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REVIEW ARTICLE

ADIPONECTIN, BLOOD PRESSURE AND HYPERTENSION - A NARRATIVE REVIEW

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Abstract: Adipokines, cytokines derived from adipose tissue, not only herald and confirm fat tissue as the largest endocrine organ but are also associated with a number of pathological states including obesity, insulin resistance and diabetes. There is a growing body of research on the role of adipokines in blood pressure regulation and development of hypertension. One of these adipokines, adiponectin, is especially interesting, given that it has numerous beneficial effects which include increasing insulin sensitivity and antiatherogenic and anti-inflammatory effects. In recent years, there has been a number of studies examining its possibly protective role in hypertension. In this narrative review we summarize the evidence on the association of adiponectin and polymorphism of the gene which encodes it with blood pressure levels and risk of hypertension, which might provide ideas for future research of adiponectin as a biomarker and potential therapeutic target in this condition.

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INTRODUCTION

A link between hypertension and obesity has been known to exist for several decades, with an abundance of evidence coming from early epidemiologic studies. This link has become especially interesting since, in recent decades, adipose tissue has started to be more frequently seen not as just an inert energy reservoir, but as the largest endocrine organ which secretes a large number of chemical compounds.[1] Cook et al. isolated the first fat tissue-derived active protein, adipsin (now known as factor D), in 1987, and Friedman et al. discovered the first major adipokine, leptin (product of ob/ob gene), in 1994, finally confirming the hypothesis of fat tissue as an active endocrine organ.[2, 3] Since then, more than 600 of such adipose tissue-derived compounds have been isolated.[4] These compounds, called adipokines or adipocytokines, have a variety of biological functions including effects on satiety, insulin sensitivity, energy balance and inflammatory, atherogenic and immune effects.[1, 4] Thus the theory of adipokines as homeostasis regulators was formed which says that different adipokines have differing and frequently mutually opposite functions which results in their balance being perceived as physiological homeostasis, while any disbalance might lead to pathological states.[5]
This narrative review will examine the association of adiponectin, a major adipokine and a frequent topic of research, with blood pressure regulation and hypertension. We aim to present its discovery, structure and mechanisms of action, followed by its effect on blood pressure and, finally, its role in disease based on recent clinical studies in hypertension.

The discovery and structure of adiponectin

Adiponectin is a protein secreted almost exclusively by adipose tissue and, with a plasma concentration of 5 to

30 mg/L, it is the most abundant adipokine in human plasma.[6] It was isolated from murine adipocytes in 1995 by Scherer et al., who named it Acrp30 (adipocyte complement-related protein of 30 kDa) due to homology with complement factor C1.[7] At approximately the same time it was also independently discovered by three more groups: 1. Hu et al. who also isolated it from murine adipocytes and named it AdipoQ, 2. Maeda et al. who scanned the human adipocyte complementary DNA library and named it Apm1 (adipose most abundant gene transcript 1), and 3. Nakano et al. who extracted and purified it from human plasma and named it GBP28 (gelatin-binding protein 28).[8-10] Today it is customary to use the term adiponectin for the human protein and Acrp30 for the corresponding protein in mice with 85% homology.[11] Structurally, adiponectin consists of a globular domain on a collagen stalk and is a member of the C1q family.[12] It is a protein built from 244 amino acids with four domains: 1. the amino-terminal signal sequence, 2. the variable region, 3. the collagen domain and 4. the carboxy-terminal globular domain. This form is termed the full-length form.[11, 13] There are also smaller mass forms formed by leucocyte esterase cleavage on at least 4 locations, which are termed globular forms (globular adiponectin). Globular adiponectin makes up around 1% of all adiponectin forms and is probably implicated in fatty acid oxidation, but its other functions are still not completely elucidated.[11, 13-15]

However, monomeric adiponectin is found only in adipocytes, while homo-oligomers consisting of trimeric adiponectin (low molecular weight, LMW adiponectin) as a basic building block are found in plasma. Aside from the LMW form, hexamers (middle molecular weight, MMW) and oligomers with 12, or more units (high molecular weight, HMW) are also found.[11, 16] Some authors postulate that the most abundant form is the HMW octadecamer.[17]

Receptors and general mechanisms of action of adiponectin

Kadowaki et al. isolated the cDNA of the first adiponectin receptor, AdipoR1 (chromosomal location of the gene at 1p36.13-q4) in 2003 by screening for potential globular adiponectin binding sites.[18] Further search for homologous genes found only one suitable gene with over 66% amino-acid sequence homology which was termed AdipoR2 (chromosomal location of the gene at 12p13.31).[18] AdipoR1 and AdipoR2 belong to the Progesteron and AdipoQ Receptor (PAQR) superfamily, consist of seven transmembrane domains and are topologically integral membrane proteins with intracellular N-terminus and extracellular C-terminus, which is contrary to topology of all other G-protein coupled receptors.[11] Aside from the heptahelical transmembrane domain, these two receptors share tri short amino acid motifs characteristic for this superfamily: 1. Ex2-3Nx3N/H, 2. Sx3HxnD and 3. Hx3H. Even though the first Scathchard plots showed that AdipoR1 is exclusively a receptor for globular adiponectin and AdipoR2 for full-length adiponectin (trimers and multimers), it has been shown in later studies that both forms probably bind to both receptors, but with different affinities – globular adiponectin has a high affinity for AdipoR1, while globular adiponectin and the full-length form have intermediate affinity for AdipoR2.[11, 16, 18] Although it is practically certain that both receptors are present in many different tissues, there are differences in their distributions, with AdipoR1 being primarily expressed in skeletal muscle and AdipoR2 in liver.[11] Mechanistically, adiponectin acts through at least three different signal pathways: 1. adenosine monophosphate kinase (AMPK) activation, 2. peroxisome proliferator activated receptor α (PPARα) activation and 3. simulation of ceramidase activity. Full-length forms bind to AdipoR1 and stimulate AMPK phosphorylation in skeletal muscle and liver, while globular adiponectin stimulates phosphorylation only in skeletal muscle. These pathways require calcium and calmodulin-dependent protein kinase kinase (Ca2+/CaMMKKβ), adenosine monophosphate and liver kinase B1 also known as serine/threonine kinase 11 (AMP/LKB1). Activation of this signal pathway in the liver decreases the expression of gluconeogenesis enzymes (phosphoenolpyruvate carboxylase and glucose-6-phosphatase).[16, 19] It is fairly certain that, aside from these three signal pathways, there is at least one additional one, probably mediated by a separate receptor. Proof of this is that adiponectin increases IL-6 expression in macrophages via NF-kappa B activation independent of AdipoR1 and AdipoR2.[20] Hug et al. identified a possible third receptor – T-cadherin coded by CDH123.[21] However, T-cadherin is an extracellular protein anchored to glycosil phosphate inositol, and it does not have an intracellular domain, so it is probably only a binding protein or a co-receptor for adiponectin. Interestingly, only eukaryotic adiponectin binds to T-cadherin, which implies necessary post-translational modifications. Also, Hug et al showed that only hexameric and HMW forms of adiponectin, and not the trimer and globular form, bind to T-cadherin.[21] Adiponectin is not bound in the cardiac tissue of mice who do not express T-cadherin, so Denzel et al. showed that its expression is necessary for the cardioprotective effects of adiponectin.[22]

Effect on blood pressure

A number of studies examined the association of adiponectin in physiology of blood pressure regulation-related pathology and pathophysiology, mainly hypertension. It is known today that adiponectin and blood pressure are related via at least three mechanisms: 1. the NO system and endothelial dysfunction, 2. the renin-angiotensin system and 3. central effect mediated via the sympathetic nervous

system.[23] Experiments measuring brachial blood flow following reactive hyperemia showed that plasma adiponectin concentration correlated with endothelial response.[24] Other studies showed that adiponectin-deficient mice have impaired endothelial response, i.e. decreased vasodilatatory response and decreased nitrate and nitrite concentration. Tan et al. demonstrated that in diabetic subjects, hypoadiponectinemia is associated with endothelial dysfunction which was remedied after adiponectin administration.[24-27]

Both full-length adiponectin and the globular form increase NO concentration, while the former also stimulates eNOS phosphorylation at Ser1179 location, thereby increasing its activity.[28, 29] Both adiponectin receptors are present in endothelial cells, and a decrease in expression of either one of them lowers NO production.[27, 30] Even though the exact mechanisms are not yet clearly elucidated, it is believed that several pathways including phosphatidylinositol 3-kinase, AMPK, cyclooxygenase-2 (COX-2), AAPL1 and Hsp90 are involved in signaling pathways via which adiponectin affects NO concentration.[31] Research has shown that the AMPK and COX-2 pathways undeniably play a large role in the association of adiponectin, endothelial dysfunction and blood pressure regulation. Adiponectin has been shown to activate the AMPK pathway which may mediate phosphorylation downstream of adiponectin signaling and in turn stimulate NO synthesis and bioavailability.[31] Additionally, it has been proven that adiponectin might mediate endothelial function via a different pathway from AMPK, i.e. the COX-2 pathway, and that recombinant adiponectin treatment increases COX-2 expression in cultured endothelial cells, which in turn promotes endothelial cell function via activation of Akt-dependent COX-2 signaling pathway.[31] Another mechanism which may be involved is adiponectin-mediated decrease in the endothelial expression of adhesion molecules and in scavenger receptor type A-1 in macrophages, which is associated with inflammatory modulation and possibly lower risk of atherosclerosis.[31] Increased angiotensin II plasma concentration increases blood pressure, while dysregulation of the renin-angiotensin-aldosterone system leads to hypertension.[32, 33] This fact coupled with the knowledge that both angiotensin II receptor blockers and adiponectin may lead to increased insulin sensitivity prompted research into the relationship of adiponectin and angiotensin. Continuous chronic angiotensin II infusion leads to decreased adiponectin plasma concentration and increased free radical activity in rats.[34, 35] It is interesting that this decrease is not dependent on angiotensin II receptor blockade (at least not subtype 2, which is the target of angiotensin blockers) and that this happens prior to the decrease in blood pressure. Increase in free radical concentration might be the cause of decrease in plasma adiponectin concentrations, especially when it is known that hydrogen peroxide inhibits adiponectin expression.[36] The mechanism of this process is almost certainly post-translational, because the concentration of adiponectin messenger RNA is left unchanged.[37] There are hints that PPARγ might be the missing link between adiponectin and angiotensin II, because of increase in PPARγ activity after administration of angiotensin II blocker telmisartan. Additionally, research showed that another angiotensin II blocker, irbesartan, increases plasma adiponectin concentration and that this increase could be prevented with selective PPARγ antagonists.[38, 39] This evidence demonstrates the mechanism of this arm of adiponectin-blood pressure relationship, but also imply that angiotensin II receptor blockers might be even more potent than was thought before and also that, in addition to antihypertensive and insulin-sensitizing effects, they may also independently increase the plasma adiponectin concentration.

The sympathetic nervous system consists of neurons which regulate a variety of body functions and it is responsible for stress-response.[40] Different pathological states, such as obesity and metabolic syndrome, are associated with higher sympathetic nervous system activity, i.e. overflow of sympathetic activity.[41] In these cases, increased sympathetic workflow leads to increased heart frequency and total peripheral resistance, which may lead to hypertension. Experimental studies in mice showed that cold stimulation, which simulates sympathetic activity, leads to decreased transcription and adiponectin secretion and that this process is reversible with epinephrine inhibitors.[42] Also, administration of β3 receptor (adipose tissue adrenergic receptor) agonists in 3T3-L1 adipocytes decreases adiponectin mRNA synthesis, and this effect is not present when blockers of this adrenergic receptor are administered beforehand.[43]

Similar to leptin, adiponectin regulates blood pressure through a centrally-mediated system.[44] Intravenous adiponectin infusions lead to dose-dependent decrease in blood pressure and sympathetic activity in mice with a similar effect, but with ten times lower doses with intrathecal administration.[44] These studies provide strong evidence of the adiponectin-sympathetic nervous system relationship both centrally and peripherally.

Hypoadiponectinemia is strongly associated with insulin resistance and consequent diabetes, and a part of this connection might lie in the regulation of insulin signaling and oxidative stress, autophagy and mitophagy via adiponectin.[45] Ahlstrom et al. showed that adiponectin induces autophagy, which attenuates high insulin/high glucose-induced endoplasmic reticulum stress and improves insulin sensitivity.[45] Liu et al. showed that in a murine model of obesity and insulin resistance induced by high-fat diet, adiponectin stimulates skeletal muscle autophagy and antioxidant potential, which in turn reduces insulin resistance.[46] An

in vitro study by Ren et al. conducted in murine C2C12 myoblasts showed that adiponectin has a moderate regulatory role in oxidative stress-induced mitophagy and suppresses apoptosis.[47]

Clinical studies of adiponectin in hypertension

The relationship between obesity and hypertension provided an impetus for further research of the effects of individual adipokines on blood pressure. A large number of clinical studies analyzed the relationship between plasma adiponectin concentration and hypertension. A review of the most important clinical studies is provided in the following text.

Adamczak et al. were the first to show in 2003 that plasma adiponectin concentration is significantly decreased in essential (primary, idiopathic) hypertension in comparison with normotensive subjects with a similar body mass index.[48] Iwashima et al. demonstrated that hypoadiponectinemia is a risk factor for hypertension independently of insulin resistance and diabetes.[49] Further research showed that there is an inverse correlation of plasma adiponectin concentration with systolic and diastolic blood pressure and also that an inverse correlation exists between plasma adiponectin concentration and future risk of developing hypertension in a prospective five-year study.[50] However, the interrelationship between plasma adiponectin and systolic and diastolic blood pressure is not simple and unambiguous. Contrary to previously mentioned results on the effects of adiponectinemia on hypertension, Murakami et al. did not demonstrate a significant difference in adiponectinemia in three populations of rural Japanese subjects between normotensives and essential hypertension patients without insulin resistance, but only between those with essential hypertension and concurrent insulin resistance.[51] Another study also concluded that there is no significant association of plasma adiponectin concentration and systolic and diastolic blood pressure in a population of over 1300 children aged 9 to 16 years.[52] A similar study including 196 children aged 12 to 18 also did not found any correlation of adiponectin with blood pressure or insulin resistance.[53] A Chinese study which enrolled over 2000 adults found an inverse relationship of adiponectin with diastolic but not systolic blood pressure.[54] As an antithesis to a Chinese prospective study which established a predictive role of adiponectin in developing hypertension Danish Copenhagen City Heart Study did not find such predictive role for adiponectin, but established one for leptin.[50, 55] British Women's Heart and Health Study, a study on a group of 500 older women, did not find an association of adiponectin and systolic or diastolic blood pressure. What is especially interesting is that this association was not present even for the HMW multimer, which is today considered the most biologically active adiponectin multimer.[56] Another interesting study is that by Imatoh et al., which was one of the first prospective studies on the relationship of adiponectin and hypertension.[57] This study found a decreasing trend in systolic and diastolic blood pressure as plasma adiponectin concentration quartile increased, and a logistic regression model adjusted for main risk factors showed that subjects in the lowest quartiles of plasma adiponectin concentration have a 3 to 4 times greater risk for hypertension.

A meta-analysis by Kim et al. is probably the most important study on adiponectin and hypertension. This meta-analysis included 48 studies (of which 5 prospective) with a total of 17 598 subjects (of which 8220 hypertensives).[58] The conclusion of the meta-analysis was that subjects with hypertension have a lower plasma adiponectin concentration compared to normotensive subjects. Also, an increase in adiponectin concentration of 1 mg/L increased the odds of hypertension by 6%. A year after the publication of this study, our group published a paper which did not show a difference in plasma adiponectin concentration between normotensives and hypertensives with normal renal function.[59] Taking into account the heterogeneity of studies included in this meta-analysis and the fact that over a fourth of the studies did not find an association of adiponectin and hypertension, the question arises of whether this association is the same in all populations and stages of hypertension and across the whole cardiometabolic continuum. This is especially interesting when noting that Mallamaci et al. found a positive association of adiponectin and hypertension.[60]

The results of the Dallas Heart Study, which examined the role of adiponectin and hypertension in 1233 initially normotensive subjects from the general United States population, followed up for a median of 7 years, showed that 32% of subjects developed hypertension, and adiponectin levels were associated with a 19% reduction in the risk of incident hypertension independent of body fat distribution.[61]

Adiponectin gene (ADIPOQ) single nucleotide polymorphisms (SNPs) have also been implicated in pathophysiology of hypertension. The relationship between ADIPOQ SNPs and hypertension is especially interesting given that around 30% to 70% of variance in plasma adiponectin concentration has a background in genetic differences.[62] Briefly, one meta-analysis which included 12 studies with 3358 hypertensives and 5121 controls in an evaluation of the association of two ADIPOQ polymorphisms (T45G and G276T) with hypertension risk and 11 studies (with a total of 3053 subjects) in an evaluation of between-genotype changes of adiponectin and/or blood found that mutation in locus G276T was associated with increased plasma adiponectin concentration and blood pressure, especially in hypertensive patients.[63] A recent study by Jhuo et al. which examined the association of ADIPOQ

SNP T94G and resistant hypertension in young-onset patients reported that this SNP was associated with around 2.8 times higher odds for resistant hypertension.[64] An especially interesting hypothesis is that different polymorphisms might predispose to different adiponectin multimer profiles, but, as far as we know, this hypothesis has not yet been confirmed.

CONCLUSIONS

Adiponectin and blood pressure, as well as adiponectin and hypertension, seem to be closely associated. Protective effects and risk-lowering effects of adiponectin are contrary to most other frequently researched adipokines and make adiponectin an interesting research target and a potential future therapeutic target. Well-designed experimental and clinical studies should be conducted evaluating potential mechanisms via which adiponectin might be used as a therapeutic target, most importantly those involving increasing insulin sensitivity and lowering blood pressure which may play an important role in diabetes and hypertension therapy, respectively. Because of the apparent great biological importance of adiponectin, heralded by, among others, high plasma concentration and the association with blood pressure, but also due to the controversial and mutually-contrary results from different studies on differing populations found in the literature, it will be important to assess the association of adiponectin with blood pressure and hypertension in well-designed prospective studies with clearly defined and homogenous populations.

DISCLOSURE

The text is mostly adapted from the Introduction of the doctoral thesis of the author (VI) titled „Association of adiponectin gene polymorphisms with blood pressure in persons with normal kidney function" defended in September 2015 and also includes a review of studies published after this date. Neither this thesis or parts of it have been published previously.

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