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Zhao V. Wang and Philipp E. Scherer

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# Adiponectin, Cardiovascular Function, and Hypertension

Zhao V. Wang, Philipp E. Scherer

Hypertension is a major risk factor for cardiovascular disease, and the latter is the leading cause of morbidity and mortality worldwide. In developed countries, hypertension ranks as the top contributing factor for mortality and third in causing disability-adjusted life years.<sup>1</sup> Hypertension is a polygenic and complex disease with rising prevalence. More than 25% of the adult population is affected by hypertension, and two thirds of those individuals reside in developing countries.<sup>2</sup> Europe shows an even higher prevalence of hypertension than North America.<sup>3</sup> With the present trends, the prevalence of hypertension is predicted to increase to 30%, or  $\approx$ 1.5 billion people, on the globe in the next 20 years.<sup>2</sup> Mechanistically, endothelial dysfunction, increased renin-angiotensin system (RAS) activity, and sympathetic nervous system (SNS) hyperactivation have been considered as important risk factors of hypertension and hint at important events taking place at the interface of the endothelium, kidney, and SNS.

Obesity is a global epidemic in children and adults. In the United States, a steady increase of the prevalence of obesity has been found in all states.<sup>4,5</sup> It is estimated that 65% of the population is overweight, which is judged by body mass index of 25.0 to 29.9, and 30% are obese (body mass index of  $\geq$ 30.0).<sup>6</sup> These numbers have been continuously rising in the past 15 years.<sup>7</sup> The National Health and Nutrition Examination Survey III for  $\approx$ 18 000 adults found that body mass index is an associated risk factor for hypertension independent of age, sex, race, and smoking.<sup>8</sup> A long-term weight/hypertension relationship study showed that weight loss of  $\approx$ 10 kg is associated with a significant decrease of both diastolic and systolic blood pressure.<sup>9</sup> Obesity and hypertension are 2 complex disorders that are closely interrelated, but the precise underlying association remains elusive.

The uncontrolled expansion of adipose tissue is the key feature of obesity. In the past 2 decades, the view of adipose tissue has gone from revolutionary change from inert energy store to the biggest endocrine organ.<sup>10</sup> Adipose tissue secretes leptin, adiponectin, resistin, visfatin, tumor necrosis factor- $\alpha$ , interleukin-6, etc. In the obese state, the secretion of leptin, resistin, tumor necrosis factor- $\alpha$ , and interleukin-6 is increased, and these molecules have been shown to be associated with insulin resistance and the progression of inflammation.<sup>10</sup> The only hormone displaying an opposite trend is adiponectin.

Adiponectin levels have been positively associated with insulin sensitization, glucose use,  $\beta$ -oxidation, and cardiovascular protection.<sup>10,11</sup>

Adiponectin may also be involved in the progression of hypertension. On a high-salt diet, Ohashi et al<sup>12</sup> showed that adiponectin-deficient animals display significantly higher systolic blood pressure compared with wild-type control animals independent of insulin resistance. Reconstitution of adiponectin expression by adenoviral infection restored normal blood pressure. Overexpression of adiponectin can also decrease the systolic blood pressure in genetically obese KKAy mice. The association between adiponectin and hypertension is also evident in clinical studies by showing that hypo adiponectinemia is a risk factor for hypertension independent of insulin resistance and diabetes.<sup>13,14</sup>

Nevertheless, despite the well-established association of adiponectin with metabolic disorders and cardiovascular disease, very few studies address the relationship between adiponectin and hypertension at a mechanistic level.<sup>15–17</sup> Recently, several studies have focused on the effects of adiponectin on the endothelium, kidney, and SNS. Here, we discuss these findings as they relate specifically to adiponectin, whereas the impact of other fat-derived hormones on hypertension is reviewed elsewhere.<sup>18,19</sup>

## Adiponectin: A Complex Secretory Molecule

Exclusively secreted from adipose tissue, adiponectin (also known as Acrp30/adipoQ/apM1/GBP28) is a 30-kDa molecule with 3 defined domains.<sup>20–23</sup> The N terminus contains a hypervariable region, which is commonly used as the antigenic site for species-specific antibody generation. The collagenous stalk containing 22 GXY repeats is followed by the globular domain at the C terminus.<sup>24</sup> Both intracellularly and extracellularly, adiponectin exists in  $\geq$ 3 different higher-order complexes: high molecular weight form (HMW; 12 to 36 mer), low molecular weight form (hexamer), and trimeric form. Numerous studies have shown that the different complexes exert distinct functions, and the ratio of HMW to the other forms serves as an independent predicting factor for metabolic disorders.<sup>25–27</sup> The total level and HMW ratio are decreased in obese patients and obese mouse models.<sup>25,28</sup> This suggests that adiponectin, especially the HMW form, may be involved in obesity-related disorders.

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From the Department of Cell Biology (Z.V.W.), Albert Einstein College of Medicine, Bronx, NY; and the Touchstone Diabetes Center (Z.V.W., P.E.S.), Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas.

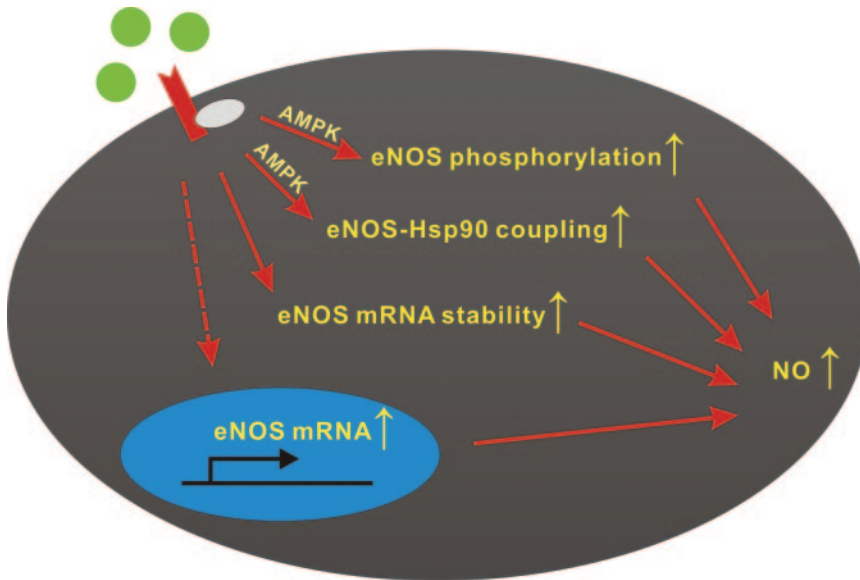
Correspondence to Philipp E. Scherer, Touchstone Diabetes Center, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8549. E-mail Philipp.Scherer@utsouthwestern.edu

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**Figure 1.** Adiponectin stimulates the enzymatic activity of eNOS via multiple mechanisms. Adiponectin exerts its beneficial effects through membrane-bound receptors and adaptor molecules in endothelial cells. Adiponectin increases the stability of eNOS mRNA and half-life, enhances the association of eNOS with Hsp90, and stimulates the phosphorylation of eNOS, which together lead to the increase of NO production. AMPK, the downstream kinase of adiponectin signaling, may play a role in this process. Whether adiponectin directly stimulates the transcription of eNOS mRNA remains to be determined. Solid arrows indicate stimulatory effects and dashed arrows indicate a hypothetical effect that remains to be demonstrated experimentally.

Ten years after the discovery of adiponectin, the receptors have been identified.<sup>29</sup> Yamauchi et al<sup>30</sup> isolated 2 related receptors from human skeletal muscle by expression cloning. These receptors are products of distinct genes but share 67% sequence identity. AdipoR1 is more ubiquitously expressed and enriched in muscle, whereas AdipoR2 is specifically present in liver. Both *in vitro* and *in vivo* experiments have implicated AdipoR1 and AdipoR2 as critical mediators for adiponectin signaling. In skeletal muscle, *in vitro* knock-down experiments show that AdipoR1 mediates peroxisome proliferator-activated receptor (PPAR) activation, AMP kinase (AMPK) activation, glucose uptake, and  $\beta$ -oxidation. In liver, AdipoR1 increases AMPK activity, thereby exerting effects on gluconeogenesis. In parallel, AdipoR2 is involved in the activation of the nuclear receptor PPAR, its downstream target genes mediating  $\beta$ -oxidation, and scavenging of reactive oxygen species. Some intracellular aspects of AdipoR1 signaling have also been elucidated. Using a yeast 2-hybrid approach, Mao et al<sup>31</sup> found that APPL1, an adaptor molecule with a pleckstrin homology domain and a phosphotyrosine binding domain, interacts with the intracellular fragment of AdipoR1. This interaction is phosphotyrosine binding domain dependent but tyrosine phosphorylation independent. The expression of APPL1 is ubiquitous, which may reflect the widespread relevance of adiponectin signaling in various tissues. Alternatively, APPL1 may interact with other receptors as well. *In vitro* studies show that overexpression of APPL1 can enhance adiponectin-stimulated AMPK activation, glucose uptake, and  $\beta$ -oxidation. APPL1 may also be involved in the crosstalk between adiponectin signaling and the insulin signal transduction cascade. This could suggest that these 2 hormones can function synergistically through the same adaptor molecule.

### Adiponectin and Endothelial Dysfunction

The endothelium is not only the inert interface between circulating blood and the vessel wall but is also a major paracrine organ that plays critical roles in controlling vascular tone, inflammation, and smooth muscle cell proliferation. NO

is considered to be the mediator for vasoconstriction and vasodilation, adhesion molecule expression and leukocyte transmigration, and smooth muscle cell growth control under physiological conditions. The endothelial NO synthase (eNOS) activity and NO production can be controlled by the availability of substrates and cofactors, transcription of eNOS, mRNA stability of eNOS, subcellular localization of eNOS protein, enzymatic uncoupling, and posttranslational modifications.<sup>32,33</sup>

Recently, a growing body of evidence shows that hypoadiponectinemia is associated with endothelial dysfunction. By measuring forearm blood flow in response to reactive hyperemia, Ouchi et al<sup>34</sup> found that plasma adiponectin levels are correlated with an endothelial vasodilation response. These results were confirmed in animal studies by showing that adiponectin-deficient mice display impaired endothelium-dependent vasodilation and NO production.<sup>34,35</sup> Similarly, Tan et al<sup>36</sup> showed that hypoadiponectinemia is associated with a lower vasodilation response in diabetic patients. The same group found that adiponectin administration increases NO production in human aortic endothelial cells. By analyzing nitrate/nitrite as NO metabolites, Ohashi et al<sup>12</sup> showed that adiponectin knockout mice had decreased nitrate/nitrite levels compared with wild-type littermates after high-salt feeding. The obesity-associated metabolic syndrome causes a decrease in the expression and secretion of adiponectin. The dysregulated production of adiponectin may be one of the critical factors mediating obesity-associated NO decrease, endothelial dysfunction, and cardiovascular disease.

Adiponectin regulates eNOS enzymatic activity and NO production by several mechanisms (Figure 1). Globular adiponectin stimulates NO production in bovine aortic endothelial cells by 50%.<sup>37</sup> Chen et al<sup>38</sup> found that full-length adiponectin shows similar effects on human umbilical vein endothelial cells. Moreover, they showed that adiponectin stimulates eNOS phosphorylation at Ser1179, which is a modification linked to the increase of eNOS enzymatic activity.<sup>39,40</sup> Interestingly, the phosphorylation stimulated by adiponectin is also phosphatidylinositol 3-kinase dependent, further underlining the parallel mechanism to insulin signal

transduction. However, in contrast to insulin signaling, Akt is not involved in this process. Instead, AMPK may mediate the phosphorylation downstream of adiponectin signaling. Both adiponectin receptors are expressed in human endothelial cells.<sup>36</sup> Knockdown of either receptor decreases the production of NO and phosphorylation of eNOS after adiponectin treatment (full-length and globular) in human umbilical vein endothelial cells.<sup>41</sup> The stimulatory effect of adiponectin on eNOS is also dependent on the adaptor molecule, APPL1. Knockdown of APPL1 significantly decreases the production of NO. In addition, globular adiponectin treatment of human umbilical vein endothelial cells also results in a doubling of eNOS mRNA primarily because of increased mRNA stability, since actinomycin D coincubation did not affect the half life.<sup>37</sup> Whether full-length adiponectin stimulates the transcription of eNOS mRNA remains to be determined.

Moreover, adiponectin treatment can regulate the subcellular localization and enzymatic activity of eNOS. In the resting state, eNOS is associated with caveolin-1 in membrane rafts structures. Agonist stimulation increases calcium release and the dissociation of eNOS. Subsequently, eNOS is phosphorylated by kinases in a heat-shock protein (Hsp)90-mediated process. In this manner, Hsp90 plays a scaffolding role for the continuous activation of eNOS after calcium release.<sup>42</sup> Either globular or full-length adiponectin induces the association between Hsp90 and eNOS, which may facilitate the recruitment of kinases to phosphorylate eNOS.<sup>41,43</sup> Knockdown of APPL1, the adaptor molecule downstream of AdipoR1, results in a decreased association of Hsp90 with eNOS and reduced NO production.

Taken together, these results suggest that adiponectin regulates eNOS enzymatic activity by various mechanisms, including an increase in the mRNA stability, Ser1179 phosphorylation, and an association with the scaffolding molecule Hsp90. As a consequence, elevated plasma adiponectin levels increase NO production and vasodilation and protect against endothelial dysfunction and subsequent cardiovascular disease.

### Adiponectin and the RAS

The RAS is an important regulatory system for blood pressure and extracellular volume control through angiotensin II signaling.<sup>44</sup> However, under pathophysiological conditions, such as obesity-associated metabolic diseases, the overproduction of angiotensin II plays an important role in the development and progression of comorbidities, such as insulin resistance and hypertension.

Mounting evidence from clinical studies shows that inhibition of RAS with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can decrease blood pressure in hypertensive patients.<sup>45</sup> This is consistent with the important role of RAS on blood pressure control. However, recent clinical trials demonstrated that angiotensin II receptor blockers exert beneficial effects beyond blood pressure control, including insulin sensitization, cardiac protection, and antidiabetes.<sup>46,47</sup> Animal studies confirmed the role of angiotensin II signaling in insulin resistance and diabetes. In the genetically insulin-resistant obese Zucker rats, acute treatment with irbesartan (an angiotensin II receptor blocker) for 1 hour significantly increases the glucose uptake and whole

body glucose disposal. During a chronic treatment for 3 weeks, the experimental group displayed higher glucose uptake, improved glucose tolerance, and insulin sensitization.<sup>48</sup> Another study using diet-induced, insulin-resistant animals found similar effects after angiotensin II receptor antagonist treatment.<sup>49</sup> Oral treatment with olmesartan, an angiotensin II receptor blocker, for 3 weeks showed hypertension-independent insulin sensitization effects.

The well-established role of adiponectin as an insulin sensitizer prompted further studies into the relation between angiotensin II receptor blocking and adiponectin production. Growing evidence from clinical studies shows that exposure to angiotensin II receptor blockers increases circulating levels of adiponectin. The angiotensin II receptor blocker-mediated increase of adiponectin may contribute to the additional beneficial effects that these drugs exhibit in hypertensive patients.<sup>50</sup> Watanabe et al<sup>51</sup> found that losartan significantly increases the adiponectin level, whereas amlodipine does not, despite similar blood pressure control. In a study comparing 5 antihypertensive drugs for their impact on adiponectin regulation, angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker administration showed increased adiponectin levels compared with other common antihypertensive drugs.<sup>52</sup>

Several mechanisms have been proposed to explain the stimulatory effect of angiotensin II receptor blocking on circulating adiponectin levels. Angiotensin II inhibits adiponectin production through angiotensin II receptor subtype 1, and angiotensin II receptor blockers may elicit their effect by inhibiting angiotensin II receptor subtype 1 signaling. In rats, angiotensin II infusion for 2 weeks significantly decreases adiponectin circulating levels.<sup>49</sup> Neither an antagonist nor an agonist of angiotensin II receptor subtype 2 treatment has any effect on the suppression of adiponectin by angiotensin II. Interestingly, the decrease of adiponectin by angiotensin II infusion occurs before the blood pressure increase. To elucidate the role of adiponectin in angiotensin II-induced hypertension, further studies using adiponectin knockout animals with angiotensin II infusion will be required.

Angiotensin II infusion is associated with increased generation of reactive oxygen species,<sup>53</sup> which may be one of the underlying reasons for the suppression of adiponectin production, because hydrogen peroxide has been shown to inhibit adiponectin expression.<sup>54</sup> Interestingly, the adiponectin mRNA levels during angiotensin II infusion in rats do not change, which points to the possible role of posttranslational regulation. The assembly and secretion of adiponectin complexes are dependent on the endoplasmic reticulum redox potential and chaperone activity.<sup>28</sup> Increased production of reactive oxygen species may affect the folding and assembly of adiponectin through the posttranslational process. Again, elucidation of the mechanism of angiotensin II-mediated effects on adiponectin secretion represents a very exciting area of research and will involve the measurements of intracellular levels of adiponectin and the analysis of its complex distribution.

Angiotensin II receptor blockers may increase adiponectin production directly by activating the nuclear receptor PPAR $\gamma$ . In 2004, 2 pioneering articles demonstrated that

some angiotensin II receptor blockers act as partial PPAR $\gamma$  agonists *in vitro* and *in vivo*.<sup>55,56</sup> Both groups studied the role of telmisartan on PPAR $\gamma$  activation and showed that telmisartan increases PPAR $\gamma$  activity by  $\approx$ 30% to 50% relative to a full agonist. Telmisartan also induces 3T3-L1 adipocyte differentiation and PPAR $\gamma$ -mediated target gene expression, including aP2 and CD36. Telmisartan treatment significantly improves insulin sensitivity in a diet-induced insulin resistance rat model.<sup>55</sup> PPAR $\gamma$  is critically involved in adiponectin gene expression.<sup>57,58</sup> The reported PPAR $\gamma$  activation may, therefore, be the link between angiotensin II receptor blocker treatment and adiponectin induction.

This hypothesis is substantiated by *in vitro* and *in vivo* assays. In 3T3-L1 adipocytes, irbesartan treatment increases the protein level of adiponectin.<sup>59</sup> However, a PPAR $\gamma$ -selective antagonist (GW9662) potently inhibits the stimulatory effect of irbesartan on adiponectin secretion, which points to the role of PPAR $\gamma$  activation in this process. The stimulatory role of irbesartan may be mediated through angiotensin II receptor subtype 2 activation or direct PPAR $\gamma$  activation as proposed by Kintscher and Unger.<sup>45</sup>

Interestingly, the increase of adiponectin by irbesartan is at the posttranscriptional level and may be because of a decrease in intracellular adiponectin degradation, an important factor determining intracellular adiponectin levels. In parallel, the treatment may improve the rate of secretion through PPAR $\gamma$ . Full PPAR $\gamma$  agonists not only act at the transcriptional level but have also been shown to activate critical chaperones in the secretory pathway and to increase the release of the HMW form.<sup>28</sup> It is likely that partial agonists such as angiotensin II receptor blockers act in a similar way. In light of the complete absence of a transcriptional effect on the adiponectin gene under these conditions, it will be interesting to take advantage of this phenomenon and to identify the target genes under those circumstances.

*In vivo* experiments in genetically obese Zucker rats confirmed the original observations in diet-induced insulin-resistant rats, further emphasizing the important role of PPAR $\gamma$ -mediated adiponectin induction in insulin sensitization of angiotensin II receptor blockers.<sup>55,59</sup> Moreover, the stimulatory effect of angiotensin II receptor blockers on PPAR $\gamma$  was examined in a cell-free system, highlighting the direct binding of the blockers with PPAR $\gamma$ .<sup>60</sup>

Collectively, angiotensin II receptor blockers may perform multiple functions including antihypertensive effects by inhibiting the angiotensin II receptor subtype 1 and angiotensin II signaling and antidiabetic effects by activating PPAR $\gamma$  nuclear receptor and concomitant adiponectin production. Also, adiponectin induction may also facilitate the antihypertensive effects of these agents by ameliorating endothelial dysfunction (as discussed earlier) and modulating SNS activity (see below).

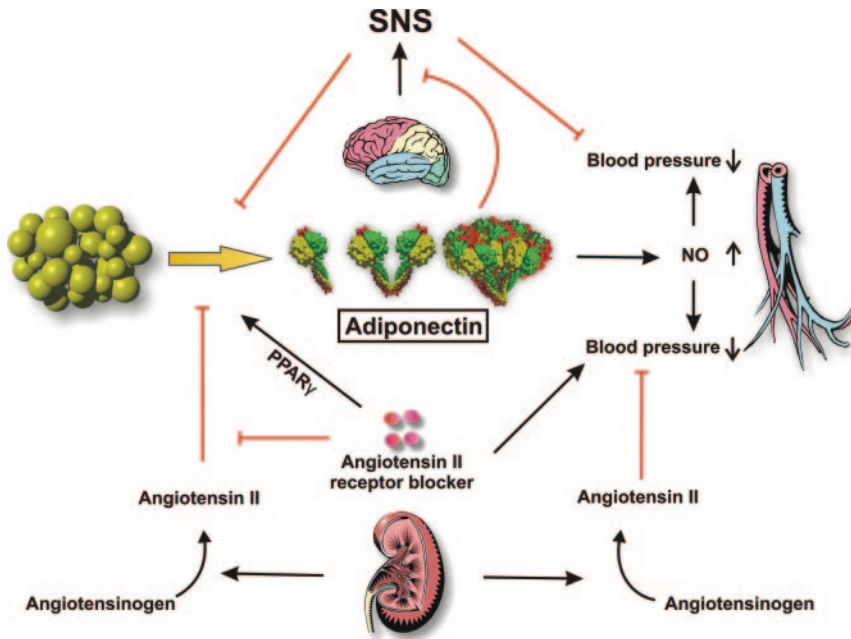
### Adiponectin and the SNS

The SNS is an autonomous regulatory system responsive to physiological stress situations. SNS activity was associated with increased body mass index independently through measurements of urinary norepinephrine in the Normative Ageing Study.<sup>61</sup> The disproportionate activation of SNS in

the obese state is proposed to play important roles in obesity-associated metabolic dysfunction.<sup>62</sup> The hyperactivation of SNS increases heart rate and peripheral vascular resistance and eventually causes hypertension. Local and systemic approaches have been used to assess SNS activity, including measurement of systemic norepinephrine levels, analysis of local or systemic sympathetic spillover, and recording of sympathetic traffic in target organs.<sup>63</sup> With these methods, SNS activity has been shown unequivocally to correlate with the hypertensive state, and the SNS is, therefore, intricately involved with the initiation, maintenance, and progression of hypertension.<sup>64</sup>

More recently, SNS overdrive has been shown to suppress adiponectin expression. To study the association between SNS activation and adiponectin regulation, Imai et al<sup>65</sup> used the cold stimulation model. They found that 24 hours of cold exposure (to 4°C) inhibits the transcription and secretion of adiponectin in mice. This reversible effect depends on SNS activation, because the treatment with norepinephrine synthesis inhibitors attenuated the suppression.  $\beta$ -Adrenergic receptor antagonist treatment releases this suppression, suggesting a local effect of sympathetic neurotransmitter signaling in adipose tissue. Although the  $\beta$ 3-adrenergic receptor is the main form expressed in adipose tissues, an indirect contribution from  $\beta$ 1/2-adrenergic receptors cannot be ruled out. The *in vivo* effect of  $\beta$ -blockers on adiponectin expression was further confirmed by an *in vitro* study. In 3T3-L1 adipocytes,  $\beta$ 3-adrenergic receptor agonist treatment dose-dependently decreases the synthesis of adiponectin mRNA.<sup>66</sup> Pretreatment with  $\beta$ 3-adrenergic receptor antagonist releases the inhibition. In hypertensive patients, 6 months of treatment with SNS blockers improved blood pressure control and increased circulating adiponectin by 30%, independent of insulin resistance.<sup>67</sup>

Because adiponectin has been found in cerebrospinal fluid and administration of adiponectin centrally affects energy homeostasis, it is tempting to speculate that adiponectin may be involved in the regulation of SNS activity from the brain.<sup>68,69</sup> Indeed, recent studies suggest that adiponectin affects SNS activity via central regulation.<sup>70</sup> By intravenous injection in rats, Tanida et al<sup>70</sup> found that adiponectin dose-dependently decreases blood pressure and sympathetic nerve activity. When they injected adiponectin directly into the lateral cerebral ventricle, they found similar effects using a 10-fold lower dose of adiponectin. By creating an electrolytic lesion in the brain, they showed that the suppressive effect was lost when the suprachiasmatic nucleus was damaged. This acute effect of adiponectin treatment on SNS activation needs to be confirmed by a long-term study with adiponectin-deficient animals. The action of adiponectin on SNS activation in the brain may be indirect and mediated via an interaction with leptin signaling. Recently, it was demonstrated that adiponectin reverses leptin-mediated suppression of food intake in the hypothalamus.<sup>71</sup> Considering the important role of leptin on SNS activation and blood pressure control, it is tempting to suggest that adiponectin may regulate SNS activity by inhibiting leptin action in the brain.<sup>19</sup>



**Figure 2.** The role of adiponectin in hypertension. Adipose tissue secretes  $\geq 3$  forms of adiponectin into circulation. Adiponectin stimulates the production of NO, and NO is involved in the regulation of blood pressure. Renin secreted from the kidney mediates the processing of angiotensinogen to produce angiotensin II. Angiotensin II plays an inhibitory role in adiponectin production. Angiotensin II receptor blockers display pleiotropic effects on blood pressure control and antidiabetic through receptor blocking and adiponectin stimulation. SNS overdrive increases blood pressure and also inhibits the production of adiponectin. Conversely, adiponectin can inhibit the activation of SNS through central actions. Black arrows indicate activation and red lines indicate inhibition.

### Conclusions and Perspectives

We are witnessing a continuous rise in the prevalence of obesity and hypertension.<sup>72</sup> Both disorders are predominant risk factors for cardiovascular disease, and the latter is the leading cause of morbidity and mortality worldwide. Obesity may induce hypertension through multiple mechanisms, including endothelial dysfunction, RAS hyperactivation, SNS overdrive, and renal-pressure natriuresis impairment.<sup>73</sup>

A large body of evidence implicates decreased adiponectin levels as a mediator of some of these effects. As such, the obesity-related downregulation of adiponectin may be the critical link to obesity-associated hypertension. Evidence from clinical studies demonstrates that antihypertensive drugs may have pleiotropic effects, including blood pressure control, antidiabetic, and cardioprotective. Adiponectin, exclusively secreted from adipose tissue, has been postulated to decrease the risk for insulin resistance, inflammation, type 2 diabetes, and cardiovascular disease. Adiponectin is increased after treatment with a subset of antihypertensive drugs and may partially mediate these beneficial effects.

Adiponectin has also been shown to mediate the beneficial effects of a major class of antidiabetic drugs, the thiazolidinediones, of which the primary target is PPAR $\gamma$ . The bifunctional angiotensin II receptor blockers also act as partial PPAR $\gamma$  agonists and may represent the next generation of pharmacological drugs to treat comorbidities associated with the metabolic disease without the recent concerns raised for one of the thiazolidinediones regarding their cardiovascular safety.<sup>74</sup> With the increasing understanding of the mechanisms for hypertension, we start to appreciate that a number of adipocyte-derived products, in particular, adiponectin, may be important contributors to the pathogenesis of hypertension (Figure 2).

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### Disclosures

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