Journal of the Academic Society for Quality of Life (JAS4QoL)

2018 Vol. 5(1) 1:1-9

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Citation: SATTAR, M. Z. A.; AFZAL, S. Regulation of Adiponectin Receptors Through PPAR-gamma Agonists in Systemic and Renal Hemodynamics in Diabetic Rats *JAS4QoL* **2018,** *5(1) 1*:1-9.
Online: http://as4qol.org/?p=2598

Received Date: 2019/04/04 Accepted Date: 2019/04/04 Published: 2019/04/18

JAS4QoL

Wisdom Note

Regulation of Adiponectin Receptors Through PPAR-gamma Agonists in Systemic and Renal Hemodynamics in Diabetic Rats

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1. Adiponectin

The adipose tissue as an object of study has dynamically entered the field of cardiology over the last decade. The communication between adipose tissue and other biological systems is accomplished through the expression of a large number of bioactive mediators, called adipokine or adipocytokines (Antoniades et al. 2009). The main adipocytokines are adiponectin (ADN), leptin, resistin, interleukin (IL-6), (Ryo et al. 2004), tumor necrosis factor-alpha (TNF-a) and the plasminogen activator-1 inhibitor (PAI-1). Adiponectin is distinguished by being not only the most abundant product of fat, but also for being one of the major involved in regulating various mechanisms in human body (Siasos, 2012). Adiponectin is a secreted protein consisting of 247 amino acids, produced exclusively by adipocytes. Adiponectin was independently identified by four laboratories; hence, the multiple names. Lodish laboratory first discovered adiponectin in 1995 as a protein named "Adipocyte Complement Related Protein of 30 kDa" (ACRP30) (Scherer et al. 1995).

The adiponectin gene is located on chromosome 3q27, with three monomers of adiponectin form a trimer (Scherer et al. 1995). Adiponectin is produced by adipose tissue, mainly synthesized in white adipose tissue while lower concentrations are produced in brown adipose tissue (Kazumi et al. 2004). The physiological concentrations of adiponectin in plasma vary

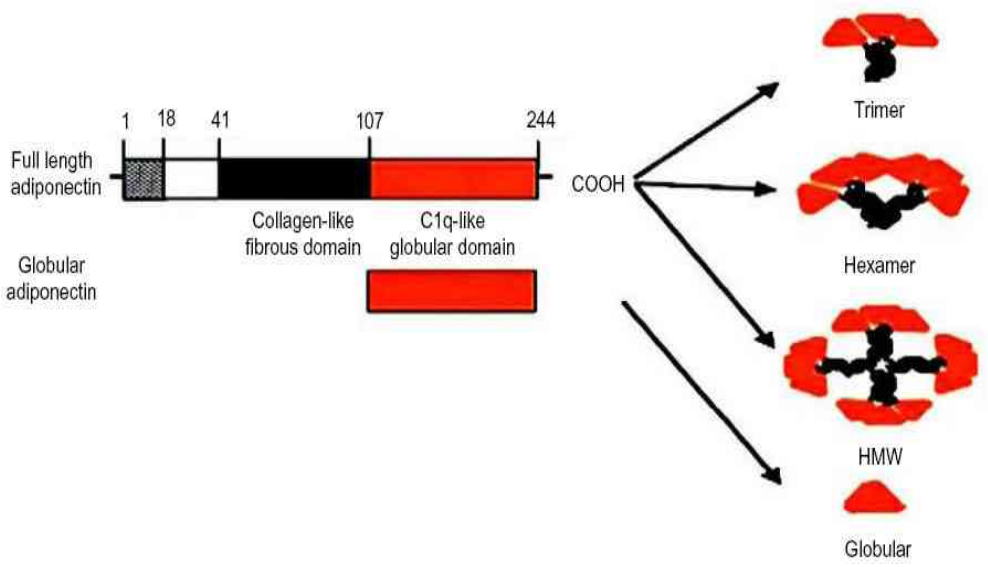

Figure 1: Domains and structure of adiponectin. (Adapted from Ebrahimi et al. 2015)

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Available online at
http://as4qol.org/?p=2598

Received: 2019/04/04
Accepted: 2019/04/04
Published: 2019/04/18

from 5 to 30μg/ml, accounting for about 0.01% of total plasma proteins (Maeda et al. 1996).

2. Interaction between Adiponectin and Peroxisome Proliferator Activated receptors

Adiponectin exerts its actions through two receptors, which are recognized and named AdipoR1 and AdipoR2 (Yamauchi et al. 2007). These receptors are membrane proteins and are structurally and functionally different from G proteins. AdipoR1 is expressed mainly in skeletal muscle and has a high affinity for binding to the globular adiponectin, whereas the AdipoR2, is primarily expressed in the liver and binds equally with the globular/ full forms of adiponectin (Yamauchi et al. 2007). Adiponectin receptors are markedly expressed in pancreatic β-cells, macrophages and atherosclerotic lesions in the brain (Chinetti et al. 2004). AdipoR1/R2 in muscle is inversely associated with circulating adiponectin concentrations (Blüher et al. 2007). The pharmacological effect of globular fragment of adiponectin appears to be stimulation of β-oxidation in skeletal muscle, whereas full-length adiponectin decreases hepatic glucose output (Schraw et al. 2008). The binding of adiponectin to its receptors increases AMP-activated protein kinase (AMPK) and the activity of PPAR ligands, the oxidation of fatty acids, and glucose uptake (Yamauchi et al. 2007) AdipoR1 is involved in the AMPK signaling pathway, while AdipoR2 is more closely associated with the peroxisome proliferator activator receptor (PPAR) pathway (Yamauchi et al. 2007).

Peroxisome proliferator–activated receptors (PPARs) are a subgroup of a super family of receptors, which are closely related to thyroid hormone (Ríos-Vázquez et al. 2006). They are present in adipose tissue, vascular smooth cells, macrophages, vascular endothelial and renal glomerular cells (Sarafidis and Lasaridis, 2006), skeletal muscle and at high levels in adipose tissue (Norris et al. 2003), endothelial cells, in macrophages and in vascular walls (Tjokroprawiro, 2006). Three PPAR isoforms have been recognized so far, PPAR-α, PPAR-β and PPAR-γ (Abbott et al. 2009). The master regulator of adipogenesis, PPAR-γ (expressed in adipose tissue), serves as a factor in the regulation and stimulation of insulin sensitivity and functions through activation of its ligands such as thiazolidinediones (TZDs) as a transcriptional regulator of genes involved in glucose and lipid metabolism (Picard et al. 2002, Evans et al. 2004). Activation of PPAR-γ promotes the transcription of adiponectin and AdipoR1 (Choi et al. 2005), whereas activation of adiponectin receptors has potential in the treatment of endothelial dysfunction related to diabetes, obesity, and atherosclerosis (Zhang et al. 2009). Activation of PPAR-γ increases and up-regulates adiponectin plasma levels in animals and humans (Fasshauer et al. 2004) by stimulating and enhancing expression of proteins involved in adiponectin assembly, such as endoplasmic reticulum oxidoreductin-1 protein (Erol-Lα), and in adiponectin secretions such as disulfide-bond A oxidoreductase-like protein (DsbA-L), normally present in the kidney (Liu et al. 2008, Qiang et al. 2007).

3. Adiponectin and thiazolidinedione

The thiazolidinediones (TZDs) are a new class of orally active anti-hyperglycemic agents, two of which, rosiglitazone and pioglitazone, are approved for clinical use in the management of T2DM in a large number of countries. In addition, to improve glycaemic control, dyslipidaemia, blood pressure and micro albuminuria, TZDs act to suppress the subclinical vascular inflammation that underlies atherosclerosis through their effects on numerous cytokines and adipokines (Schernthaner, 2009). The primary molecular target mediating the insulin-sensitizing actions of the TZDs is PPAR-gamma (PPAR-γ). Ligands to PPAR-γ are considered insulin sensitizers because they enhance insulin mediated glucose uptake into skeletal muscle (Olefsky, 2000). It is also evident that TZDs manipulate plasma adiponectin (ADN) levels by increasing glucose clearance in the skeletal muscle by restraining gluconeogenesis in the liver, and improving insulin sensitivity (Yamauchi et al. 2001, Combs et al. 2002, Hirose et al. 2002). On the other hand, independently of adiponectin, TZDs decrease adipocyte size, serum FFA levels, and expression of TNF-α and resistin, thus contributing to the amelioration of insulin resistance in skeletal muscle (Kadowaki et al. 2006). Pioglitazone (TZDs) derivative acts as a full agonist for PPAR-γ (Kintscher and Unger 2005) and is used therapeutically to improve insulin resistance, resulting in an increased number of small adipocytes, which are responsive to insulin (Evans et al. 2004).

4. Adiponectin and the renin angiotensin aldosterone system (RAAS)

Antihypertensive drugs, such as angiotensin receptor blockers (ARBs) are reported to improve insulin sensitivity (Miyazaki et al. 2005). Potential mechanisms of the RAAS blocking agents being able to

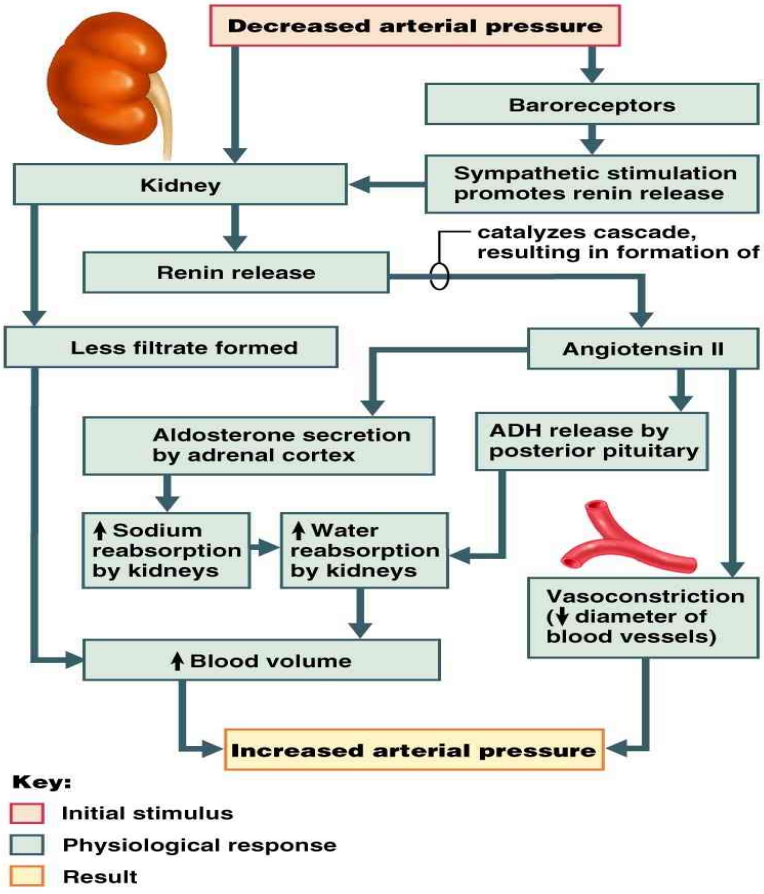

Figure 2: Role of kidney and renin-angiotensin-aldosterone system in blood pressure control. (Adapted from Pearson Education, Inc Publishing, 2006).

affect adiponectin levels include direct effects on glucose insulin-stimulated glucose uptake, and induction of PPAR-γ activity promoting differentiation in adipocytes (Schupp et al. 2004). However, clinical trials have demonstrated that ARBs exert beneficial effects beyond blood pressure control, including insulin sensitization, cardiac protection, and diabetes control (Julius et al. 2004). The ARBs mediate the increase of adiponectin which may contribute to the additional beneficial effects that these drugs exhibit in hypertensive patients (Furuhashi et al. 2003). One of the mechanisms underlying this effect may be an increase in adiponectin levels and insulin sensitivity (Koh et al. 2006). Dose-response agonism of PPAR-γ occurs with the full agonist (pioglitazone), whereas, ARBs act as partial agonists for PPAR-γ, having a different order of potency, i.e, (irbesartan>losartan) (Schuppe et al. 2004). Moreover, induction of hypertension with ANG II leads to a decrease in plasma adiponectin concentrations associated with blood pressure elevation (Ran et al. 2006). The reported PPAR-γ activation may, therefore, be a link between ARBs therapy and adiponectin induction. Moreover, long-term ARBs therapy is associated with significant reduction in pulse wave velocity, and with an increase in adiponectin serum levels. Therefore, long-term treatment of essential hypertension with ARBs inhibits the progression of arterial stiffness by increasing adiponectin independently of blood pressure reduction (Vlachopoulos et al. 2006). Furthermore, earlier studies have indicated decreased plasma adiponectin concentrations in hypertensive patients with renal dysfunction (Mallamaci et al. 2002, Adamczak et al. 2003).

5. Modulation of exogenous administration of adiponectin, and PPAR-γ agonists on the adrenergic control of systemic and renal haemodynamics

A large number of studies have provided evidence that experimentally induced diabetes and altered renal function plays a key role in the pathogenesis and maintenance of essential hypertension and renal induced secondary hypertension (Pinho et al. 2007). Pioglitazone, a (TZD) derivative, acts as a full PPAR-γ agonist (Yki-Jarvinen. 2004) and is used therapeutically to improve insulin resistance, increasing the number of small adipocytes, which are more responsive to insulin (Evans et al. 2004). In the last decade, there are findings that ARBs (e.g. irbesartan) activate PPAR-γ as a partial PPAR-γ agonist, and therefore, at post-transcriptional level induce adiponectin expression, which self-regulate their AT1R blocking properties (Clasen et al. 2005).

6. Direct and adiponectin-mediated mechanism of action of TZDs and ARBs.

In addition, α1-adrenoceptor mediated vasoconstriction has been studied in different vascular beds in type2 diabetic rat models (Yoshida et al. 2003), while the functional contribution of α1-adrenoceptor subtypes to renal haemodynamics in normal and pathophysiological conditions has been explored (Abdul Sattar. 1994). Collectively this evidence suggests that the vascular AT1 receptors synergistically interact with α1-adrenoceptors. Interestingly, studies from our laboratory have indicated that the blockade of endogenous Ang II by AT1 blockers alters vascular reactivity to exogenous noradrenaline (Abdulla et al. 2009). In addition, the interaction between Ang II and adrenergic neurotransmission play an important

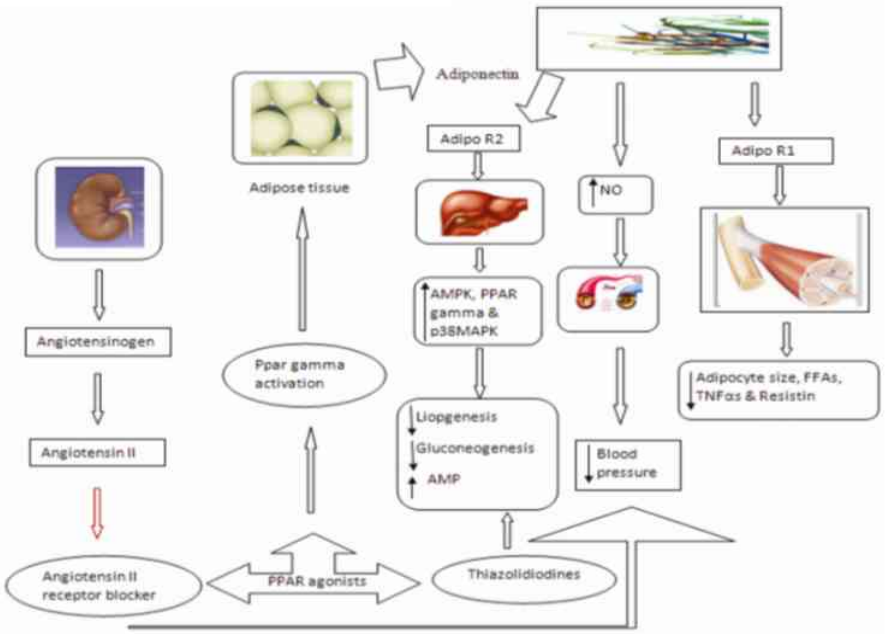

Figure 3: The role of adiponectin through PPAR-γ in diabetes and hypertension.

role in modulation of the vascular reactivity in pathological states in rat (Abdulla et al. 2009).

SNS and RAAS contribute to the development of hypertension in diabetic rats. These systems are non-independent, but mutually interact with each other in performing their regulatory functions. The reports from preceding discussion have strengthened the view that increased production of ROS and oxidative stress is an inevitable element in hypertension, diabetes, and impaired and defective vasodilatation in systemic and renal vasculature.

7. Adiponectin and diabetic complications

Diabetes mellitus (DM) and hypertension have received increasing attention because of rising epidemics of these throughout the world. Diabetes is characterized by fasting hyperglycemia, polydipsia, glycosuria and polyuria, whereas diabetic patients are susceptible to cardiovascular diseases such as hypertension, atherosclerosis, and congestive heart failure (Stratmann and Tschoepe, 2011). Moreover, hypertension is frequently accompanied by type2 diabetes; hence, many hypertensive patients receive a combination therapy of antihypertensive and antidiabetic drugs. The cardiovascular system works in conjugation with the kidney, and the endocrine and nervous systems in order to maintain the blood pressure (Germann et al. 2002). These homeostatic functions are disturbed in damaged kidneys due to pathological states such as diabetes and hypertension (Sima et al. 2004). It has been reported that in the presence of hypertension the induction of diabetes with streptozotocin (STZ) results in accelerated renal injury (Tesch and Allen, 2007). Despite use of antihypertensives, reduction in the blood pressure helps to prevent the diabetic cardiovascular and renal complications (Konzem et al. 2002). Several mechanisms such as enhanced RAAS activity (Ogihara et al. 2002), increased formation of reactive oxygen species (Sowers 2004b), and aldosterone induced increased SNS activity (Lago et al. 2007) have been proposed as areas to investigate with regard to the pathophysiology of hypertension in association with diabetes. Therefore, the interaction between endothelial dysfunction and insulin resistance has become quite well understood from clinical studies (Steinberg and Baron 2002), and increased oxidative stress is closely linked with diabetes and its complications (Wolff 1993).

Oxidative stress has been demonstrated to be a factor in hypertension and diabetes. It has been suggested that AT1-antagonists mediate their effects partially by decreasing the oxidative stress (Yoshida et al. 2003). Furthermore, earlier studies have shown that oxidative stress-induced damage, has a significant pressure on the regulation of gene expression of adiponectin (Kamigaki et al. 2006) in the vascular endothelium and myocardium by inhibition of inducible nitric-oxide synthase and NADPH oxidate protein expression and resultant oxidative/nitrative stress (Luo et al., 2005). Earlier epidemiological studies together with different animal models have suggested an association between adiponectin and oxidative

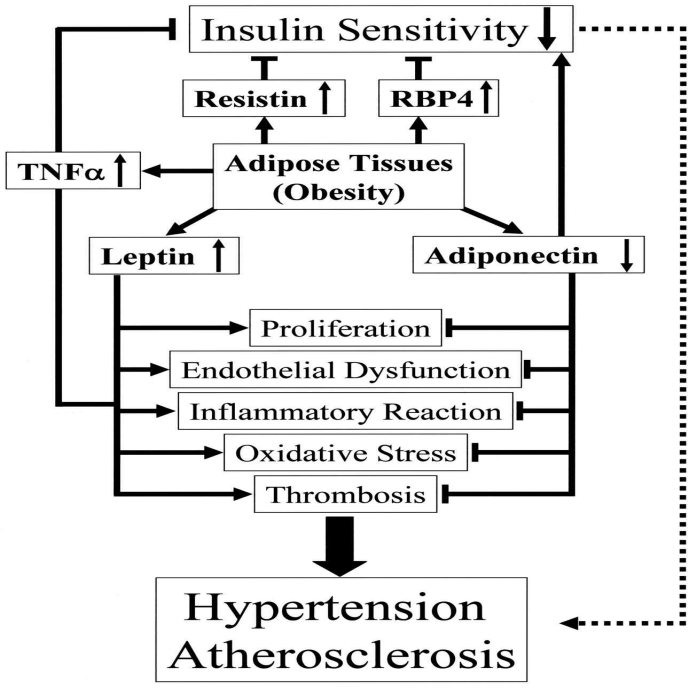

Figure 4: Adipocytokines interact in a complex way to regulate vascular function and ultimately the development of cardiovascular diseases. (Adapted from Katagiri et al. 2007). RBP4 = retinol-binding protein, TNFα = tumor necrosis factor alpha

stress, whereby decreased circulating adiponectin levels and increased oxidative stress, are closely linked to each other. It is, noteworthy, that oxidative stress negatively modulates adiponectin gene expression (Hattori et al. 2005), whereas, adiponectin also adjusts oxidative stress, leading to anti-diabetic and anti-arteriosclerotic effects (Nakanishi et al. 2005). Insulin resistance and hypertension are suggested to be responsible for endothelial dysfunction and thereby participate in the elevated blood pressure and altered oxidative potential in diabetic model. Therefore, treatment with PPAR-γ ligand is considered useful for insulin-resistant patients with complications such as hypertension and vascular disorders (Takatori et al. 2013).

Previous studies have focused on the possible mechanisms leading to high blood pressure and deteriorating anti-oxidative potential for the combined state of hypertension and diabetes. However, few in vivo studies have explored the vascular activity and the mechanisms that may trigger the alteration in systemic and renal haemodynamics in this model. A recent study done by Afzal et al., 2016, investigated endogenous levels of adiponectin and explored the antihypertensive, anti-diabetic, and antioxidant potential of adiponectin in combination with PPAR-γ agonists (irbesartan and pioglitazone), to evaluate the pathophysiological role and potential implications of adiponectin for the combined state of hypertension and diabetes. This study is unique in that it investigated the impact of exogenous administration of adiponectin on the existence of interactive relationship between PPAR-γ, RAAS and SNS, which may play a role in the control of renal and systemic vascular responsiveness to adrenergic agonists and angiotensin II and were in any way dependent on circulating levels of adiponectin. The use of blood pressure lowering and anti-diabetic agents in this study were capable of enhancing antioxidant potential through NO dependent or independent mechanism and were therefore found to have beneficial effects in diabetic hypertensive model. Moreover, in this study the renoprotective potential of adiponectin in combination with partial and full PPAR-γ agonists was also investigated. The data from this study adds to our understanding of the combined treatment protocol of adiponectin with the full but not partial PPAR-γ agonist in humans. Studying the renal and systemic vascular responsiveness of Ang II and adrenergic agonists to adiponectin agonists and its receptors may be useful tool to exploring the mechanism of high blood pressure in diabetic model. However, further molecular work necessary to support findings in this domain.

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