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Review

Angiotensin II and the development of insulin resistance: Implications for diabetes

J. Alberto Olivares-Reyes*, Araceli Arellano-Plancarte, J. Ramon Castillo-Hernandez

Laboratory of Signal Transduction, Department of Biochemistry, Center for Research and Advanced Studies of the National Polytechnic Institute, CINVESTAV-IPN, A.P. 14-740, Mexico, 07360, D.F., Mexico

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ABSTRACT

Angiotensin II (Ang II), the major effector hormone of the renin–angiotensin system (RAS), has an important role in the regulation of vascular and renal homeostasis. Clinical and pharmacological studies have recently shown that Ang II is a critical promoter of insulin resistance and diabetes mellitus type 2. Ang II exerts its actions on insulin-sensitive tissues such as liver, muscle and adipose tissue where it has effects on the insulin receptor (IR), insulin receptor substrate (IRS) proteins and the downstream effectors PI3K, Akt and GLUT4. The molecular mechanisms involved have not been completely identified, but the role of serine/threonine phosphorylation of the IR and IRS-1 proteins in desensitization of insulin action has been well established. The purpose of this review is to highlight recent advances in the understanding of Ang II actions which lead to the development of insulin resistance and its implications for diabetes.

Contents

* Corresponding author at: Laboratory of Signal Transduction, Department of Biochemistry, CINVESTAV-IPN, Av. IPN 2508, Col. San Pedro Zacatenco, Mexico, D.F. CP 07360, Mexico. Tel.: +52 55 5747 3951; fax: +52 55 5747 3391.
E-mail address: jolivare@cinvestav.mx (J.A. Olivares-Reyes).

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1. Introduction

The renin–angiotensin system (RAS), in particular angiotensin II (Ang II), plays an important role in cardiovascular homeostasis by regulating vascular tone, fluid and electrolyte balance and the sympathetic nervous system (Hunyady and Catt, 2006; Jackson, 2001). Given the importance of RAS in regulating cardiovascular and renal systems, its deregulation has been implicated in a number of major cardiovascular diseases, including endothelial dysfunction, atherosclerosis, hypertension, renal disease, stroke, myocardial infarction and congestive heart failure (Carey and Siragy, 2003). The development of specific inhibitors of critical enzymes of the RAS, such as angiotensin I-converting enzyme (ACE) inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) have also shown the involvement of this system in several others pathologies such as different types of cancer (e.g. prostate, pancreatic, breast and lung cancer) and metabolic diseases (e.g. obesity and type 2 diabetes mellitus) (Ager et al., 2008; Hunyady and Catt, 2006).

Type 2 diabetes mellitus (DM2) (formerly called non-insulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes) represents one of the most prominent metabolic disorders, affecting millions of people worldwide. DM2 is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia and its frequent association with hypertension, nephropathy, and cardiovascular disease has implicated the RAS as an important key factor in the initiation and progression of these disorders (Giacchetti et al., 2005; Savoia et al., 2006). Interestingly, several lines of evidence have suggested that RAS impairs insulin sensitivity (Giacchetti et al., 2005; Liu, 2007; Henriksen, 2007), whereas hyperinsulinemia and insulin resistance promotes the development of cardiovascular disorders by upregulating the number and activity of Ang II receptors (Nickenig et al., 1998; Samuelsson et al., 2006; Banday et al., 2005), indicating a close relationship between RAS, insulin resistance and DM2.

It has been demonstrated that inhibition of RAS (by ACE-I and ARBs) prevents the development of DM2 (Stump et al., 2006; Yusuf et al., 2000). For instance, clinical trials have shown that patients with cardiovascular risk or diabetes treated with an ACE-I such as ramipril, enalapril or perindopril showed an important reduction in the incidence of diabetes compared with placebo-treated patients (Yusuf et al., 2000; The SOLVD Investigators, 1991; Marre and Leye, 2007). ARBs also reduce the incidence of diabetes development and improve insulin sensitivity in clinical and experimental studies (Henriksen, 2007; Henriksen et al., 2001; Sharma and Engeli, 2006). Interestingly, the above observations appeared to be independent of the hypotensive action of RAS blockers, suggesting that Ang II, the main effector of RAS, may have the ability to directly inhibit insulin action; however, the exact mechanisms for the Ang II-induced insulin resistance remain largely unknown. In this context, several reports have indicated that infusion of Ang II can lead to insulin resistance and consequently to an increase of the plasma level of insulin (hyperinsulinemia), whereas the administration of ARBs and ACE-I significantly improve insulin sensitivity in hypertensive patients (Kudoh and Matsuki, 2000; Henriksen, 2007; Henriksen et al., 2001). This review focuses on the role of Ang II, in the development of insulin resistance and its implication for diabetes.

2. Insulin

2.1. Molecular mechanisms of insulin signaling

Insulin is a 51-amino acid peptide hormone that is synthesized and secreted by pancreatic β-cells in response to elevated levels of glucose in the blood, controlling critical energy functions such as glucose, lipid and protein metabolism. The biological actions of insulin are mediated by specific cell surface receptors with intrinsic tyrosine kinase activity. Activation of the insulin receptor (IR) phosphorylates intracellular substrates that include IR substrate (IRS) family members (IRS-1–IRS-4), Shc and JAK-2, which, in turn, serve as docking proteins for downstream signaling molecules, which are able to activate different signaling pathways (Myers and White, 2002; Taniguchi et al., 2006). Two major signaling pathways are activated in response to insulin: the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. The MAPK pathway regulates gene expression and cell growth, whereas the PI3K/Akt pathway is responsible for most of the metabolic actions of insulin (Taniguchi et al., 2006; Myers and White, 2002). Activation of PI3K is initiated when IRS proteins are phosphorylated on multiple tyrosine (Tyr) residues by the activated IR. Following Tyr phosphorylation, IRS proteins act as docking proteins for several Src homology 2 (SH2) domain-containing molecules, including PI3K. The interaction between the IRS proteins and PI3K occurs through the p85 regulatory subunit of the enzyme and results in an increase in catalytic activity of the p110 subunit. PI3K is essential for many insulin-induced metabolic processes, including stimulation of glucose transport, and of glycogen and protein synthesis, mainly through Akt activation. Akt serves as a multifaceted intermediary protein by propagating IR signaling to diverse downstream biological effectors (Fig. 1) (Sale and Sale, 2008; Saltiel and Kahn, 2001).

2.2. Regulation of insulin signaling

Given the importance of insulin in the regulation of metabolic and growth-promoting functions, its actions are highly regulated by autoregulation (homologous desensitization), whereby downstream enzymes inhibit crucial upstream components, mainly the IR and IRS proteins. Alternatively, signals from apparently unrelated pathways can inhibit insulin signaling (heterologous desensitization). These regulatory mechanisms define the duration and extent of insulin signaling. The IR and the IRS proteins undergo serine/threonine (Ser/Thr) phosphorylation, which may attenuate signaling by decreasing insulin-stimulated Tyr phosphorylation of both proteins (Gual et al., 2005; Boura-Halfon and Zick, 2008). This mechanism represents a key step in the feedback control process of insulin signaling. Interestingly, many of the Ser/Thr kinases involved in the negative modulation of IRS are downstream effectors of PI3K, such as atypical protein kinase C (aPKC) ζ, mTOR and S6K1 (Hiratani et al., 2005; Ravichandran et al., 2001). Conversely, regulation of IR activity is mostly associated to Ser/Thr phosphorylation by PKC, receptor internalization and receptor dephosphorylation by specific Tyr-phosphatases (Youngren, 2007). Interestingly, it is becoming apparent that inducers of insulin resistance such as tumor necrosis factor-α (TNF-α), free fatty acids (FFAs), Ang II and cellular stress, make use of similar mechanisms by activating a set of IRS Ser/Thr kinases that phosphorylate the IRS proteins and inhibit their function (Herschkovitz et al., 2007; Austin et al., 2008; Carvalheira et al., 2003).

2.3. Insulin resistance

Insulin resistance is a common pathological state in which target cells (adipocytes, muscle and liver) fail to respond to normal levels of circulating insulin (Le Roith et al., 2003; Kahn et al., 2006). This condition occurs in a wide variety of pathological states, including obesity, hypertension, chronic infection and cardiovascular diseases, and is a central component of DM2 (Kahn et al., 2006; Sowers, 2004). At the molecular level, insulin resistance is the consequence of impaired insulin signaling that may result from mutations or

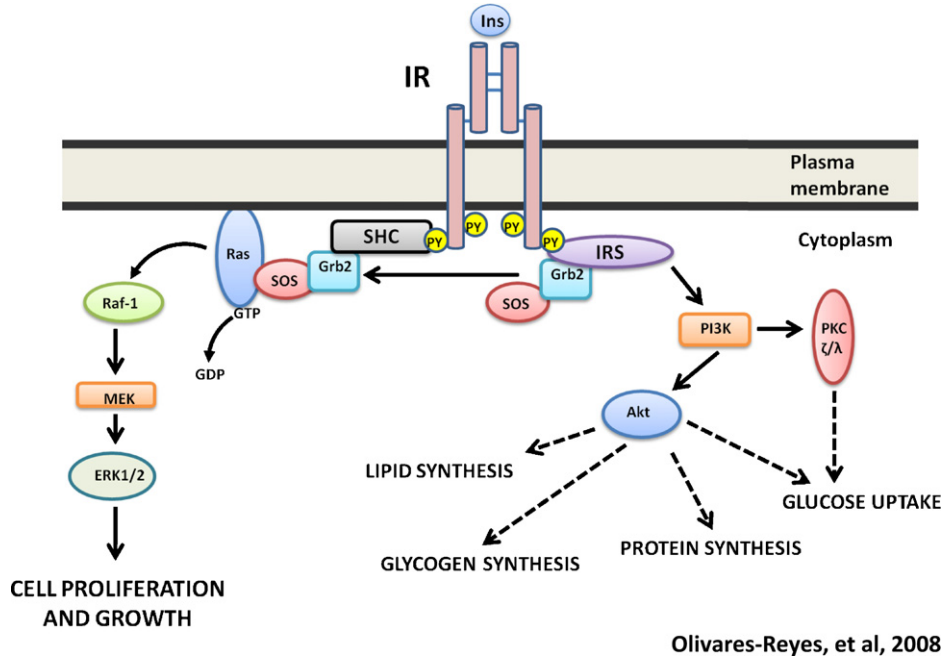

Fig. 1. The insulin signaling pathway. The binding of insulin to its receptor leads to autophosphorylation on the insulin receptor (IR)-β subunit and the Tyr phosphorylation of insulin receptor substrate (IRS) proteins and other signaling molecules such as Shc. Phosphorylated IRS serve as docking proteins for other signaling proteins, such as PI3K and Grb2. Binding of PI3K to phosphotyrosines on IRS-1 induces its activation and the initiation of a downstream cascade of events leading to the phosphorylation and activation of Akt and aPKC ζ/λ. Activation of theses downstream effectors appears to be important for glucose transport, protein, glycogen, and lipid synthesis, whereas activation of Grb2 dependent or independent of IRS-1 (but dependent of Shc) leads to activation of MAPK signaling pathways that control cell proliferation and growth.

post-translation modification of the IR itself or any of its downstream effector molecules, including the IRS proteins, PI3K, and Akt. Studies in insulin-resistance animal models and humans have consistently demonstrated that impaired insulin signaling is mostly a consequence of postreceptor perturbations. Thus, multiple levels of postreceptor defects have been identified as mechanisms underlying insulin resistance (Kim et al., 2008; Draznin, 2006): (a) increased Ser/Thr phosphorylation of IRS proteins (Paz et al., 1997; Shulman, 2000; Draznin, 2006; Zick, 2005); (b) increased degradation of IRS proteins (Shah et al., 2004b; Egawa et al., 2000; Hiratani et al., 2005); (c) increased activity of Tyr-phosphatases including SHIP2, PTEN, and PTP-1B (Galic et al., 2005; Xue, 2007); (d)

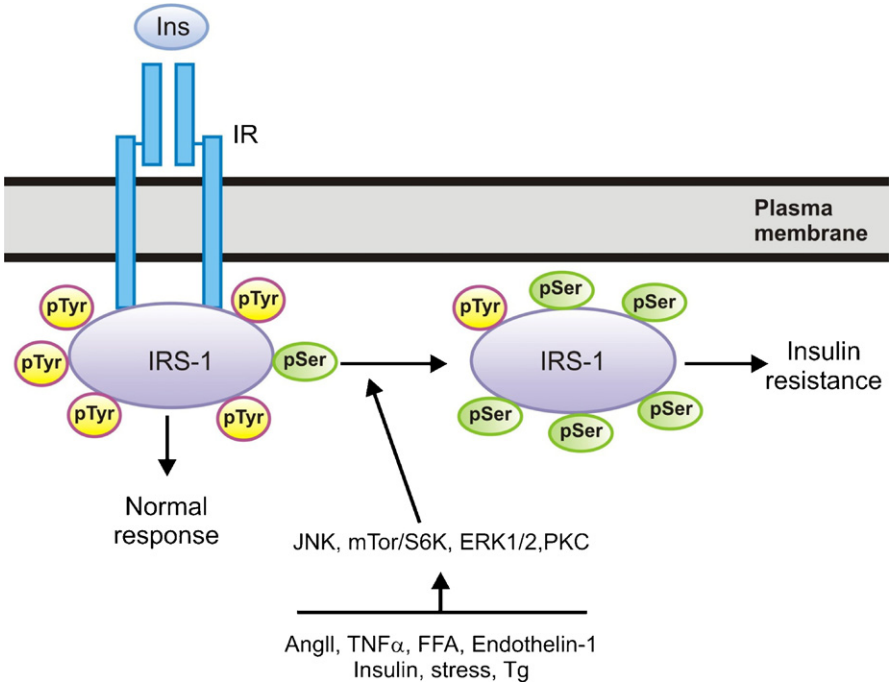

Fig. 2. Serine/Threonine phosphorylation of IRS-1. IRS-1 interacts with the juxtamembrane domain of the IR, which phosphorylates the IRS proteins. Tyrosine phosphorylated IRS proteins leads to activation of several downstream effectors of the insulin (Ins) signaling. However, prolonged insulin stimulation and other stimuli such as angiotensin II (Ang II), tumor necrosis factor-α (TNF-α), free fatty acids (FFA), triglycerides (Tg), endothelin-1 and cellular stress activate IRS kinases that phosphorylate the IRS-1 proteins on Ser/Thr residues leading to impairment of insulin response and insulin resistance.

decreased activation of IR downstream signaling molecules including Akt and aPKC (ζ/λ) (Andreozzi et al., 2004; Draznin, 2006; Waraich et al., 2008; Kim et al., 2002). At the receptor level, impairment of IR autophosphorylation has been demonstrated in muscle of insulin-resistant subjects and animal models (Youngren, 2007; Senn et al., 2003; Meyer et al., 2002).

Several studies have strongly suggested that a major negative regulatory role on insulin action is via increased Ser/Thr phosphorylation of IRS proteins (principally IRS-1) (Draznin, 2006; Fantin et al., 2000; Morino et al., 2006; Muoio and Newgard, 2008; Nandi et al., 2004; Perseghin et al., 2003; Shulman, 2000; Solinas et al., 2007; Zick, 2005). Ser/Thr phosphorylation in specific residues can induce the dissociation of IRS proteins from the IR, block Tyr phosphorylation sites of IRS proteins, release the IRS proteins from intracellular complexes that maintain them in close proximity to the receptor, induce degradation of IRS proteins, or turn IRS proteins into inhibitors of the IR kinase (IRK) (Zick, 2005). Thus, in contrast to a signal promoting Tyr phosphorylation, excessive Ser/Thr phosphorylation of IRS proteins could become detrimental for normal metabolic insulin signaling, causing insulin resistance (Fig. 2).

IRS proteins contain more than 70 Ser/Thr residues that are potential targets for phosphorylation. A number of serine kinases that phosphorylate IRS and weaken insulin signaling have been identified: JNK (Ser^{307}), PKCθ (Ser^{1101}), PKCζ (Ser^{323}), PKCα (Ser^{307}), salt inducible kinase (Ser^{794}), MAPK (Ser^{616}), mTor/S6K-1 (Ser^{616}/Ser^{636}) among others (Arkan, 2005; Draznin, 2006; Shulman, 2000; Zick, 2005).

3. Angiotensin II

3.1. Molecular mechanisms of Ang II signaling

The actions of Ang II are initiated through its interaction with two G-protein coupled receptors (GPCRs), the AT_1 and the AT_2 receptor subtypes (AT_1R and AT_2R). The majority of the biological actions of Ang II are mediated via the AT_1R that signals via the $G_{q/11}$ protein, leading to activation of phospholipase C-β and the subsequent generation of second messengers diacylglycerol (DAG) and inositol trisphosphate (IP_3), which in turn stimulate the activity of the protein PKC and mobilize intracellular Ca^{2+} from intracellular reservoirs (Hunyady and Catt, 2006) (Fig. 3). In recent years, several research groups, including our own, have shown that AT_1Rs also are connected to signaling pathways usually associated with growth factor and cytokine receptors, mainly through its coupling to the transactivation of tyrosine kinase growth factor receptors to mediate important cellular events such as growth, proliferative and antiproliferative effects and migration (Higuchi et al., 2007; Hunyady and Catt, 2006; Olivares-Reyes et al., 2005; Shah and Catt, 2002; Shah et al., 2002, 2004a) (Fig. 3).

4. Angiotensin II and insulin resistance

4.1. The cardiovascular system

4.1.1. Overview of cardiovascular actions of insulin

Insulin plays a key role in the regulation of several aspects of the cardiovascular physiology, including cardiac contractility, vascular tonicity and metabolism of lipids, glucose and proteins (Bertrand et al., 2008; Muniyappa et al., 2007). One of its primary roles is the activation of endothelial NO synthase (eNOS) that lead to production of the potent vasodilator NO from vascular endothelium (Zeng et al., 2000; Kahn et al., 1998). eNOS activation is mediated through a phosphorylation-dependent mechanism that requires activation of the PI3K/Akt pathway (Montagnani et al., 2002; Zeng et al., 2000; Dimmeler et al., 1999). Thus, insulin-induced NO production by the endothelium diffuses both into the lumen and to the smooth muscle cells (VSMCs) where it activates guanylate cyclase to increase cGMP levels that induce relaxation. The insulin-induced increase in blood flow induces a subsequent augmentation of glucose disposal in classical insulin target tissues (Bertrand et al., 2008; Muniyappa et al., 2007). Insulin can also attenuate contractility by regulating the RhoA/Rho kinase (ROK) pathway that is stimulated in response

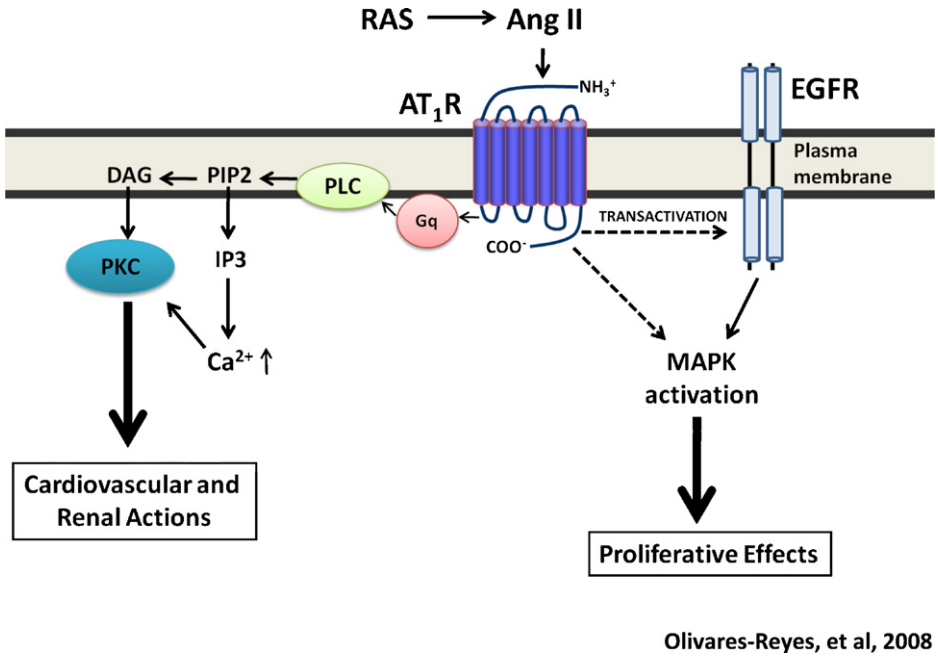

Fig. 3. The Ang II signaling pathway. Upon Ang II binding the AT_1R (a G_q protein-coupled receptor) promotes activation of phospholipase C (PLC) that produces IP3 and diacylglycerol (DAG), both of which trigger part of the downstream signaling pathways mediated by Ang II. Activation of PKC represents a crucial step in Ang II signaling, controlling critical process involved in the regulation of cardiovascular and renal physiology. The proliferative effects of Ang II are mediated by the activation of the mitogen activated protein kinase (MAPK) signaling pathway, essentially through at least two different mechanisms, one involving receptor Tyr (RTK) transactivation, such as the epidermal growth factor receptor (EGFR), the other independent of RTK transactivation. RAS, renin–angiotensin system.

to contractile agonists through the PI3K/Akt pathway (Chitaley and Webb, 2002; Lee and Ragolia, 2006; Bertrand et al., 2008).

In the heart, insulin regulates glucose transport primarily through glucose transporter GLUT4 (insulin-dependent), glycolysis, glycogen synthesis, lipid metabolism, protein synthesis, growth, contractility and apoptosis. In mammalian heart, both insulin and IGF-1 cause positive ionotropic effects through the PI3K/Akt pathway that lead to the activation of L-type Ca^{2+} channels and enhance Ca^{2+} influx. Additionally, insulin also promotes Ca^{2+} influx activating in the reverse mode the Na^{+}/Ca^{2+} exchanger (Ren et al., 2000; von Lewinski et al., 2005).

Evidence from clinical and experimental studies supports the notion that impairment of insulin action in the cardiovascular system is a key factor in the development of hypertension, cardiovascular disease and metabolic disorders such as obesity and DM2 (Bertrand et al., 2008; Fujii et al., 2008; Muniyappa et al., 2007).

4.1.2. Angiotensin II and insulin resistance: impact on cardiovascular insulin response

Several lines of evidence have shown that Ang II plays important roles in the development of hypertension, cardiovascular disease and insulin resistance (Henriksen, 2007; Folli et al., 1997). The use of agents that inhibit Ang II actions, such as the ACE-I and ARBs, not only reduce blood pressure but also improve insulin sensitivity in hypertensive and insulin resistant patients (Yusuf et al., 2000; Fogari et al., 1998). For example, the Heart Outcomes Prevention Evaluation (HOPE) study evaluated the effects of ramipril (an ACE-I) on cardiovascular events in a high-risk population of men and women, including many with diabetes (Yusuf et al., 2000). Patients receiving ramipril exhibited a risk reduction of 32% for stroke, 20% for myocardial infarction, 26% for cardiovascular death and 16% for all-cause mortality. Interestingly, the study also showed a significant reduction in the development of diabetes in those patients without diabetes at the onset of the study. Furthermore, in another study, the ACE-I perindropil was reported to reduce insulin resistance in obese hypertensive patients without diabetes (Fogari et al., 1998). Thus, these and other clinical trials suggest that ACE-I therapy can improve insulin sensitivity and also delay the development of diabetes in patients at high risk for the development of this disease (Sowers et al., 2001; Abuissa et al., 2005).

The mechanism whereby ACE-I improve glucose metabolism and protect against the development of clinical diabetes may involve at least two processes: (1) the improvement of blood flow through the microcirculation to adipose tissue and skeletal muscle and/or (2) the improvement of insulin action at the cellular level by interfering with the Ang II-induced alteration of insulin signaling (Sowers et al., 2001).

Further evidence supporting a role of Ang II in the etiology of insulin resistance comes from investigations using hypertensive and insulin resistant animal models. One of the best characterized is the TG(mREN2)27 (Ren2) rat, a monogenetic model of both hypertension and insulin resistance (Sloniger et al., 2005; Mullins et al., 1990). The Ren2 rat, which harbors the mouse Ren-2 renin gene, is an experimental model of excessive tissue local RAS activity with severe cardiovascular defects, such as hypertension, left-ventricular hypertrophy, and cardiac failure (Blendea et al., 2005; Wei et al., 2006; Whaley-Connell et al., 2007). Interestingly, this model also exhibits a whole body and skeletal muscle insulin resistance (Holness and Sugden, 1998; Blendea et al., 2005). Insulin-stimulated glucose-transport activity is substantially reduced in isolated skeletal muscles from Ren2 rats (Blendea et al., 2005; Sloniger et al., 2005), likely due to an impairment of the IR/IRS-1-dependent insulin signaling pathway by the actions of excess Ang II (Sloniger et al., 2005). A recent study from Wei et al. (2007), demonstrated that chronically elevated tissue Ang II levels observed in the Ren2 model promote NADPH oxidase-derived reactive oxygen species (ROS) production via the AT_1R, leading to vascular inflammation, insulin resistance, reduced eNOS activity, apoptosis, and remodeling.

4.1.2.1. Role of Ang II in endothelial insulin resistance. The vascular endothelium is essential to maintain normal vascular tone and blood fluidity and to limit vascular inflammation throughout the circulatory system (Lerman and Zeiher, 2005). Experimental and clinical evidence suggests that several pathological conditions such as insulin resistance, obesity, and diabetes cause a combination of endothelial dysfunctions, which may diminish the anti-atherogenic role of the vascular endothelium (Kim et al., 2006; Hadi and Suwaidi, 2007). Ang II, which is produced locally by endothelial cells, represents an important contributor to regulate normal endothelial and vascular functions, including contraction, growth, proliferation and differentiation. However, Ang II is also involved in both the pathogenesis of insulin resistance and endothelial dysfunction. Diverse studies have shown that inhibitors of RAS alter insulin resistance favorably, while ACE-I and ARBs improve endothelial dysfunction (Schlaifer et al., 1997; Watanabe et al., 2005; Julius et al., 2004). In human umbilical vein endothelial cells (HUVECs), Ang II activates JNK and MAP-kinase pathways, leading to increased serine phosphorylation of IRS-1 (Ser^{312} and Ser^{616}, respectively), impaired insulin-induced PI3K/Akt/eNOS signaling pathway, and endothelial dysfunction (Andreozzi et al., 2004). In addition to effects on insulin signaling, activation of AT_1Rs by Ang II also induces oxidative stress (Wei et al., 2007; Rajagopalan et al., 1996), resulting in upregulation of pro-inflammatory transcription factors, such as nuclear factor κB (NF-κB) (Hernandez-Presa et al., 1997). These, in turn, regulate the generation of inflammatory mediators (e.g. C-reactive protein, cytokines and adhesion molecules) that lead to endothelial dysfunction and vascular injury (Arenas et al., 2004; Cui et al., 2006; Takeda et al., 2001; Pastore et al., 1999; Savoia and Schiffrin, 2007). Interestingly, elevated levels of proinflammatory cytokines including TNF-α, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1) in response to Ang II can be also related to insulin resistance, since these proinflammatory mediators negatively regulate insulin signaling through activation of JNK, ERK1/2 and p38MAPK in endothelial cells and mouse aortas (Andreozzi et al., 2007; Li et al., 2007; Savoia and Schiffrin, 2007) (Fig. 4). Altogether, these observations suggest that these proinflammatory cytokines produced and released by Ang II contribute importantly not only to endothelial and vascular dysfunction but also to the development of insulin resistance and DM2.

4.1.2.2. Role of Ang II in VSMC insulin resistance. In VSMCs, insulin plays important roles in regulation of glucose metabolism and vasodilatation and exerts antioxidant and anti-inflammatory effects via signaling through the PI3K/Akt pathway (Bergandi et al., 2003; Cooper et al., 2007). Ang II, in contrast, causes vasoconstriction and enhances the expression of pro-inflammatory cytokines, adhesion molecules, inflammatory pathways and growth (Mehta and Griendling, 2007).

There are several reports of the adverse effects of Ang II on insulin signaling in VSMCs. For example, Folli et al. (1997) showed that in rat aortic smooth muscle cells (RASMCs), Ang II impairs insulin-mediated IRS-1 tyrosine phosphorylation and the IRS-1/PI3K association by a mechanism that involves an increased phosphorylation of the IR, IRS and the p85 subunit of PI3K on Ser residues (Fig. 4).

Taniyama et al. (2005) reported that Ang II also impairs insulin signaling in RASMC by a different mechanism that involves proteasome-dependent degradation of IRS-1 via Src, PDK1 and ROS-mediated phosphorylation of IRS on Ser^{307}.

Other kinases such as PKC have also been shown to interfere with insulin signaling via Ang II. In this context, Motley et

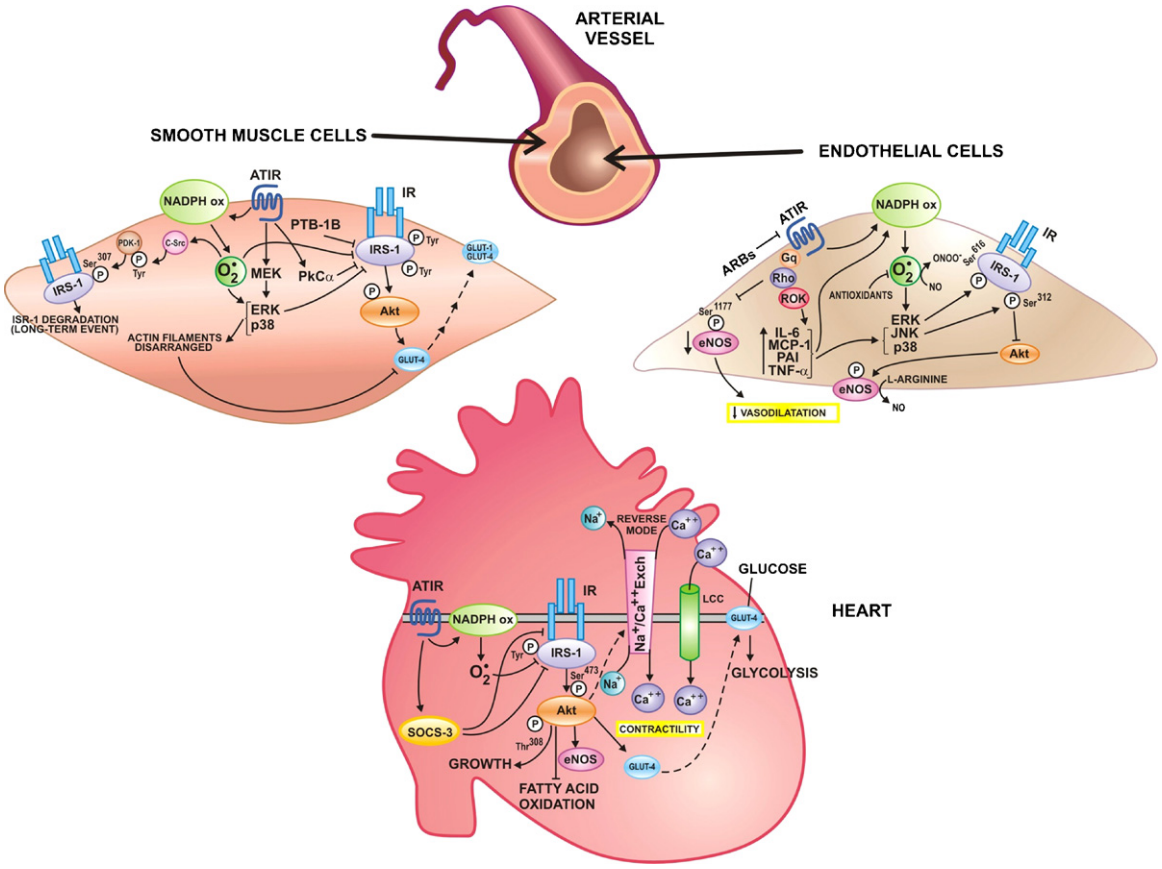

Fig. 4. Modulatory effects of Ang II on the cardiovascular actions of insulin. In vascular smooth muscle cells (VSMCs), endothelium and cardiomyocytes, Ang II phosphorylates IRS proteins on distinct Ser/Thr sites. This phosphorylation impairs the association of IRS to IR, decreases its Tyr phosphorylation and association to downstream signaling molecules such as IP3K. Additionally, in VSMCs Ang II appears to impair IR Tyr phosphorylation by activation of protein tyrosine phosphatases, such as PTP-1B and in the heart through suppressor of cytokine signaling-3 (SOCS-3) synthesis, which affects IRS-1 function.

al. (2003) showed that Ang II inhibits insulin-induced activation of Akt through the AT_1R in VSMCs by blocking IRS-1 function. This inhibition requires PKC-α activation by Ang II (Motley et al., 2003). Furthermore, it has also been demonstrated that Ang II-induced ERK1/2 activation inhibits insulin-dependent glucose uptake through IRS-1 phosphorylation at Ser^{307} and Ser^{616} in RASMC (Izawa et al., 2005). Similar results were found by Igarashi et al. (2007), in VSMCs from both non-diabetic and diabetic rats (Fig. 4).

In primary VSMCs from Ren2 rats, Ang II increases TNF-α levels (Wei et al., 2007). TNF-α is a multifunctional cytokine involved in the pathogenesis of many disease conditions including vascular inflammation, obesity, and insulin resistance (Imoto et al., 2006; Cooper et al., 2007). Thus, Ang II-induced TNF-α upregulation could also contribute to the development of insulin resistance observed in different pathological conditions.

Masori et al. (2007) recently demonstrated that Ang II induces insulin resistance by an alternative mechanism that downregulates the insulin-independent glucose transporter-1 (GLUT1) via disarrangement of actin filaments in the cell membrane of the VSMC line A10. These effects are partially dependent on either P38 or ERK1/2 activation (Masori et al., 2007). Although GLUT1 is an insulin-independent transporter, its downregulation by Ang II also alters the net glucose uptake in these cells.

4.1.2.3. Role of Ang II in heart insulin resistance. In the heart insulin regulates the metabolism by modulating glucose transport, glycolysis, glycogen synthesis, lipid metabolism, protein synthesis, growth, contractility, remodeling, and apoptosis in cardiomyocytes (Muniyappa et al., 2007; Cooper et al., 2007). There is increasing evidence that alterations in energy substrate transport and utilization by cardiomyocytes represent a primary cause of the pathogenesis of heart diseases including diabetic cardiomyopathy. In this context, it has been reported that increased Ang II levels and insulin resistance coexist at the early stage of cardiomyopathies. In this regard, Alfarano et al. (2008) recently examined whether Ang II increases insulin resistance in immortalized cardiomyocytes (HL-1 cells). In these cells, insulin increases the transport of glucose and fatty acids in a PI3K-dependent mechanism. Interestingly, in cells exposed to Ang II, insulin failed to stimulate the uptake of either glucose or palmitate, an effect that was reversed by irbesartan (an AT_1R selective antagonist) and PD98059 (an inhibitor of ERK1/2 activation), suggesting the involvement of Ang II/AT_1R-mediated MAPK activation to inhibit insulin signaling.

In the heart, an intravenous infusion of Ang II inhibits insulin-mediated activation of PI3K and Akt (Carvalheira et al., 2003) and promotes a significant expression of suppressor of cytokine signaling-3 (SOCS-3). It was shown that SOCS-3 interacts with key components of the insulin signaling including the IR, JAK-2, IRS-1 and IRS-2 proteins, impairing insulin-induced GLUT4 translocation and glucose uptake (Calegari et al., 2005). The inhibition of SOCS-3 expression partially restores insulin-induced IR, IRS-1 and IRS-2 Tyr phosphorylation, PI3K and Akt activity, suggesting that SOCS-3 participates as a late event in the negative cross-talk between Ang II and insulin in the heart (Calegari et al., 2005) (Fig. 4). More recently, Tabbi-Anneni et al. (2008) reported that the use of captopril (an ACE-I) improves myocardial energetics and restores the responsiveness of ob/ob mouse hearts to insulin. Interestingly, captopril also normalized AMP-activated protein kinase (AMPK) activity suggesting an improvement of the energetic status in the heart of

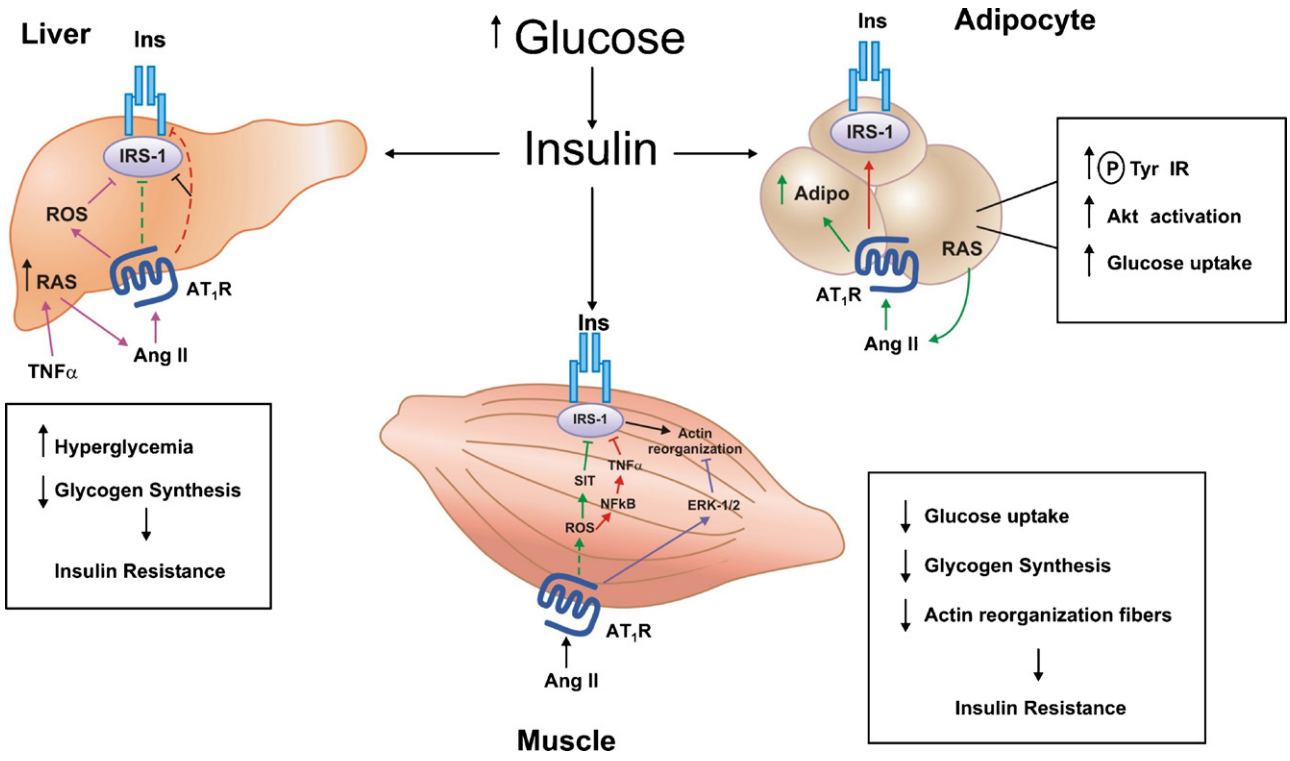

Fig. 5. Modulatory effects of Ang II on the metabolic actions of insulin. In adipose cells, it has been proposed that locally produced Ang II is capable of upregulating insulin signaling. By contrast, in liver and muscle cells, Ang II appears to downregulate insulin signaling through the generation of reactive oxygen species (ROS) and/or the activation of serine kinases such as NFκB and ERK1/2 that phosphorylates IRS-1 on Ser/Thr residues. RAS, renin–angiotensin system; Adipo, adipogenesis.

obese insulin-resistant mice (Tabbi-Anneni et al., 2008). AMPK is an important sensor of cellular energy reserves under energetic stress or demand (Misra and Chakrabarti, 2007; Towler and Hardie, 2007) and its increased activity in the heart of diabetic and obese animal models is considered as an indicator of reduced energetic reserves (Tabbi-Anneni et al., 2008; Wang and Unger, 2005).

Additionally, it has been demonstrated that oxidative stress also plays a central role in Ang II actions on insulin signaling in the heart. Recent observations by Whaley-Connell et al. (2007) demonstrate that Ang II-mediated oxidative stress can promote myocardial tissue remodeling in the transgenic Ren2 rat and contributes to an insulin resistance states in the heart. In cardiomyocytes, similar to VSMCs and endothelium, pharmacological disruption of Ang II action improves insulin sensitivity. Thus, this Ang II-induced abnormality may contribute to altered cardiac mechanical-energy coupling in the Ren2 model of chronic Ang II overexpression (Whaley-Connell et al., 2007; Cooper et al., 2007).

4.2. The metabolic system

4.2.1. Overview of metabolic actions of insulin

Insulin directly or indirectly affects the function of virtually every tissue in the body. However, its metabolic actions on liver, muscle and adipose tissue are the focus of intensive research worldwide due to the fact that theses tissues represent the most responsible for metabolism and energy storage and play important roles in the development of insulin resistance, obesity, and DM2.

Insulin elicits a remarkable array of biological responses and is the primary hormone responsible for controlling the uptake, utilization, and storage of cellular nutrients. Insulin increases the uptake of glucose from blood and enhances its conversion to glycogen and triglycerides. At the same time insulin inhibits the breakdown of triglyceride and glycogen, and in the liver can inhibit gluconeogenesis and ketogenesis. Insulin also promotes the synthesis of proteins. These actions are brought by a combination of rapid effects (such as the stimulation of glucose transport in fat and muscle cells and the regulation of the activity of key enzymes in metabolism), and more long-term mechanisms which involve changes in gene expression (Davis and Granner, 2001; Gribble, 2005; Heesom et al., 1997).

4.2.2. Angiotensin II and insulin resistance: impact on metabolic insulin response

Individuals with essential hypertension frequently display associated insulin resistance of skeletal muscle glucose uptake, hyperinsulinemia, dyslipidemia and central adiposity, in a condition described as “insulin resistance syndrome” (DeFronzo and Ferrannini, 1991). There is evidence that suggest that one contributor to the development of insulin resistance is overactivity of the RAS. Animal models and clinical investigations have demonstrated that ACE-I and AT_1R antagonist treatment can ameliorate peripheral insulin resistance (Henriksen et al., 2001; Henriksen, 2007). Because the importance of insulin actions on metabolism, in the following section, we will be discuss the effect of Ang II on insulin action in adipose tissue, skeletal muscle and liver.

4.2.2.1. Role of Ang II in adipose tissue insulin resistance. In adipose tissue insulin promotes glucose uptake through activation of a series of signaling cascades. Much of this glucose is then converted to α-glycerophosphate, which is used in the esterification of fatty acids and permits their storage as triglycerides. To a minor extent, glucose can also be converted to fatty acids. Mice carrying an adipose tissue-specific deletion of the GLUT4 gene rapidly develop marked muscular and hepatic insulin resistance, whereas mice carrying a muscle-specific deletion of GLUT4 develop hepatic and adipose insulin resistance secondary to the resulting hyperglycemia. These data suggest that adipose tissue plays an important role in whole body glucose homeostasis. Although adipose tissue

glucose uptake accounts for only a small part of that for the whole body, the mechanism of insulin action in this tissue is of utmost importance (Juan et al., 2005; Kim et al., 2001).

Interestingly, it has been shown that after the liver, white adipose tissue is the most abundant source of angiotensinogen (the Ang II precursor). Ang II generated from adipose angiotensinogen (from a local RAS) has been implicated in adipocyte growth and differentiation. Moreover, overfeeding leads to increased local formation of angiotensinogen and Ang II, and may contribute to the close relationship between adipose tissue mass and the blood pressure. In human studies, local Ang II formation in adipose tissue is increased in obese hypertensive subjects. It has been shown that RAS blockade decreases adipocyte size without change the percentage of epididymal fat pads and was accompanied by improvement of insulin sensitivity (Furuhashi et al., 2004). Based upon these findings, the adipose RAS may play an important role in the pathogenesis of obesity and insulin resistance (Boschmann et al., 2001).

At the molecular level, the effect of Ang II on insulin signal transduction is controversial. Baba et al. (1998) reported that in adipocytes derived from surgically removed fat tissue, Ang II treatment had no effect on IR Tyr kinase activity (Baba et al., 1998; Sechi et al., 1997). By contrast, recently Juan et al. (2005) reported that Ang II treatment increased adipocyte insulin-stimulated Tyr phosphorylation of the IR, Akt phosphorylation, and translocation of GLUT4 to the plasma membrane, providing evidence that Ang II can potentiate insulin-stimulated glucose uptake through the AT_1R. They concluded that Ang II enhances insulin sensitivity, suggesting that dysregulation of the insulin sensitizing effect of Ang II may be involved in the development of insulin resistance (Juan et al., 2005) (Fig. 5).

4.2.2.2. Role of Ang II in skeletal muscle insulin resistance. Skeletal muscle is particularly important in the development of insulin resistance, since it is responsible for 75–95% of insulin-mediated glucose disposal. Insulin resistance of skeletal muscle glucose transport is frequently associated with essential hypertension, with a potential role of RAS and Ang II in the pathogenesis of both conditions. Recent evidence indicates that inhibition of RAS not only improves cardiovascular outcomes, but also may have metabolic benefits. Adverse effects of the RAS appear to act directly on skeletal muscle, since interstitial infusion of Ang II has been shown to induce insulin resistance. Several studies have suggested that Ang II-induced skeletal muscle insulin resistance is mediated by oxidative stress (Blendea et al., 2005; Henriksen, 2007; Sowers, 2004; Wei et al., 2006, 2008). Ang II promotes ROS generation in skeletal muscle by increasing NADPH oxidase activity and the translocation of its cytosolic subunits p47phox and p67phox to the plasma membrane and impairs insulin-mediated IRS-1 tyrosine phosphorylation, Akt activation, GLUT4 plasma membrane translocation, and skeletal muscle glucose uptake, all of which are significantly attenuated by AT_1R blockade or antioxidant treatment (Blendea et al., 2005; Wei et al., 2006). In L6 myotubes, the inhibitory effect of Ang II treatment on insulin-induced Akt activation and GLUT4 translocation was related to increased NFκB activation and TNF-α expression. These inhibitory effects were diminished by treatment of myotubes with valsartan, the antioxidant N-acetylcysteine, and the NADPH oxidase inhibiting peptide (gp91 ds-tat) or the NFκB inhibitor (MG-132), suggesting that NFκB plays an important role in Ang II/ROS-induced skeletal muscle insulin resistance (Wei et al., 2008). In L6 myotube cells, Ang II also reportedly inhibits insulin-induced actin fiber reorganization and consequently glucose uptake by a mechanism that depends on ERK1/2 activation; this occurred via AT_1R, PKC and p38 MAP kinase activation and was independent of Gαq and EGF receptor transactivation (Nazari et al., 2007) (Fig. 5).

4.2.2.3. Role of Ang II in liver insulin resistance. The liver is an important organ for glucose uptake and storage, and may account for disposal of up to one-third of an oral glucose load. Insulin resistance in the liver has been suggested to be a later factor in the development of hyperglycemia, with increased hepatic glucose production that correlates with fasting hyperglycemia in diabetic patients. In addition, the liver is the major site for insulin clearance, a process that is mediated in part, via receptor-mediated uptake and degradation. The role of the liver in glucose homeostasis and the development of insulin resistance and DM2 was revealed in liver-specific IR knockout (LIRKO) mice. This mice display severe primary insulin resistance and a defect of insulin clearance, and age-dependent nodular hyperplasia of the liver and liver dysfunction. Thus, isolated liver insulin resistance is sufficient to cause severe defects in glucose homeostasis (Michael et al., 2000).

Accumulating evidence links the RAS and liver insulin states. It was recently shown that hepatic expression of the angiotensinogen gene is upregulated in type 2 diabetic patients with and without obesity. Takeshita et al. (2008) found an interesting relationship between the hepatic RAS, TNF-α and insulin resistance. They found that TNF-α upregulates the hepatic RAS component mRNAs including ACE, angiotensinogen, and AT_1R in THLE-5b cells (a hepatocyte cell line). In this cell line, TNF-α and RAS coordinately stimulate PAI-1 production, suggesting a cross-talk between both systems, and a possible mechanism by which TNF-α and Ang II induce insulin resistance (Takeshita et al., 2008). To support the fact that Ang II impairs liver insulin signaling, Munoz et al. (2006) found that in the liver of obese Zucker rats, long-term treatment with irbesartan (an AT_1R blocker) increased IR tyrosine phosphorylation, decreased IR Ser^{994} phosphorylation, augmented IRS-1 and -2 abundance and tyrosine phosphorylation, augmented association between IRS and PI3K, increased insulin-induced Akt phosphorylation and interestingly decreased hepatic steatosis. However, the molecular mechanism by which Ang II impairs liver insulin signaling remains to be resolved (Fig. 5).

5. Insulin resistance and type 2 diabetes: contribution of RAS

DM2 is the most common endocrine disorder, affecting over 170 million people worldwide, and by the year 2030 the World Health Organization estimates that 365 million of people will be afflicted with diabetes. This epidemic is also expected to trigger a steep rise in the complications associated, such as ischemic heart disease, stroke, neuropathy, retinopathy and nephropathy. Approximately 75–80% of people with diabetes die of cardiovascular disease. People with DM2 have two to four times higher risk of coronary heart disease than the rest of the population, and their prognosis is poorer. The risk of coronary, cerebrovascular and peripheral vascular diseases is also significantly higher. Premature mortality caused by diabetes results in an estimated 12–14 years of life lost (Alberti et al., 2007).

DM2 is a heterogeneous, polygenic disorder in which dysfunction in a number of metabolic pathways appears to be important in its development. Although it remains unclear exactly which event triggers the disorder, DM2 is primarily characterized by insulin resistance, followed by relative insulin secretion deficiency and hyperglycemia, and finally beta-cell dysfunction (defined as the loss of early phase of insulin release in response to hyperglycemic stimuli) that is the key element in the underlying pathophysiology of DM2.

There remains the question of how insulin resistance could be associated with the beginning of the development of DM2. Evidence for this comes from cross-sectional studies that have demonstrated that insulin resistance is a consistent finding in patients with DM2,

and prospective studies that have shown that insulin resistance is the best predictor of whether or not an individual will later become diabetic (Abdul-Ghani et al., 2007; Bonora et al., 1998; Warram et al., 1990).

Mild to moderate insulin resistance is a common occurrence among human populations; given its association with obesity, age and physical activity it is especially common in industrialized nations (Myers and White, 2002). In non-diabetic individuals, pancreatic β-cells are able to compensate appropriately for insulin resistance by increasing insulin secretion. However, chronically elevated levels of glucose caused by severe insulin resistance state leads to β-cells dysfunction undermining β-cells compensation and resulting in the development of DM2. (Muoio and Newgard, 2008; Asghar et al., 2006).

As showed here, the role of RAS on insulin resistance has been well documented and its impact on the development of metabolic disorders, including DM2, is a critical issue to understand the cardiovascular and renal complications observed specially among patients with DM2. Recent clinical trials have suggested that inhibitors of the RAS, such as ACE-I and ARBs, may reduce the incidence of new-onset diabetes in patients with or without hypertension and at high risk of developing diabetes (Zanchetti and Ruilope, 2002; Jandeleit-Dahm et al., 2005). The reduced incidence of DM2 by the use of RAS inhibitors has been explained by haemodynamic-dependent effects, such as improved delivery of insulin and glucose to the peripheral skeletal muscle, and haemodynamic-independent effects, including direct effects on glucose uptake and insulin signaling pathways, all of which decrease insulin resistance (Jandeleit-Dahm et al., 2005).

Independently of Ang II-induced impairment of insulin signaling at both the molecular and cellular level, it has been shown that Ang II is also capable of altering the metabolic actions of insulin through several other mechanisms. For example, Ang II can reduce β-cell function and mass, possibly by increasing oxidative stress and apoptosis, in addition to increasing profibrotic pathways and vascular damage in db/db mice, a model of type 2 diabetes with obesity (Shao et al., 2006; Tikellis et al., 2004). In addition, there is now evidence that the pancreas may contain an in situ active RAS, which appears to be upregulated in fat diabetic rats (Tikellis et al., 2004). Thus, ACE inhibitors and ARBs may act by attenuating the deleterious effect of angiotensin II on vasoconstriction, fibrosis, inflammation, apoptosis and β-cell death in the pancreas, thereby protecting a critical β-cell mass essential for insulin production.

Interestingly, the insulin resistance state of hyperinsulinemia and hyperglycemia, two closely related states to insulin resistance, are associated with upregulation of RAS components, including the AT_1R and Ang II (Samuelsson et al., 2006; Shinozaki et al., 2004; Giacchetti et al., 2005; Fiordaliso et al., 2001). Since RAS induces insulin resistance and insulin resistance upregulates RAS components both conditions generate a vicious cycle that could explain renal and cardiovascular dysfunctions observed in diabetic individuals.

6. Conclusions

Ang II actions, mediated mainly through AT_1Rs, and the signaling pathways they regulate have the potential to alter the strength and duration of the insulin response. Intracellular interactions between insulin-dependent biochemical events and signals transduced via Ang II signaling pathways may occur at multiple levels, including at the level of receptor function, IRS, and IRS-regulated modulation of downstream effectors.

While significant progress has been made in defining the biochemistry of the insulin-response signaling pathway, in elucidating the cross-talk that occurs between insulin and other factors, including hormones, growth factors and cytokines, important scientific gaps remain to be explored. For example, now it is clear that local RAS may influence cellular activity, not only in response to Ang II, but also to others hormones and growth factors that signal independently of RAS. However, our current knowledge of how local RAS and other cellular factors regulate insulin action in target tissues in vivo remains to be elucidated. Because of this, information generated by studies of signaling cross-talk within and between insulin-responsive tissues not only represents important efforts to understand the etiology and phatophysiology of diabetes, but also may have significant implications for the design of new therapeutic approaches to prevent and treat diabetes and its complications.

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