant alleviation of hepatomegaly, steatosis and necro-inflammation associated with various liver diseases. In adiponectin knockout mice, there is a pre-existing condition of hepatic steatosis and mitochondrial dysfunction, which might contribute to the increased vulnerabilities of these mice to the secondary liver injuries induced by obesity and other conditions. This review aims to summarize recent advances on delineation of the structural, molecular and cellular mechanisms underlying the hepato-protective properties of adiponectin. Arq Bras Endocrinol Metab. 2009;53(2):201-212.

Keywords
Adiponectin; NASH; hepatic steatosis; insulin resistance

RESUMO

A adiponectina é uma adipocitocina com ação insulino-sensibilizadora com múltiplos efeitos benéficos sobre as complicações clínicas da obesidade. Essa adipocitocina é secretada pelos adipócitos na circulação sistêmica em três isoformas oligoméricas, incluindo formas em trímeros, hexâmeros e complexas de alto peso molecular (HMW). Cada forma oligomérica da adiponectina apresenta propriedades biológicas distintas e ativam diferentes vias de sinalização celular em diversos tecidos. Suas atividades hepatoprotetoras têm sido descritas em vários estudos clínicos e experimentais. Em humanos, os níveis reduzidos da adiponectina sérica, características da obesidade, representam um fator de risco independente para a doença hepática gordurosa não-alcoólica (NAFLD), incluindo variados graus de disfunções hepáticas. Em animais, a elevação dos níveis circulantes de adiponectina, por manipulações genéticas ou farmacológicas, conduz a uma atenuação da hepatomegalia, da estateose e da necroinflamação usualmente associadas a várias doenças hepáticas. No animal sem o gene da adiponectina (knockout), existe uma condição preexistente de estateose e disfunção mitocondrial que contribui para a vulnerabilidade desses animais aos processos de lesões teciduais hepáticos induzidos pela obesidade e outras condições. Esta revisão sumariza os recentes avanços na compreensão e caracterização dos mecanismos celulares, moleculares e estruturais das ações hepatoprotetoras da adiponectina. Arq Bras Endocrinol Metab. 2009;53(2):201-212.

Descritores
Adiponectina; NASH; estateose hepática; resistência à insulina
INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common type of chronic liver injury in many countries (1,2). NAFLD includes a spectrum of syndromes ranging from simple steatosis, nonalcoholic steatohepatitis (NASH) to fibrosis, cirrhosis and hepatocellular carcinoma (3). The overall prevalence of NAFLD is 15%-40% in Western countries and 9%-40% in the Asian population (4), and has dramatically increased over the past 15 years, mainly as a consequence of its close association with two major worldwide epidemics, obesity and type 2 diabetes mellitus (T2DM) (5). Mortality in patients with NAFLD is significantly higher than that in the age and gender-matched general population (6). Disease progression to NASH and cirrhosis appears to be very slow, and only a few patients develop life-threatening advanced liver disease. In many cases of NAFLD, the risks of developing metabolic and cardiovascular morbidities are much higher than of hepatic diseases (7, 8). In fact, NAFLD is considered as the hepatic manifestation of the metabolic syndrome, which refers to a cluster of cardiovascular risk factors associated with insulin resistance, including central obesity, hypertension, dyslipidemia and T2DM (9). The association between NAFLD and metabolic syndrome has been established in many cross-sectional and prospective studies (8). NAFLD significantly increases the risk of diabetes and is a better predictor of the development of metabolic disorders than obesity itself (10). Recent studies have reported an association of NAFLD with multiple classical and non-classical risk factors for cardiovascular diseases (7). NAFLD predicts future cardiovascular events independently of other prognostic factors, including the component of metabolic syndrome. In summary, NAFLD is associated with a future high incidence of metabolic and cardiovascular complications and should be considered beyond a hepatic disease confined to classical boundaries. Understanding the disease and its management is a vital issue in nowadays clinical practice.

PATHOGENESIS OF NAFLD

Although the pathogenesis of NAFLD remains largely unknown, insulin resistance, oxidative stress and inflammation play important roles in the development and progression of NAFLD (11,12). Fatty liver itself is a status of insulin resistance. Hepatic fat accumulation can lead to hepatic insulin resistance, which may occur before the alterations in peripheral insulin actions and may induce peripheral insulin resistance (13,14). Insulin regulates the uptake, oxidation and storage of fuel within insulin-sensitive tissues including the liver, skeletal muscle and fat. Peripheral insulin resistance impairs glucose uptake from blood into skeletal muscle and adipose tissue; serum non-esterified fatty acid (NEFA) levels may also be elevated due to the failure of insulin to suppress lipolysis (15,16). In the liver, insulin resistance is associated with increased cellular contents of fatty acids and their metabolites (fatty acyl-CoAs, diacylglycerides and ceramides) (17-19). Hyperinsulinemia caused by insulin resistance, in the presence of increased circulating levels of NEFA, enhances the hepatic uptake of fatty acid and promotes lipogenesis (1,20). In addition, defects in mitochondrial β-oxidation, enhanced fatty acid synthesis and impaired secretion of triacylglyceride (TG)-rich very low density lipoproteins (VLDL) also contribute to hepatic steatosis (21-23). A growing body of evidence from animal models suggests a “two-hit” hypothesis responsible for the development of NAFLD (24-26). With this theory, the first hit is the occurrence of fatty liver (steatosis), followed by a second event leading to the development of NASH. The potential secondary hits include endotoxin exposure, alcohol consumption and virus infections etc., which expand hepatic lipid stores, cause hepatocellular injury, promote oxidative stress and inflammation in the liver. Lipotoxicity and the release of cytokines and other pro-inflammatory mediators play important roles during this process. Moreover, inflammation in the development of NASH can further impede insulin signaling (27). Histologically, NASH is manifested by hepatocyte nuclear ballooning, hepatocyte apoptosis, Mallory’s hyaline and inflammation foci (28). NAFLD patients have a high circulating FFAs level correlating with the severity of liver disease. Overloaded FFAs may exhibit lipotoxicity by inducing the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) (29).

VISCERAL OBESITY, ADIPOKINES AND NAFLD

Obesity, especially visceral obesity, is frequently associated with NAFLD and their coexistence in the same individual increases the likelihood of having more advanced forms of liver disease (30,31). NAFLD occurs in 60% ~95% of people with obesity (32). Visceral fat is
a key mediator of NASH and is strongly associated with alanine aminotransferase (ALT) levels in the nondiabetic obese population (31, 33, 34). The importance of visceral fat in the pathogenesis of NAFLD has also been shown in many animal models including fa/fa obese rats. In these animals, surgical resection of intra-abdominal fat depots reverses hepatic insulin resistance and steatosis (35).

Recent evidence suggests that visceral adipose tissue is a metabolic and inflammatory organ that signals and modulates the action and metabolism of the brain, liver, muscle and cardiovascular system (36,37). The imbalanced production of pro- and anti-inflammatory adipokines secreted from fat contributes to the pathogenesis of NAFLD (38). Modulation of endocrine/immune/inflammatory interactions of adipose tissue may provide novel therapeutic (pharmacologic) targets for the treatment of NAFLD. For example, in patients with severe lipodystrophy, injection with leptin reverses nonalcoholic fatty liver diseases (39,40). However, in cases of NAFLD associated with obesity, serum levels of leptin are increased and the liver becomes refractory to the “anti-steatotic” effects of leptin (41-43). Leptin infusion is therefore unlikely to be of therapeutic value for patients with NAFLD. Tumor necrosis factor α (TNFα), a pro-inflammatory adipokine, interferes with insulin signaling and favors steatosis, and may play a casual role in the pathogenesis of NASH (38). Circulating levels of TNFα and hepatic expression of its type 1 receptor are increased in NASH, but could not discriminate steatohepatitis from steatosis (44-46). Neutralization of TNFα activity improves fatty liver disease in animals (47). Conversely, nutritional steatohepatitis can still be produced experimentally in both TNFα and TNFα type 1 receptor knockout mice, suggesting that this adipokine might not be an essential mediator of NAFLD (48,49).

In contrast to leptin and TNFα, adiponectin is more closely implicated in the pathogenesis of NAFLD/NASH. Unlike other adipokines, serum levels of adiponectin are decreased in obesity and its associated medical complications (50). A negative association between serum levels of adiponectin and liver enzyme levels has been shown in healthy subjects (51). Numerous epidemiological investigations in diverse ethnic groups have identified lower adiponectin level as an independent risk factor for non-alcoholic fatty liver diseases and liver dysfunctions (37). Compared with healthy controls, adiponectin levels are lower by more than 50% in NASH patients (52). Adiponectin expression is decreased by 20%~40% during the development of NAFLD, from simple steatosis to NASH (52,53). Moreover, NASH patients with lower levels of adiponectin show higher grades of inflammation, suggesting that adiponectin deficiency is an important risk factor for the development of fatty liver, steatohepatitis and other forms of liver injuries (52-55). In patients with T2DM, plasma adiponectin concentrations are inversely related to hepatic fat content (56). Hui and cols. have shown a direct relationship between hypoadiponectinemia and NASH independent of insulin resistance (52). Animal-based studies have demonstrated that adiponectin possesses potent protective activities against various forms of liver injuries, including those induced by carbon tetrachloride, lipopolysaccharide (LPS)/D-galactosamine, pharmacological compounds, bile duct ligations and methionine-deficient diet etc. (57-61). In animal models of both alcoholic and nonalcoholic steatohepatitis, exogenous adiponectin reduces hepatomegaly, depletes lipid accumulation, quenches hepatic inflammation and decreases hepatic expression and plasma concentrations of TNFα (62). Adiponectin knockout mice exhibit an enhanced pattern of hepatic fibrosis induced by carbon tetrachloride (58). The lack of adiponectin expression could accelerate hepatic tumor formation in a NASH model in mice (63). Among the known adipokines, adiponectin stands out for its insulin-sensitizing and anti-inflammatory roles, and may be used as a promising drug candidate for the treatment of liver diseases.

**STRUCTURAL BASIS AND SIGNALING MECHANISMS UNDERLYING THE HEPATO-PROTECTIVE FUNCTIONS OF ADIPONECTIN**

Adiponectin, also termed Acrp30, AdipoQ, apM1 or GBP28, was originally identified by four independent groups in both mice and humans (64-67). This adipokine has attracted much attention because of its multiple beneficial effects on a cluster of obesity-related metabolic and cardiovascular dysfunctions. Hypoadiponectinemia is a key etiologic factor contributing to almost all the major pathological conditions associated with obesity (68). The physiological functions and clinical relevance of adiponectin in obesity-related medical complications have been extensively reviewed elsewhere (50,69-72). In the following sections, we will discuss recent advances on the structural regulations of adiponectin as well as the molecular evidences support-
ing the role of adiponectin as a major protective agent against obesity-related NAFLD.

Polymorphism of the multimeric structures of adiponectin

A unique feature of adiponectin structure is its ability to assemble into several characteristic oligomeric isoforms, including trimer (low molecular weight, LMW), hexamer (middle molecular weight, MMW) and the oligomeric complexes consisting of 18 protomers or above (high molecular weight, HMW) (73). Adiponectin presents predominantly in the circulation as these three oligomeric complexes (74-79). The trimeric adiponectin is the basic building block of adiponectin. The subunits in the trimer are associated via hydrophobic interactions. The hexameric adiponectin is formed by two LMW adiponectin molecules linked by disulfide bonds. The structural properties of the HMW adiponectin remain poorly characterized due to the heterogeneous nature of this isoform. Analysis of adiponectin oligomers by non-denaturing and non-heating gel electrophoresis shows that the human HMW adiponectin composes of a mixture of 18-30 mers, or even larger molecular weight species (73,78,80,81). Dynamic light scattering and transmission electron microscopy shows that the bovine HMW adiponectin forms a bouquet-like architecture resembling that of complement C1q (82). Six globular objects can be seen atop a thin stalk, which presumably correspond to the six LMW adiponectins. The stalks bunch together in a manner that is consistent with the requirement for NH2-terminal disulfide bonding. The side views of HMW adiponectin suggest a conical structure of the oligomer with the COOH-terminal portion forming the base. Interestingly, these globular domains are arranged in a tight ring. This circular arrangement might enable polyvalent interactions of the globular domains with a single receptor. Recently, the HMW oligomeric structures formed by multiples of adiponectin trimers have been determined by single-particle analysis of electron micrographs (83). Pleomorphic ensembles of collagen-like stretches of the trimers lead to a highly dynamic structure of HMW adiponectin, which could be classified into two major classes, the fan-shaped (class I) and bouquet-shaped (class II). In both of these conformations, the globular domains assume a variety of arrangements, covering an area of up to $4.9 \times 105 \, \text{Å}^2$ and up to 320Å apart. The conformational flexibility of the HMW oligomer can allow it to access and cluster disparate target ligands or receptors, which may be necessary to activate cellular signaling leading to the remarkable functional diversity of adiponectin.

The HMW adiponectin as a major bioactive form in liver

Obese individuals have different distribution of adiponectin oligomers compared with lean control. Relatively lower content of HMW adiponectin is closely associated with obesity-related metabolic complications (81). The increases in the ratio of HMW versus total adiponectin, but not total adiponectin level per se, correlate well with improved insulin sensitivity during treatment with the insulin-sensitizing drug thiazolidinediones in both diabetic mice and patients with T2DM. On the other hand, weight reduction by either calorie restriction or gastric bypass surgery results in a selective elevation of the HMW adiponectin, but not the trimeric and hexameric complexes (84-86). In line with these data from the epidemiological studies, there is also genetic evidence supporting the role of HMW adiponectin as a major insulin-sensitizing isoform in humans. Kadowaki and colleagues have reported two rare mutations (G84R and G90S) located within the collagenous domain which are closely associated with insulin resistance and T2DM (76). Interestingly, subjects with either of these mutations have extremely low levels of HMW adiponectin. Moreover, recombinant adiponectin with either of these mutations expressed in NIH-3T3 fibroblasts failed to form HMW oligomers. An independent inverse association exists between ALT and HMW adiponectin (87). Taken together, these epidemiological and genetic data suggest that the beneficial effects of adiponectin in humans might be mediated primarily by its HMW isoform, and the deficiency of this oligomer is an important etiological factor that links obesity with its medical complications.

Evidence from both in vitro and animal-based studies also supports the role of the HMW oligomer as the major active form in mediating the multiple actions of adiponectin in the liver tissue. Recombinant adiponectin produced from mammalian cells, which can form the HMW oligomers, potently decreases hyperglycemia in diabetic mice through inhibition of hepatic glucose production (88). However, bacterially generated full-length adiponectin, which lacks the capacity to form the HMW adiponectin, is almost inactive. Intravenous
injection of the HMW adiponectin, but not the hexameric adiponectin, leads to a dose-dependent decrease in serum glucose levels (81). The formation of the HMW oligomers is obligatory to mediate the insulin-sensitizing effects of adiponectin on suppression of hepatic gluconeogenesis in primary rat hepatocytes (80). Acute injection of recombinant adiponectin enriched with the HMW oligomers results in a marked activation of AMP-activated kinase (AMPK) in the liver, while chronic infusion with this protein leads to prolonged alleviation of hyperglycemia and insulin resistance in db/db diabetic mice (89). These animal-based evidences are consistent with the clinical observations showing that the ratio of HMW/total adiponectin correlates closely with hepatic insulin sensitivity (81). The role of the HMW oligomer as a predominant active form of adiponectin mediating its hepatic actions is also supported by two recent independent reports demonstrating that the insulin-sensitizing effects of the PPARγ agonists thiazolidinediones were diminished in ob/ob obese mice with the targeted mutation of the adiponectin gene (90,91). Notably, treatment with thiazolidinediones has been shown to cause a selective elevation of the HMW oligomeric adiponectin (79,81). In addition to the hepatic insulin-sensitizing activity, the HMW adiponectin has also been suggested to be the most potent isoform for alleviation of fatty liver disease in high fat diet-induced obese mice (92), and inhibition of apolipoprotein B and E release from human hepatocytes (93). HMW adiponectin dose-dependently suppressed growth factor-induced hepatic stellate cell proliferation (94). Together, these data suggest that the beneficial effects of adiponectin in the hepatic tissue are mediated predominantly by its HMW form.

Receptors and postreceptor signaling pathways mediating the hepatoprotective functions of adiponectin

Two adiponectin receptors (adipoR1 and adipoR2) have been identified and found to be expressed in various tissues (95). AdipoR1 is abundantly expressed in skeletal muscles, whereas adipoR2 is present predominantly in the liver, suggesting a role of adipoR2 in hepatic adiponectin signaling (68,96). The physiological roles of adipoR1 and adipoR2 have recently been investigated by several laboratories in adipoR1/2 knockout mice. Both adipoR1 and adipoR2 knockout mice exhibit mild insulin resistance (97). In adipoR1/R2 double knockout mice, the binding and actions of adiponectin are abolished, resulting in increased tissue triglyceride content, inflammation and oxidative stress (97). AdipoR2 knockout mice reported by Liu and cols. displayed reduced diet-induced insulin resistance, but promoted T2DM (98). These data support the physiological roles of adipoR1 and adipoR2 as the predominant receptors for adiponectin in the regulation of glucose and lipid metabolism. Despite this information, the detailed roles and expression of adipoRs in NAFLD are not conclusive (99-102).

Adiponectin has been shown to stimulate AMP-activated protein kinase (AMPK) in almost all its major target tissues, including skeletal muscle, liver, heart, endothelium, adipocytes and brain (75,89,103-106). Notably, most biological effects of adiponectin in these target tissues are abrogated by expression of a dominant negative version of AMPK, supporting its obligatory role in mediating adiponectin’s multiple actions. The precise mechanisms whereby adiponectin activates AMPK through its receptors remain to be determined. APPL1, an adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif, appears to be a key signaling molecule that couples adiponectin receptors and its downstream AMPK activation (103,107). Adiponectin enhances the binding of APPL1 to both adipoR1 and adipoR2, and these interactions are essential for subsequent phosphorylation and activation of AMPK. Studies also indicate the important role of APPL1 in the metabolic syndrome (108,109). AMPK activation in turn phosphorylates acetyl Coenzyme A carboxylase (ACC) and attenuates ACC activity. Inhibition of ACC reduces lipid synthesis and enhances fatty acid oxidation by blocking the production of malonyl-CoA, an allosteric inhibitor of carnitine palmitoyl transferase 1 (CPT-1), the rate-limiting enzyme in fatty acid oxidation. In addition, activation of AMPK downregulates the expression of sterol regulatory element-binding protein 1c (SREBP1c), a transcription factor that regulates cholesterol and lipid synthesis. Reduction of SREBP1c results in downregulation of genes involved in lipogenesis, including ACC, fatty acid synthase (FAS), and glycerol-3-phosphate acyltransferase (GPAT) (104,110,111).

PPARα is a transcription factor controlling the transcription of a panel of genes encoding fatty acid oxidation enzymes, such as FATP, acyl-CoA oxidase (ACOX) and long chain acyl-CoA synthetase (LCAS). Adiponectin stimulates PPARα activity possibly through PPARY
coactivator-1α (PGC-1α) (112). These signaling pathways mediated by adiponectin lead to enhanced fat oxidation, reduced lipid synthesis and prevention of hepatic steatosis (Figure 1).

Adiponectin and fatty liver diseases

Inflammatory cytokines are key mediators of hepatic inflammation, cell death, fibrosis, as well as regeneration after massive or focal liver injury (38,113). Adiponectin levels are negatively associated with mediators of inflammation, including IL-6 and C-reactive protein (CRP); but positively related to anti-inflammatory cytokine IL-10 (114,115). It suppresses TNF-α functions via inhibition of its expression and antagonizing its activities (61,62,116,117). In the liver, cytokines such as interleukin-6 (IL-6) and TNFα, are mainly produced from Kupffer cells and hepatic stellate cells (HSC), and partly from inflamed hepatocytes (52,118,119). Adiponectin ameliorates NASH and liver fibrosis through suppressing the activation of Kupffer cells and hepatic stellate cells (HSC) (Figure 2). In porcine blood-derived macrophages, adiponectin suppresses both TNFα and IL-6 production stimulated by LPS and induces IL10 expression. The attenuation of proinflammatory cytokine production by adiponectin is mediated in part by attenuating the translocation of NFκB to the nucleus (120). Adiponectin can also induce the expression of anti-inflammatory cytokine interleukin-1-receptor antagonist (IL-1RA) (121,122). The anti-inflammatory effects of adiponectin in macrophages may involve Toll-like receptor-4 (TLR-4) signaling pathway. However, the mechanisms by which adiponectin suppresses TLR-4 mediated responses are not well understood (123).

The transformation of hepatic stellate cells (HSC) into myofibroblasts is the key step initiating the fibrotic process during liver injury (124,125). The activated hepatic stellate cells increase the accumulation of extracellular matrix. Both adiponectin receptors, adipoR1 and adipoR2, are expressed in HSC. Adiponectin treatment maintains HSC quiescence, inhibits platelet-derived growth factor (PDGF)-stimulated proliferation and migration of human HSCs, and reduces the secretion of monocyte chemoattractant protein-1 through AMPK-dependent mechanisms (94,125,126). Additionally, adiponectin also regulates hepatic expression of TGFβ1, a pro-fibrotic factor involved in HSC activation (58,127). Inhibition of adipoR2 expression by short hairpin RNA-expressing adenovirus can induce TGFβ1 expression, and overexpression of adipoR2 diminishes TGFβ1 mRNA level.

Regulatory role of adiponectin on mitochondria activities

Mitochondrial dysfunction represents a central mechanism linking obesity with associated metabolic complications (128). In patients with NASH, the hepatic mitochondria exhibit ultrastructural lesions and decreased activity of the respiratory chain complexes (129,130). In this condition, the decreased activity of the respiratory chain results in accumulation of reactive oxygen species (ROS) that oxidize fat deposits to form lipid peroxidation products, which in turn, cause steatohepatitis, necrosis, inflammation and fibrosis. The increased mitochondrial ROS formation in steatohepatitis could directly damage mitochondria DNA (mtDNA) and respiratory chain polypeptides, induce NFκB activation and the hepatic synthesis of TNFα (131). Oxidative phosphorylation reactions mediated by mitochondria respiratory chain (MRC) complexes are directly involved in regulating intracellular ROS activities and
Figure 2. A summary of multiple pathways underlying the protective effects of adiponectin against liver injury.

preventing accumulation of lipids and lipid peroxidation products in the liver.

We have found that mice without adiponectin show an increased lipid accumulation even under normal chow feeding. This pre-existing hepatic steatotic condition might be the direct consequence of dysregulated mitochondria functions (117). Adiponectin treatment restores the MRC activities, decreases the levels of mitochondrial lipid peroxidation products through regulating hepatic mitochondrial functions, which might represent a common mechanism underlying the multiple beneficial activities of this hormone in various obesity-related pathologies. Moreover, we have provided evidence supporting an essential role of uncoupling protein 2 (UCP2), a mitochondria inner membrane transporter, in mediating the beneficial effects of adiponectin on MRC activities. The protein and mRNA levels of UCP2 are decreased in the liver tissues of adiponectin knockout mice and can be significantly up-regulated by adiponectin treatment. Over-expression of adipor2 up-regulates mRNA levels of UCP2, catalase, and superoxide dismutase 1 in the liver (97). Furthermore, the effects of adiponectin on the MRC activities are dramatically attenuated in Ucp2-deficient mice, suggesting that the increased UCP2 expression might be obligatory for adiponectin to elicit its activities on mitochondria...
functions (Figure 2). It is known that UCP2 possesses anti-oxidant activities through inhibition of ROS production from mitochondria (132). It can also inhibit the production of pro-inflammatory cytokines in both macrophage and Kupffer cells (133). A growing body of evidence suggests that UCP2 may play a beneficial role in various stages of fatty liver diseases (133,134). These results suggest the existence of a reciprocal relationship between uncoupling proteins and adiponectin. However, the detailed signaling mechanisms underlying adiponectin-induced UCP2 expression are not clear and warrant further investigations.

**ELEVATION OF ADIPONECTIN PRODUCTION AS A THERAPEUTIC STRATEGY FOR THE TREATMENT OF NAFLD**

To date, there have been very few effective drug treatments for NAFLD and NASH. Early diagnosis and management of the underlying condition remains the mainstay of treatment. The present “gold standard” for treatment of NAFLD is weight reduction or a reduction of central obesity (4). These “life-style adjustment” or anti-obesity measures (including bariatric surgery) impressively reduce liver cell injury, inflammation and hepatic fibrosis, as well as steatosis (135,136). The potential for correcting steatosis by dietary or pharmacological approaches should provide a sound therapeutic approach for the treatment of steatosis and steatohepatitis. Strategies to block oxidative stress are of great interest, with some evidence that ALT normalization or histological improvement occurs with vitamin E (alone or with vitamin C or pioglitazone) and betaine (137). However, more definitive studies are needed before these or other antioxidants and antifibrotic agents (including silymarin) can be routinely recommended.

Adiponectin and its agonists might represent emerging therapeutic agents for the treatment and/or prevention of liver dysfunctions. Adiponectin replacement therapy is not yet available as a treatment option. Pharmacological intervention aimed at elevating adiponectin production might hold promise for the treatment and/or prevention of NAFLD. We have recently reported the identification of two structurally related natural compounds (astragaloside II and isoastragaloside I) from the medicinal herb Radix Astragali that possess such an activity (138). Astragaloside II and isoastragaloside I selectively increase adiponectin secretion in primary adipocytes without any obvious effects on a panel of other adipokines. Furthermore, an additive effect on induction of adiponectin production has been observed between these two compounds and rosiglitazone. Chronic administration of astragaloside II and isoastragaloside I in both dietary and genetic obese mice significantly elevated serum levels of total adiponectin and selectively increased the composition of its high molecular weight oligomeric complex. These changes are associated with an alleviation of hyperglycemia, glucose intolerance and insulin resistance. These results suggest that pharmacological elevation of circulating adiponectin alone is sufficient to ameliorate insulin resistance and diabetes. The two natural compounds might also provide the lead as a novel class of therapeutics for obesity-related diseases, such as NAFLD.

**CONCLUSION REMARKS**

Adiponectin is an abundant adipocyte-derived hormone with well established anti-inflammatory and insulin sensitizing properties. The significance of adiponectin in protecting obesity-related NAFLD has been increasingly recognized. Despite the knowledge advances made in recent years, the detailed molecular and cellular mechanisms underlying its hepatoprotective functions remain largely uncharacterized. Nevertheless, adiponectin-based therapeutics for NAFLD represent a promising area for further investigation.

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