The role of adiponectin in human vascular physiology

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A B S T R A C T

Adiponectin (ApN) is an adipose tissue-derived hormone which is involved in a wide variety of physiological processes including energy metabolism, inflammation, and vascular physiology via actions on a broad spectrum of target organs including liver, skeletal muscle, and vascular endothelium. Besides possessing insulin sensitizing and anti-inflammatory properties ApN also exerts a pivotal role in vascular protection through activation of multiple intracellular signaling cascades. Enhancement of nitric oxide generation and attenuation of reactive oxygen species production in endothelial cells along with reduced vascular smooth muscle cell proliferation and migration constitute some of ApN's vasoprotective actions. Additionally, recent data indicate that ApN has direct myocardio-protective effects. Decreased plasma ApN levels are implicated in the pathogenesis of the metabolic syndrome and atherosclerosis and may serve as a diagnostic and prognostic biomarker as well as a rational pharmaco-therapeutic target to treat these disorders. This review article summarizes recent work on the cardiovascular actions of ApN.

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1. Introduction

Atherosclerosis and the metabolic syndrome are leading causes of morbidity and mortality worldwide and are closely linked to obesity and adipose tissue dysfunction. Far from being a passive energy storage depot, adipose tissue is now recognized to constitute the largest endocrine gland in the body and to actively participate in the regulation of many biological processes [1–3]. This is achieved through the expression and secretion of a large number of bioactive mediators that are collectively known as 'adipokines' [1–3]. This group of peptides includes (but is not limited to) tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), apelin, visfatin, leptin, and ApN [3,4].

ApN is the most abundant adipose tissue-derived hormone. It has insulin sensitizing properties and is down regulated in obesity thereby contributing to the metabolic dysregulation associated with this disorder [3,4]. In addition, ApN links adipocytes to vascular function. Over the past few years a number of experimental and clinical studies have extensively examined the role of ApN in vascular homeostasis and firm evidence indicates that ApN exerts anti-inflammatory and anti-atherogenic effects both on the myocardium and the vascular wall [3,4]. In addition ApN may serve as a clinical biomarker of cardiovascular disease [3,4]. In this review we examine

the physiological role of ApN in the vasculature and its role in the pathogenesis of atherosclerosis.

2. Biosynthesis of ApN and ApN receptors

The ApN gene is located on chromosome 3q26 and encodes a 247 amino acid protein [5–9]. ApN is secreted into the circulation where it can be detected as a wide range of multimers with distinct biological functions [5–9]. Three isoforms are predominantly found in plasma: a low molecular weight trimer, a medium molecular weight hexamer, and a high molecular weight multimer. Remarkably, these isoforms collectively account for 0.01% of total serum protein (serum concentration 5–30 μg/ml). Additionally, proteolytic cleavage of the full length protein produces a globular fragment that can also be detected in plasma albeit at much lower concentrations [5–9].

ApN is principally produced from white (and in rodents also brown) adipose tissue and specifically from mature adipocytes. Three main adipose tissue depots are recognized: subcutaneous, visceral and perivascular. Interestingly plasma levels of ApN are more closely related to the amount of visceral than total body fat [10]. This is of particular interest given the close association between visceral obesity and metabolic/cardiovascular disease [11]. Epicardial fat is also a source of ApN [11]. Lower levels are also expressed in the liver, cardiomyocytes, skeletal muscle, colon, salivary glands, placenta, and pituitary but the contribution of these tissues to the circulating ApN pool is relevantly small. Apart from plasma, ApN can also detected in breast milk and in cerebrospinal fluid albeit at low concentrations [5,12].
ApN production is subject to multiple regulatory mechanisms. These include transcriptional, translational, and post translational modifications. Several factors are capable of modulating ApN gene expression, most notably peroxisome proliferator activator receptor γ (PPAR-γ) [9]. Activation of this nuclear receptor by the thiazolidinedione (TZD) class of anti-diabetic drugs stimulates ApN expression and secretion in adipose tissue [9]. Furthermore, a number of other transcription factors including forkhead box 01 (Fox01), sterol-regulatory-element-binding protein-1c (SREBP-1c), and CCAAT/en-hancer-binding protein-α (C/EBP-α) also stimulate ApN gene expression [9]. In contrast, reactive oxygen species (ROS), TNF-α and interleukin-6 (IL-6), namely agents linked with inflammation and obesity and known to induce insulin resistance are negative regulators of ApN expression levels [9]. Impaired multimerization and secretion caused by endoplasmic reticulum (ER) stress, oxidative stress, and pro-inflammatory cytokines lead to reduced plasma levels of Apn and are associated with insulin resistance [9]. Interestingly, ApN secretion in 3T3-L1 adipocytes was shown to be up-regulated by endothelin-1, a potent vasoconstrictive substance that is elevated in many disease states including diabetes and obesity. This finding suggests that other vascular-derived factors might similarly control ApN expression and/or secretion [13]. Finally, environmental factors have also been implicated in the regulation of circulating ApN levels. Specifically, a Mediterranean-type diet and consumption of nuts, coffee, and moderate amounts of alcohol are positively correlated with plasma ApN concentration (and protection from diabetes and cardiovascular disease). In contrast high-fat diet and inactivity exert the opposite effects [5].

ApN exerts its physiological effects predominantly via AdipoR1 and AdipoR2 receptors. While these receptors contain seven transmembrane domains they are considered to be structurally and functionally distinct from G-protein coupled receptors [4] and upon activation engage a broad range of intra-cellular signaling intermediaries/cascades including AMP-activated protein kinase (AMPK). Apart from AdipoR1 and AdipoR2, T-cadherin, a glycosylphosphati-dylinositol (GPI) linked cell surface molecule, has also been recently reported to constitute a putative ApN receptor [12]. AdipoR1 and AdipoR2 are ubiquitously expressed. However, AdipoR1 is predominantly detected in skeletal muscle and has higher affinity for globular ApN whereas, AdipoR2 is abundantly expressed in the liver and has high affinity for the full length form of Apn [14]. These findings are consistent with the observations that full length ApN has a greater effect on hepatic metabolism, whereas both (globular and full length) forms of ApN elicit metabolic effects in skeletal muscle. Both forms of ApN receptor can be found in endothelial cells and cardiomyocytes [15].

3. Effects of ApN on endothelial inflammation

The anti-inflammatory properties of ApN are mediated partly through activation of AdipoR1 and AdipoR2 in monocytes, macrophages, and endothelial cells and serve to attenuate inflammatory cell accumulation in sites of vascular injury [16,17]. ApN inhibits the production of pro-inflammatory cytokines and chemokines from both immune and endothelial cells as well as the ability of these cells to become activated in response to various inflammatory stimuli. Furthermore, it inhibits the growth of myelomonocytic progenitors [16,17] as well as down-regulating the expression of scavenger A receptors and suppressing the transformation of macrophages to foam cells [17,18]. ApN may also protect (at least in part) against systemic inflammation by promoting the clearance of early apoptotic cells by macrophages through a mechanism involving calreticulin and by down-regulating systemic inflammatory markers/mediators such as C-reactive protein (CRP), TNF-α and IL-6 [16,17]. Surprisingly, in contrast to the reduced ApN levels observed in chronic, systemic low grade inflammation (e.g. associated with visceral obesity) circulating ApN is elevated in most chronic inflammatory and autoimmune disorders such as rheumatoid arthritis and in type 1 diabetes mellitus [19].

4. Effects on vascular physiology-endothelial function

ApN exerts a fundamental role in vascular physiology by modulating the cross-talk between endothelial cells, smooth muscle cells, leukocytes, and platelets [20]. Apart from maintaining vascular homeostasis, ApN also protects from vascular injury and atherogenesis [8,16,18]. Furthermore, in human subjects, plasma ApN levels are positively associated with arterial vasodilation in response to nitroglycerin (a measure of endothelium-independent vasodilation) independent of insulin sensitivity [21].

Endothelium derived nitric oxide (NO) is a paracrine factor notable for its beneficial actions on the vascular system namely, promotion of vasodilation and inhibition of platelet aggregation, monocyte adhesion and smooth muscle cell proliferation. NO depletion is one of the earliest and most important steps in atherogenesis [16]. ApN acting via AdipoR1 and AdipoR2 potentiates NO production through activation of the AMPK signaling pathway. AMPK in turn activates endothelial nitric oxide synthase (eNOS) through phosphorylation at Ser1177 and facilitates complex formation between eNOS and heat shock protein 90 (HSP-90) which is required for maximal eNOS activation [12,16,18,22,23]. Additionally phosphatidylinositol 3-kinase (PI3K)-Akt signaling cascade has been also implicated in up-regulation of NO production. PI3K-Akt pathway is involved in the reduction of IL-8 (chemotactic agent) [16]. PI3K-Akt is thought to interact with AMPK and contributes in the enhancement of HSP-90/eNOS complex formation [22–24] (Fig. 1).

Endothelial dysfunction, characterized by several abnormalities, including impaired nitric oxide (NO) production, is a key finding associated with insulin-resistant states [21]. When endothelial dysfunction is present, the relative lack of NO production contributes to hypertension and several concomitant pathologies, including increased expression of adhesion molecules on the endothelial cell surface and other inflammatory changes that underlie the early process of atherosclerosis [21]. A variety of substances that adversely influence endothelial function have been recognized, including free fatty acids, cytokines (such as TNF-α), and pro-oxidant molecules, including oxidized low density lipoprotein (oxLDL) [21]. These mediators activate signaling kinases and are also closely linked to the endothelial production of ROS (superoxide and H₂O₂) which play a key role in the development of atherogenesis in the context of the metabolic syndrome and diabetes [21]. ApN attenuates ox-LDL and hyperglycemia induced ROS generation via activation of the cAMP/PKA cascade [25]. Recent evidence also suggests that ApN potently inhibits vascular endothelial growth factor (VEGF)-induced ROS generation which when combined with the anti-inflammatory actions of ApN (which also leads to reduced ROS production) indicates that ApN has a broad anti-oxidant role in the vasculature [25].

High glucose and TNF-α activate the NF-κB cascade in endothelial cells leading to increased expression of IL-8 and adhesion molecules, thereby promoting endothelial activation [26–28]. Endothelial activation is a key step in the pathogenesis of vascular diseases and is responsible for the increased interaction between endothelial cells and leukocytes, vascular smooth muscle cell (VSMC) proliferation, chemotaxis and vascular damage [26–28]. In this respect ApN has been shown to inhibit endothelial NF-κB signaling via a cAMP-dependent pathway [26–28]. Specifically, treatment of cultured human endothelial cells with ApN blocked IκB kinase (IκB) activation thereby inhibiting proteolytic degradation of the NF-κB inhibitor IκB. This effect was abrogated by treatment with both a cAMP and a PKA inhibitor thereby implicating this pathway in ApN mediated NF-κB down-regulation [26–28].
ApN also protects against increased endothelial cell permeability induced by TNF-α and angiotensin-II in a cAMP/PKA manner and prevents cell migration [26,29]. The actions of ApN probably differ depending on whether the endothelium is normal or injured; ApN protects the normal endothelium from injury while promoting recovery of damaged endothelium [18,30]. Moreover, ApN protects endothelial cells from pro-inflammatory cytokine-induced apoptosis possibly by inhibiting caspase 3 activity via the cAMP/PKA pathway [25,31]. The various anti-atherogenic actions of ApN on endothelial cells are summarized in Fig. 1.

Neointimal formation consequent to aberrant VSMC proliferation and migration is responsible for intimal thickening during the development of vascular diseases. ApN potently suppresses VSMC proliferation and migration in vitro [16,18]. In vivo, adiponectin protects from neointimal thickening following arterial injury in animal models and may thus be useful in preventing vascular restenosis following angioplasty [32]. These actions of ApN may be mediated via the NO pathway which inhibits VSMC proliferation and via inhibition of growth factor stimulated extracellular signal regulated kinase (ERK) signaling [18,33]. Additionally, ApN may potently inhibit growth factor signaling via direct binding to various growth factors [18]. Finally, recent experimental data also suggest that locally produced ApN (derived from periadventitial fat) may play a role in the regulation of microvascular network flow and function [15] and protection against neointimal formation after angioplasty [34].

In summary, ApN has emerged as a key role playing molecule in the protection and integrity of the vasculature. Decreased ApN levels (and therefore function) as seen for instance in obesity and the metabolic syndrome [35], are likely to be one of the steps involved in atherosclerotic vascular disease (Fig. 2).

5. ApN and endothelial progenitor cells

Endothelial progenitor cells (EPCs) are a heterogeneous population of circulating cells involved in vascular repair and neovascularization. EPCs are reduced in patients with cardiovascular disease displaying hypoadiponectinemia [36]. Furthermore, reduced circulating EPC number may be causally linked with the cardiovascular complications of diabetes. ApN has been shown to protect some EPC sub-populations from apoptosis and could thus modulate the ability of EPCs to promote repair following vascular damage. Reciprocally, the neutrophil elastase activity of EPCs may modulate local ApN activity by promoting generation of the globular form of ApN [37]. In a very recent study, Chang et al. [38] investigated whether ApN plays a role in modulating the bioavailability of circulating EPCs and their ability to promote endothelial repair in vivo. Of note the number of circulating EPCs decreased in an age-dependent manner in ApN deficient mice. Further work is needed to determine the relative contributions of ApN to EPC biology in vivo.
knockout mice compared with wild type controls. The authors concluded that the athero-protective effects of ApN in this mouse model are due (in part) to its ability to counteract hyperglycemia-mediated decrease in circulating EPC number [38].

6. ApN and myocardium

ApN is synthesized and secreted by human cardiomyocytes which also express AdipoR1 and AdipoR2 [15]. ApN may serve (at least in part) to regulate energy homeostasis in cardiac muscle by promoting fatty-acid oxidation [39]. Recent data also suggest that ApN may exert direct cardio-protective actions. Specifically, two recently published studies have demonstrated that ApN accumulates in damaged myocardial tissue in response to ischemia/reperfusion injury [40] and protects the myocardium by inhibiting inducible NOS and NADPH-oxidase expression and resultant oxidative stress [41]. ApN may protect against myocardial ischemia/reperfusion injury through AMPK and COX-2-dependent mechanisms [42]. Additionally, ApN may modulate coronary plaque vulnerability as determined by angiographic lesion complexity [43]. Finally, cardiomyocyte-derived ApN acting in an autocrine manner may protect cardiomyocytes from hypertrophy via a PPAR-gamma dependent mechanism [39].

Based on the proposed cardioprotective actions of ApN the expression of its receptors in normal and infracted mouse hearts was recently examined [44,45]. AdipoR1 and AdipoR2 were found to be expressed at similar levels in the left ventricle and skeletal muscle. Of note, AdipoR1 and AdipoR2 expression was decreased following myocardial infarction [44,45]. As in other tissues (e.g. skeletal muscle and liver) the metabolic effects of ApN in the heart downstream of AdipoR1 and AdipoR2 seem to be mediated by AMPK. AMPK not only improves myocardial glucose and lipid metabolism but also prevents ventricular contractile dysfunction in the ischemic heart [44,45]. One possible molecular target of ApN signaling in the heart may be endothelin 1 (ET-1). ET-1 induces cardiomyocyte hypertrophy and ApN seems to inhibit ET-1 expression [44]. Based on the evidence presented above, it is reasonable to assume that as well as being a key player in vascular homeostasis ApN exerts an important role in the pathophysiology of ischemic heart disease [46]. However, most of the mechanistic data currently available are based on observations from cell culture and animal models, and extrapolations to humans should be made with caution [46].

7. Clinical implications

Several studies have demonstrated the association of ApN with atherogenic risk factors, endothelial dysfunction, and ischemic heart disease in humans. These are summarized in Table 1. It is important to note that all of these studies are correlative and direct evidence that ApN protects against vascular disease in humans is still lacking. However, these findings do indicate that use of serum ApN levels and genetic polymorphisms may be useful biomarkers in the early diagnosis and prognosis of cardiovascular disease [49–51].

8. Therapeutic interventions targeting ApN

Only a few experimental data on the use of recombinant adiponectin in animals are currently available. Specifically, administration of adiponectin was shown to reduce myocardial infarct size following ischemia–reperfusion in both adiponectin-deficient and wild-type mice [42]. Adiponectin therapy was also shown to be a useful adjunct in acute myocardial infarction presumably in mice [53]. In the absence of human recombinant adiponectin preparations current interventions aim at elevating circulating adiponectin levels indirectly. In this respect, weight loss and physical exercise along with the adaptation of a Mediterranean-
Table 1

The clinical impact of adiponectin in CAD risk factors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Study design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. [54]</td>
<td>14,598 participants, 2,623 patients</td>
<td>Meta-analysis, prospective</td>
<td>ApN levels were inversely correlated with the risk of DM2 across diverse populations (RR [95% CI], p: 0.72 [0.67–0.78], p &lt; 0.001). Plasma ApN was inversely correlated with BMI and insulin resistance in both genders and directly correlated with HDL, ApoA1, and HOMA.</td>
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<tr>
<td>Shand et al. [48]</td>
<td>197 patients (109 men and 88 women), BMI &gt; 25 with characteristics of the metabolic syndrome</td>
<td>Cross-sectional study</td>
<td>Serum ApN was associated with increased insulin sensitivity (p &lt; 0.05), reduced abdominal fat and high basal lipid oxidation (p &lt; 0.01). Total and HMW ApN were inversely correlated with the risk of DM2 in women (odds ratio [OR] comparing the highest with the lowest quintiles, 0.17 [95% CI, 0.12–0.25] for total adiponectin and 0.10 [CI, 0.06–0.15] for high-molecular-weight adiponectin). ApN was associated with inflammatory markers and markers related to atherogenesis and endothelial dysfunction in diabetic patients and subjects at risk for diabetes. Decreased plasma ApN concentrations were associated with dyslipidemia (p &lt; 0.0001). Association between ApN and metabolic syndrome (inverse correlation with BMI, waist circumference, diastolic blood pressure, triglycerides, and glucose). The odds ratio (OR) for prevalent MetS-IDF and MetS-AHA/NLHBI in subjects of the 1st quartile group was 3.25 [95% CI: 2.24–4.71] and 3.21 [95% CI: 2.26–4.55]. HMW ApN was a sensitive biomarker for the prediction of insulin resistance and metabolic syndrome (OR 0.713 [95% CI: 0.620–0.805]).</td>
</tr>
<tr>
<td>Lara-Castro et al. [55]</td>
<td>68 subjects (33 women, 35 men), 21 patients with DM2</td>
<td>Cross-sectional study</td>
<td>Hypoadiponectinemia was associated with impaired endothelium-function. Plasma adiponectin correlated with endothelium-dependent vasodilation in controls (p = 0.02) and diabetic patients (p = 0.04) (association independent of diabetes).</td>
</tr>
<tr>
<td>Heidemann et al. [56]</td>
<td>1038 healthy women at risk of diabetes</td>
<td>Prospective, case-control study</td>
<td>Plasma adiponectin correlated with endothelium-dependent vasodilation in controls (p = 0.02) and diabetic patients (p = 0.04) (association independent of diabetes).</td>
</tr>
<tr>
<td>Shetty et al. [57]</td>
<td>77 subjects with or at risk of DM2</td>
<td>Cross-sectional study</td>
<td>Hypoadiponectinemia was shown to predict the development of hypertension (OR: 2.76; [95% CI: 1.06–7.16]).</td>
</tr>
<tr>
<td>Matsubara et al. [58]</td>
<td>352 women, 16–86 years old, with a wide range of BMI</td>
<td>Cross-sectional study</td>
<td>The C11377G SNP was found to have an independent effect on systolic blood pressure and waist/hip ratio.</td>
</tr>
<tr>
<td>Zhao et al. [59]</td>
<td>2049 adults (60–96 years old) from major cities in China</td>
<td>Prospective study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Hara et al. [60]</td>
<td>298 patients admitted for diabetes treatment or coronary angiography</td>
<td>Prospective study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Torigoe et al. [61]</td>
<td>100 young healthy men</td>
<td>Prospective study</td>
<td>The C11377G SNP was found to have an independent effect on systolic blood pressure and waist/hip ratio.</td>
</tr>
<tr>
<td>Tan et al. [62]</td>
<td>146 patients (73 diabetic, 73 controls)</td>
<td>Cross-sectional study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Chow et al. [63]</td>
<td>577 subjects (249 men, 328 women)</td>
<td>5-year prospective study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Pischon et al. [64]</td>
<td>18,225 males (40–75 years old) free of diagnosed CVD</td>
<td>Case–control study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Persson et al. [65]</td>
<td>244 &lt; 60-year-old survivors of a first myocardial infarction</td>
<td>Retrospective case–control study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
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<tr>
<td>Matsuo et al. [66]</td>
<td>70 patients undergoing coronary angiography</td>
<td>Prospective study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Avery et al. [67]</td>
<td>255 families, 1425 individuals</td>
<td>Cross-sectional study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
</tr>
<tr>
<td>Hoefle et al. [68]</td>
<td>402 men undergoing coronary angiography</td>
<td>Prospective study</td>
<td>ApN was significantly predictive of vascular events among men undergoing coronary angiography.</td>
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</table>

9. Conclusions

A plethora of experimental data support the notion that, in addition to its insulin-sensitizing effects in tissues involved in glucose and lipid metabolism, ApN exerts potent and direct anti-inflammatory and atheroprotective effects on the vasculature. These studies raise the specter of utilizing this hormone as a diagnostic and predictive cardiovascular disease biomarker and additionally as a rational target for the development of novel therapeutic strategies. Detailed characterization of the ApN signaling pathway in the vasculature and perivascular fat (as well as metabolic tissues) is likely to also provide novel tools in the management of atherosclerosis and metabolic disease.

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