Inhibition of Renin-Angiotensin System: Implications for Diabetes Control and Prevention

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Abstract: Several large-scale clinical studies have consistently demonstrated that use of inhibitors of renin-angiotensin system such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was associated with significant reduction of new-onset diabetes in patients with insulin resistance such as primary hypertension. Such observations stimulated major investigations into the interaction of angiotensin and insulin signaling systems, which in turn led to the discovery of a cross talk at several steps between the 2 pathways. Evidence from these clinical trials and from the experimental models of insulin resistance including our findings in ZSF rat and other animal models will be discussed in this review.

Key Words: angiotensin inhibitors, insulin signaling, diabetes prevention

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Diabetes mellitus is emerging as a global epidemic in the past few years, and the implications from the disease burden and health care costs are so overwhelming that the need for major effective interventions at primary and secondary levels of preventions cannot be overemphasized. Whereas the mechanisms underlying insulin resistance continue to unfold,[1] we are far from a complete and clear understanding of the molecular basis of peripheral resistance to the action of insulin. In the context of an explosive growth of diabetes, the unexpected observation in multiple clinical trials, which showed a primary prevention of diabetes in patients treated with inhibitors of renin-angiotensin-aldosterone system (RAAS), was welcomed by the biomedical community with great enthusiasm. A number of basic investigations led to the unraveling of several interactive mechanisms in the signaling pathway of angiotensin and insulin.[2–4] The findings from such investigations from many laboratories including ours are the focus of this review article, which summarizes the in vivo and in vitro studies relating to "angiotensin-insulin cross talk."

CLINICAL SPECTRUM OF DISORDERS WITH INSULIN RESISTANCE

Resistance to the action of insulin has been conventionally well known to be the underlying mechanism in type 2 diabetes mellitus and in metabolic syndrome. Metabolic syndrome is a constellation of clinical manifestations that include obesity, systemic hypertension, hyperlipidemia, diabetes mellitus, or impaired glucose tolerance. Whereas the existence of such a syndrome is not universally accepted, insulin resistance is believed to be the pathogenic mediator of all these features and contribute to the associated high cardiovascular morbidity and mortality.[5] In addition, several other clinical disorders are believed to be associated with insulin resistance including some lipodystrophies, several states of hormonal excess (such as catecholamines and glucocorticoids), and polycystic ovary syndrome. However, the most interesting condition of these is essential hypertension,[6] in which insulin resistance may be the underlying pathogenic mechanisms, with full-blown diabetes occurring in a minority. This aspect is fully discussed as a separate presentation in this symposium.

Obesity is on the rise globally and has been held as the primary reason for increase in type1 diabetes worldwide. Several investigators have demonstrated activation of RAAS in obese subjects, which in turn may play a major role in hypertension and renal disease seen in such individuals.[7] Activation of RAAS with consequent increased angiotensin II levels has been incriminated in a number of clinical consequences of obesity and metabolic syndrome including hypertension, dyslipidemia, and renal manifestations. In addition, diabetes, which often develops in such subjects, has been linked to angiotensin activation through protein tyrosine phosphatases. Such interactions between angiotensin and glucose metabolism have been hypothesized as important in pharmacologically modulating insulin sensitivity in populations with diabetes and at risk for diabetes.[8–10]

RAAS INHIBITION—IMPACT ON DIABETES AND GLYCEMIC INDICES

Inhibitors of RAAS have been traditionally used not only to control systemic blood pressure but were proven successful in improving the functional status in heart failure and renal function in proteinuric nephropathy, notably, diabetic nephropathy. More recent long-term large-scale clinical trials have shown that RAAS are also effective in decreasing cardiovascular events and mortality from the same. However, many such studies have demonstrated a significant and totally unexpected improvement in glycemic control in diabetic patients and prevention of new-onset diabetes mellitus (NODM) in nondiabetic patients enrolled in these clinical studies (Table 1). The following discussion focuses on these findings from a few selected clinical studies of many such studies.

HOPE (Heart Outcomes Prevention and Evaluation) Study

This large-scale clinical study involving more than 9000 subjects including approximately 3000 diabetic subjects assessed the role of an angiotensin-converting enzyme (ACE) inhibitor, ramipril, in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure.[13] This study included patients older than 55 years who had evidence of vascular disease or diabetes

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TABLE 1. Summary of Clinical Trials Showing the Effects of Inhibitors of Renin-Angiotensin System on New Onset of Diabetic Mellitus and Glycemic Control in Diabetic Patients

	Inhibitors of Renin-Angiotensin System and Antidiabetic Effects				
Study	Patients	Sample	Duration (Years)	Drugs	Results
UKPDS[11]	HT + T2DM	1148	9	Captopril vs atenolol	Captopril lowered mean HbAlc (7.0 ± 1.4 vs 7.5 ± 1.4%; $P = 0.0044$)
CAPP[12]	HT	10,935	6	Captopril vs conventional Rx	Incidence of new onset diabetes was lower in captopril group (RR, 0.86; $P = 0.039$)
HOPE[13]	High risk for CVD	9297	4.5	Ramipril vs Placebo	Fewer patients in the ramipril group had NODM
ALLHAT[14]	HT + I RF for CVD	33,397	4.9	Lisinopril vs chlorthalidone vs amlodipine	NODM at 4 yrs was lower in the lisinopril group (8.1 vs 11.6%; $P < 0.001$). It was 9.8% in the amlodipine group
LIFE[15]	Ess HT + LVH	9193	4	Losartan vs atenolol	NODM lower in losartan group: 6% vs 8% (RR, 0.75; $P < 0.001$)
CHARM[16]	CHF	7599	3.2	Candesartan vs placebo	NODM less in candesartan (6% vs 7.5%; $P < 0.02$)
VALUE[17]	HT + high risk for CVD	15,245	4.2	Valsartan vs amlodipine	NODM less in valsartan (13% vs 16%; RR, 0.77; $P < 0.0001$)
ASCOT-BPLA[18]	HT + 3 CV risk factors	19,257	5.4	Amlodipine + perindopril vs atenolol + thiazides	NODM less common in amlodipine + perindopril group (RR, 0.68; $P < 0.0001$)

Adapted from Jandelit-Dahm et al.[20]

plus one other cardiovascular risk factor. They were randomized to receive ramipril, 10 mg per day, or matching placebo for a mean duration of 5 years. The primary end point of the study was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The secondary end points were death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes.

The study was terminated well before the scheduled time owing to overwhelmingly convincing results that showed significant advantage of ramipril in reducing the cardiovascular events and mortality. The relative risk of composite outcome in the ramipril group compared with placebo was 0.78, and cardiovascular death was 0.75 and stroke 0.69, results that established therapeutic advantages of ACE inhibition in patients at risk for cardiovascular diseases. These findings were so powerful that they warranted modification of the guidelines from the American Heart Association and the American College of Cardiology to include ACE inhibitors in the treatment of coronary disease.

One of interesting findings of the study was reduction of NODM by 32% in the nondiabetic patients treated with ramipril. This observation was not only unanticipated but also very surprising and interesting. The significance of this finding was not readily understood until it was observed again in many other similar studies using inhibitors of renin-angiotensin systems.

Effects of Other ACE Inhibitors on New-Onset Diabetes

Another study that involved the use of ACE inhibitors in cardiovascular disease was "The antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial"—ALLHAT study,[14] which was published 2002. In this study, more than 3300 patients with hypertension and one risk factor of cardiovascular disease were randomized to receive either lisinopril, chlorthalidone, or amlodipine to assess impact on cardiovascular events. Interestingly, in this study, the NODM at 4 years was lower in the lisinopril group compared with the other groups ($P < 0.001$). Similar results were observed in the Captopril Prevention project or the CAPP[12] study (approximately 11,000 patients), with incidence of NODM being lower in the captopril group (relative risk [RR], 0.86; $P = 0.039$). The results from UK Prospective Diabetes Study Group or UKPDS[11] study published in 1998 showed that captopril lowered hemoglobin A_{1c} significantly compared with atenolol, suggesting that ACE inhibitors improved glycemic control in type 2 diabetes.

Angiotensin Receptor Blockers and New-Onset Diabetes Mellitus

In other large clinical trials, therapeutic inhibition of renin angiotensin axis at a more distal level (at the level of angiotensin receptors) also produced similar reduction of NODM. The Losartan Intervention for Endpoint reduction in hypertension or LIFE study,[15] which involved examining cardiovascular outcomes in patients with essential hypertension with left ventricular hypertrophy, compared losartan, an angiotensin receptor blocker (ARB), with atenolol, a β-blocker. Of a total of 9190 randomized subjects, new-onset diabetes mellitus was seen in 6% in the ARB group versus 8% in the β-blocker group (RR, 0.75; $P < 0.02$). In another study (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity [CHARM]) that examined the effects of ARB on outcomes in congestive heart failure subjects,[16] NODM was significantly less in the candesartan arm (6%) compared with the placebo arm (7.5%; $P < 0.02$). In a more recent study, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE), which was designed to evaluate the cardiovascular outcomes in hypertensive subjects with high risk for cardiovascular disease,[17] valsartan group was associated with lower incidence of NODM than amlodipine group (11.5% vs 14.5% ; RR, 0.77; $P < 0.0001$). Finally, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study,[18] which examined cardiovascular end points in 19257 subjects randomized to receive either amlodipine and an

ACE inhibitors versus atenolol and thiazides, the incidence of NODM was lower in the group that received ACE inhibitors (RR, 0.68; $P < 0.0001$).

Thus, most studies that examined the effect of inhibitors of RAAS, whether ACEi or ARBs, have shown an unexpected and impressive reduction in NODM.[19] These studies are summarized in Table 1. A meta-analysis of 10 such randomized controlled trials involving more than 76,000 patients with systemic hypertension or CHF demonstrated an overall 22% risk reduction of NODM after a mean follow-up of 4.5 years.[20]

There were a few studies in which the results were not in agreement with most of the studies related to the RAAS inhibition and prevention of diabetes. In the ONgoing Telmisartan Alone in combination with Ramipril Global Endpoint Trial (ONTARGET) study,[21] the investigators compared the ACE inhibitor ramipril with the ARB telmisartan and the combination of the 2 drugs in patients with vascular disease or high-risk diabetes. Angiotensin II type 1 receptor blockade and selective peroxisome proliferator-activated receptor gamma modulation with molecules such as telmisartan could provide greater protection from new-onset diabetes. In summary, 8576 patients were assigned to receive 10 mg of ramipril per day, 8542 patients were assigned to receive 80 mg of telmisartan per day, and 8502 patients were assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. After a mean follow-up of 56 months, telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the 2 drugs was associated with more adverse events without an increase in benefit. In a related study, Telmisartan Randomized AssessmeNt Study in aCE-iNtolerant subjects with cardiovascular Disease (TRANSCEND), the new-onset diabetes in patients receiving Telmisartan was not lower than the controls.[22]

The NAVIGATOR Study

A very recent study, which was designed to examine the impact of ARB in patients' impaired glucose tolerance with CV disease or risk, randomized approximately 9300 subjects to receive either valsartan or placebo.[23] It was a double-blind randomized study with 2 × 2 factorial design, and the mean follow-up was for 5 years. In this study, the cumulative incidence of NODM was 33.1% in valsartan group compared to 36.8% in the placebo (RR, 0.86; $P < 0.001$). However, there was no difference in the CV outcomes between the 2 groups.

Glycemic Control in Diabetic Subjects Treated With RAAS Inhibitors

In addition to decreasing NODM, the use of RAAS inhibitors have demonstrated significant benefit in the glycemic control of established diabetic subjects. This was evident from many anecdotal observations[24,25] and from large randomized controlled studies. For example, in the UKPDS study, which examined the use of captopril in patients with type 2 diabetes, the mean hemoglobin A_{1c} was lower in the treatment group (7.0 ± 1.4 vs 7.5 ± 1.4% in the atenolol group; $P < 0.004$).

ANGIOTENSIN SIGNALING

Angiotensin II is the final mediator of RAAS. Renin produced by the juxtaglomerular apparatus in the kidney mediates the conversion of angiotensinogen to angiotensin I, which in turn is converted to angiotensin II, a reaction mediated by ACE. Renin is a self-limiting enzyme released from juxtaglomerular cells in the response to changes in hydrostatic pressure sensed at the glomerular afferent arterial and sodium concentration sensed by macula densa. Renin acts to cleave to angiotensinogen synthesized by the liver, to form angiotensin I, which in turn is converted to angiotensin II by the action of ACE. Angiotensin II exerts its actions by receptors of which AT_1 and AT_2 are important. Most of that action of angiotensin II is mediated by binding with AT_1 receptor, which is widely distributed in the vasculature, kidney, adrenal gland, heart, liver, and brain. The AT_2 receptor is widely expressed in the fetal tissues but expressed in a limited amount in adult life. Activation of AT_1 receptor leads to systemic and renal vasoconstriction, endothelial dysfunction, oxidative stress, activation of inflammatory cytokines, and sodium reabsorption in the kidney; whereas AT_2 receptor activation leads to opposite effects such as systemic renal vasodilatation, decreased renal sodium reabsorption, and decreased inflammation. Recently, another signaling pathway was described involving ACE 2, which converts angiotensin I to angiotensin 1 to 7 (Ang 1–7) through Ang 1–9 and also converts angiotensin II directly to Ang 1–7. Ang 1–7 counterbalances many effects of angiotensin II by causing vasodilation, natriuresis, and antiproliferative effects. Angiotensin II binding to AT_2 receptor results in activation of membrane-bound nicotinamide adenine dinucleotide phosphate oxidase and reactive oxygen species (ROS) formation leading to oxidative stress. Increased superoxide generation reacts with nitric oxide (NO) to form peroxynitrite, which is in general very cytotoxic, and also reduces the availability of NO leading to vasoconstriction. Furthermore, ROS is considered an important mediator of angiotensin II actions including epidermal growth factor receptor phosphorylation, activation of extracellular signal-regulated kinases 1 and 2 and tyrosine kinase activation and induction of nuclear factor kappa B, AP-1.[26] In addition, ROS such as superoxide facilitates the formation of oxidized low-density lipoprotein, which is taken up by endothelial cells leading to endothelial injury. One other mechanism of endothelial dysfunction involving angiotensin II is mediated by increased circulating levels of free fatty acids that stimulate endothelial dysfunction.[27] Through these various mechanisms, oxidative stress induced by angiotensin II blocks NO result in vasoconstriction.

INSULIN SIGNALING PATHWAYS

Insulin is secreted by β cells of the islets of Langerhans in the pancreas in response to several factors but primarily by an increase in ambient glucose concentration in the plasma and also by glucagon levels. The primary function of insulin is to facilitate entry of glucose in many cell types such as skeletal muscle and adipose cell and liver, whereas in some cells, glucose entry is insulin independent. Type 1diabetes is characterized by insufficient pancreatic secretion of insulin while resistance to the action of insulin at the tissue level characterizes type 2 diabetes. The insulin signaling pathways involved in health and disease are the focus of discussion in another part of this symposium. However, the broad outlines of these pathways are discussed in this section (Fig. 1). Insulin binds with its receptor, which has 2 extracellular α subunits and 2 transmembrane β subunits linked by disulfide bonds. Insulin binding to the α subunit of the insulin receptor protein results in autophosphorylation of several tyrosine residues in the β subunit. These residues are then recognized by phosphotyrosine-binding domains of its adaptor protein, the insulin receptor substrate (IRS) protein. Activation of the receptor protein thus leads to phosphorylation of the key tyrosine residues of the IRS proteins. The activation of IRS results in activation of and binding with phosphatidylinositol

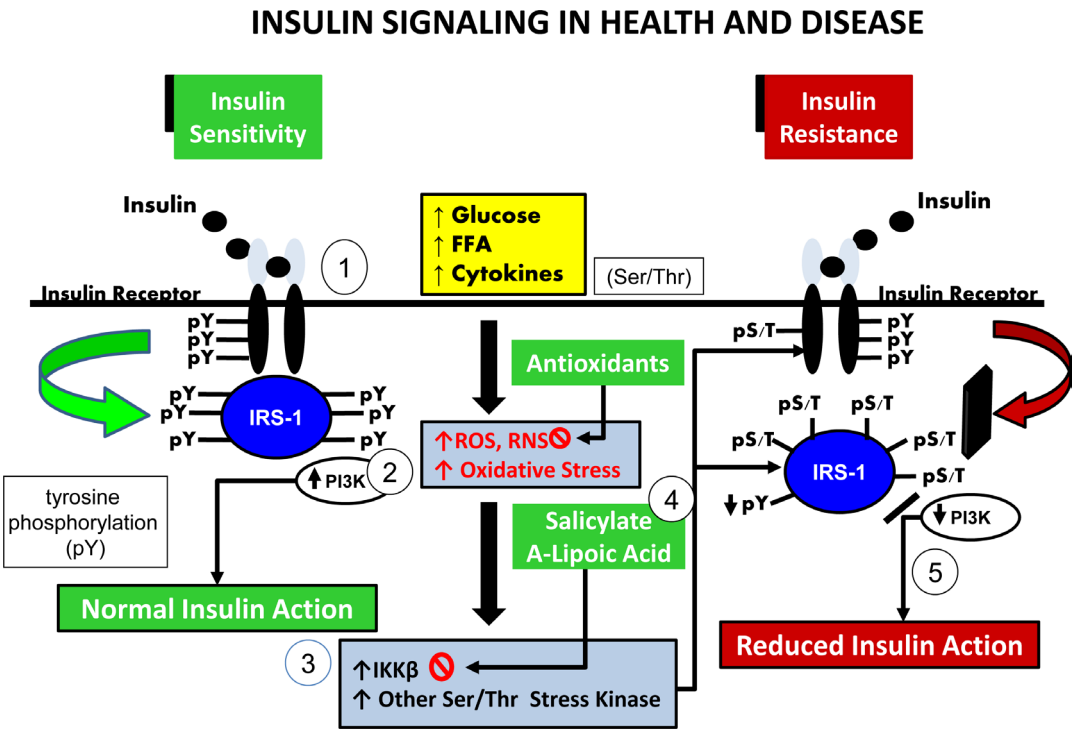

FIGURE 1. Insulin signaling pathways in healthy humans and insulin-resistant states. Signaling in healthy adult involves phosphorylation of insulin receptor IRS-1 of several tyrosine residues while in metabolic syndrome in other insulin states, the phosphorylation occurs at serine-threonine sites on IRS-1 protein.

3-kinase (PI3K) leading to an increase of the phosphatidylinositol (3,4,5)-trisphosphate phospholipid. The latter leads to activation of phosphoinositide dependent kinase 1 and phosphoinositide dependent kinase 2, which in turn leads to activation of protein kinase. Protein kinase facilitates translocation of glucose transporter-4 to the cell membrane, which in turn mediates cellular uptake of glucose. Whereas the exact mechanisms that lead to insulin resistance are unknown, factors such as oxidative stress[28] impair the activity of PI3K by causing phosphorylation of the insulin receptor protein and IRS1 protein at the serine/threonine residues instead of tyrosine sites and impair GLUT4 translocation, thereby resulting in insulin resistance.[29] In addition, adiponectin acting through specific receptors modulates insulin action by promoting tyrosine phosphorylation of IRS proteins through adenosine monophosphate (AMP) kinase activation.[30] Furthermore, it is likely that vitamin D also may play a role in regulating insulin signaling through modulation of adiponectin levels, as there is a positive correlation between vitamin D levels and adiponectin levels. This relationship is not affected by RAAS activity, although RAAS activation inhibits adiponectin levels.[31,32]

EVIDENCE OF ANGIOTENSIN-INSULIN CROSS TALK

Several lines of evidence suggest close regulatory and functional interaction between angiotensin and insulin signaling pathways,[33,34] adequate enough to be characterized as a cross talk.[35,36] Insulin signaling interactions with angiotensin have been incriminated in cardiac hypertrophy.[37] It has been previously shown that angiotensin II infusion can affect insulin signaling.[38] Studies by several investigators examining downstream events of insulin signaling have shown that such events are modified by angiotensin II, resulting in insulin resistance primarily mediated by protein tyrosine phosphatase.[8] Furthermore, chronic angiotensin II treatment of vascular smooth muscle cells decreased IRS-1 protein level and phosphorylation level. This phenomenon was reversed by antioxidants, *N*-acetylcysteine and ebselen, indicating that these changes are mediated by ROS.[39] Additional evidence for angiotensin insulin cross talk comes from a study[36] that shows that suppressor of cytokine signaling-3 participates, as a late event, in the negative cross talk between angiotensin II and insulin, producing an inhibitory effect on insulin-induced glucose transporter-4 translocation.

STUDIES WITH ZSF RAT

Effects of angiotensin inhibition on insulin signaling in experimental diabetes was one of the areas of investigations in our laboratory. We recently characterized the phenotypic features of ZSF rats with special focus on renal structure and function.[40] These rats are phenotypically normal at birth but after 8 weeks develop progressive obesity, hypertension, insulin resistance with diabetes mellitus, hyperlipidemia, and heart failure. Using this animal model, we examined the effect of angiotensin receptor blockade on insulin signaling pathways.

Our experiments demonstrated that chronic treatment of ZSF rats with ARBs improved glycemic indices as demonstrated by lower fasting plasma glucose and HbA1C levels. These effects are partly accounted for by a modest increase in pancreatic insulin secretion, which is mediated by modulation of pancreatic NO release, as the effects are blocked by nitric oxide synthase inhibitors. However, the effects are more significantly accounted for by improving peripheral insulin resistance. In experiments involving cultured myocytes from ZSF rats, we demonstrated that losartan (an ARB) significantly augmented radiolabeled glucose uptake in a time-dependent fashion. Furthermore, losartan increased plasma adiponectin and, more significantly, adiponectin receptor levels.

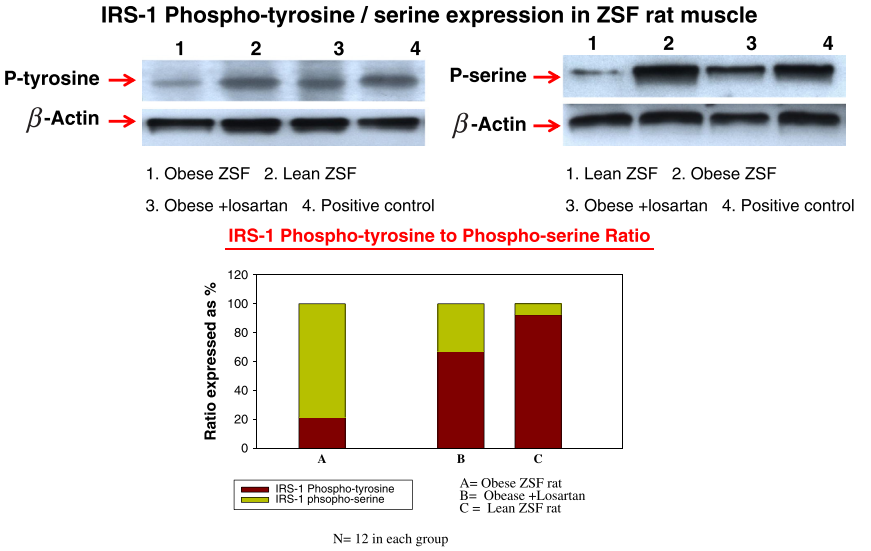

FIGURE 2. Experiments in ZSF rats treated with losartan, an ARB showing increased phosphoserine expression compared to lean controls and untreated obese ZSF rats.

Investigating further into the effects of angiotensin on insulin signaling pathway in vivo in ZSF rats, we demonstrated that the phosphorylation of IRS-1 is selectively channeled on to serine-threonine residues instead of tyrosine impairing PI3K activation (Fig. 2). Collectively, all these effects lead to inhibition of transmembrane translocation of glucose transporter-4 protein from the cytoplasm.

OTHER ANIMAL STUDIES

Previous studies have demonstrated that angiotensin II infusion into rats is associated with insulin resistance and fasting hyperglycemia.[41] Similar interaction between angiotensin II and insulin signaling were demonstrated in the rat kidney that involved protein kinase A–dependent mitogen-activated protein kinase cascade.[42]

PROPOSED MECHANISMS FOR CROSS TALK

The preceding sections have extensively discussed functional interaction and cross talk between angiotensin II and insulin signaling pathways at multiple levels. Whereas these interactions seem to complicate the understanding of physiological processes involved in homeostasis with potentially important pathophysiological implications, we attempt to simplify this cross talk with our proposed scheme of events represented in Figure 3. Essentially, the oxidative stress induced by angiotensin signaling through activation of nicotinamide adenine dinucleotide phosphate triggers serine-threonine phosphorylation of insulin receptor substrate and inhibits PI3K activity, thereby preventing the transmembrane translocation of glucose transporter-4. This cascade of events results in angiotensin-mediated insulin resistance. Additional cross talk

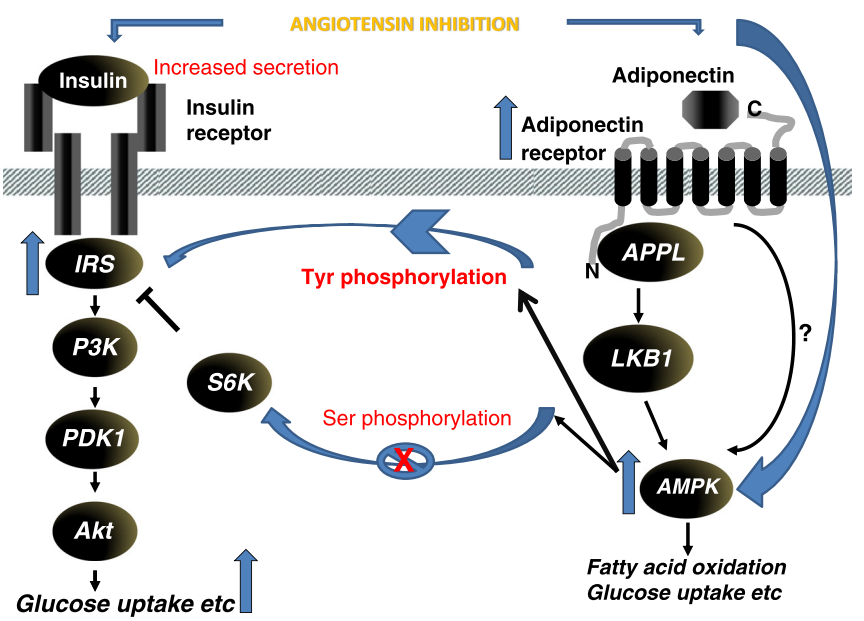

FIGURE 3. Proposed mechanisms of angiotensin inhibition on insulin signaling pathways and insulin sensitivity.

exists through adiponectin-induced regulation of insulin signaling processes. Conversely, use of angiotensin inhibitors such as ACE inhibitors or ARBs reverses these changes and promotes insulin sensitivity. In addition, these agents may enhance insulin sensitivity by augmenting the expression of adiponectin receptor protein, which further increases IRS-1 activation possibly by activating AMP kinase.

SUMMARY

Clinical use of RAAS inhibitors in nondiabetic patients is associated with primary prevention of diabetes, as demonstrated by several large-scale randomized prospective clinical trials. Furthermore, several anecdotal observations and other studies have shown better glycemic indices in diabetic patients receiving RAAS inhibitors. Experimental and clinical studies point out multiple sites of interaction in the signaling mechanisms of angiotensin II and insulin. Studies from several investigators and laboratories including ours have demonstrated significant angiotensin-insulin cross talk at several levels, including adiponectin and adiponectin receptor, AMP kinase, insulin receptor substrate, and PI3K. Unraveling the mechanistic details of such interaction opens up new opportunities to develop innovative preventive and therapeutic strategies in insulin-resistant states and metabolic syndrome.[43]

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