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Renin-angiotensin-aldosterone system and glucose homeostasis

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Abstract

The renin-angiotensin-aldosterone system is inappropriately activated in obesity. In individuals at risk for diabetes, inhibition of the renin-angiotensin-aldosterone system protects against kidney and heart disease, and also reduces the incidence of diabetes in large clinical trials. At a cellular level, angiotensin II and aldosterone induce insulin resistance by increasing oxidative stress and altering insulin signaling, leading to decreased glucose transport. Angiotensin II also contributes to oxidative stress, inflammation, and apoptosis in pancreatic β -cells. Aldosterone diminishes glucose-stimulated insulin secretion *in vivo* and *in vitro* from isolated pancreatic islets and cultured β -cells through a mineralocorticoid receptor-independent mechanism. We review these findings in the context of pharmacological strategies to interrupt the renin-angiotensin-aldosterone system to highlight the potential application of these strategies to the prevention of diabetes progression.

The renin-angiotensin-aldosterone system and diabetes

Approximately 246 million adults worldwide have diabetes.¹ This number is expected to grow to 380 million by the year 2025.^{1,2} Diabetes is associated with a dramatically increased risk of heart attack, stroke, and renal failure, as well as disability.³ The cost of diabetes-related health care was estimated to be \$232 billion in 2007. With an expected 7 million incident cases of type 2 diabetes mellitus (T2DM) per year worldwide,² there is a pressing need to develop strategies to prevent the development of T2DM in high risk individuals, such as those with the metabolic syndrome. Because recent clinical studies demonstrate a protective effect of renin-angiotensin-aldosterone system (RAAS) blockade on T2DM incidence, we review the mechanisms by which these drugs may confer protection.

The RAAS is essential to increasing sodium and fluid reabsorption when the body is challenged by sodium restriction or fluid loss (Figure 1). In the kidney, renin secretion by the juxtaglomerular apparatus is triggered by reduced sodium chloride delivery to macula densa cells in the distal nephron. Renin converts angiotensinogen into angiotensin I (Ang I), which is largely inactive. Ang I is cleaved by Ang I converting enzyme (ACE) to angiotensin II (Ang II). Ang II activates the Ang II type 1 (AT₁), Ang II type 2 (AT₂), and other receptors. AT₁ activation produces intense vasoconstriction in the systemic vasculature and raises blood pressure, whereas AT₂ produces vasodilatation. In the adrenal gland, Ang II stimulates aldosterone secretion from glomerulosa cells via AT₁. Aldosterone increases

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renal sodium chloride and water reabsorption by activation of the mineralocorticoid receptor (MR) in the principal cells in the distal nephron. An expanded discussion of the RAAS is provided elsewhere.⁴

The RAAS is pathologically activated in certain conditions such as essential hypertension, renal artery stenosis, and congestive heart failure. Hyperaldosteronism can result from inappropriate secretion by the adrenal and produces resistant hypertension with hypokalemia and metabolic alkalosis. Drugs which block the RAAS at various steps in the pathway are widely available (Figure 1), and include direct renin inhibitors, ACE inhibitors (e.g., ramipril, lisinopril, captopril, etc.), AT₁ receptor blockers (ARBs; e.g., valsartan, losartan, etc.), and MR antagonists (spironolactone and eplerenone). Under conditions of adequate sodium intake, the RAAS is suppressed, and pharmacologic blockade has little effect on blood pressure. RAAS blockade effectively reduces blood pressure in essential hypertension, however, and this effect is accentuated by diuretic administration.

ACE inhibitors and ARBs have long been used to prevent cardiovascular and renal damage in diabetic patients.⁵⁻⁷ Recent studies suggest that drugs that decrease the formation or actions of Ang II may also reduce the incidence of diabetes.^{8,9} We review here the evidence that the RAAS is activated in obesity and diabetes, including the mechanisms by which Ang II induces insulin resistance and affects pancreatic inflammation and apoptosis. We also examine recent data implicating aldosterone as a major effector in the development of insulin resistance and decreased pancreatic β -cell function. Finally, we consider the implications of these studies for the development of pharmacologic strategies to reduce incident diabetes.

The renin-angiotensin-aldosterone system is activated in obesity

Adipocytes express angiotensinogen (a precursor to Ang II), renin, and the Ang II type 1 (AT₁) receptor, with some species variability.¹⁰ The local formation of Ang II appears to be increased in obesity and leads to activation of nuclear factor kappa B (NF κ B) and the formation of inflammatory cytokines.¹⁰ Ang II also inhibits preadipocyte recruitment, leading to the storage of lipids outside of adipose tissue, lipotoxicity and insulin resistance, effects than can be blocked by AT₁ receptor inhibition.¹¹ In animal models of obesity, aldosterone is inappropriately elevated during high fat feeding, demonstrated by an increase in circulating aldosterone despite net positive sodium balance.¹² In humans, plasma aldosterone concentrations correlate with body mass index or indices of insulin resistance.¹³ Cell culture studies demonstrate that human adipocytes produce aldosterone-stimulating substances, such as oxidized derivatives of linoleic acid.^{14,15} Conversely, weight loss in humans results in decreased circulating angiotensinogen, plasma renin activity, and aldosterone concentrations, as well as lipid angiotensinogen.¹⁶⁻¹⁸ These data suggest that adipocyte-derived factors inappropriately activate the RAAS, and provide a rationale for targeting this system in obese patients to prevent cardiovascular and metabolic complications.

Angiotensin converting-enzyme inhibitors and angiotensin receptor blockers decrease the incidence of diabetes in high-risk populations

ACE inhibitors and ARBs decrease the incidence of new onset diabetes in large randomized clinical trials in patients with heart failure or at risk for coronary artery disease.⁸ In the first prospective randomized clinical trial designed to test the hypothesis that interrupting the RAAS would improve glucose homeostasis, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study, treatment with the ACE inhibitor ramipril did not significantly reduce the incidence of new-onset diabetes in patients with

impaired fasting glucose (IFG) (18.1% versus 19.5%, $P=0.15$).¹⁹ A greater proportion of subjects randomized to ramipril achieved fasting normoglycemia (42.5 vs. 38.2%; $P<0.001$ vs. control), however, and the median 2-hour OGTT glucose was lower in the ramipril group (135.1 vs. 140.5 mg/dl; $P=0.01$).

The NAVIGATOR study compared the effect of the ARB valsartan versus placebo on the development of diabetes in patients with impaired glucose tolerance and cardiovascular risk factors or disease.⁹ The incidence of diabetes was modestly but significantly lower in the valsartan-treated group compared to the placebo group (31% versus 33%; hazard ratio in the valsartan group, 0.86 with a 95% confidence interval [CI] of 0.80 to 0.92; $P<0.001$).

Compared to traditional anti-diabetic agents, ACE inhibition and ARBs have modest effects on glycemia. Treatment with the biguanide metformin reduced the incidence of T2DM in the Diabetes Prevention Program study, as did troglitazone.^{20,21} In the DREAM study, rosiglitazone significantly decreased the incidence of new onset T2DM.²² Thiazolidinediones are also associated with increased risk of cardiovascular events, however.^{23,24} Therefore, the need to develop pharmacological strategies to reduce the incidence of T2DM without increasing the risk of cardiovascular events remains. Randomized trials have established the cardiovascular benefits of ACE inhibitors, ARBs, and renin inhibition in high-risk populations.²⁵⁻²⁷

Angiotensin II and aldosterone decrease insulin sensitivity

The mechanism(s) whereby preventing the formation or action of Ang II could decrease the incidence of diabetes probably involves many pathways, including improved blood flow and decreased sympathetic activity. Activation of the RAAS also causes insulin resistance directly (Figure 2).

In muscle, Ang II inhibits phosphorylation of insulin receptor substrate (IRS)-1, preventing increases in phosphatidylinositol 3 (PI3)-kinase and subsequent translocation of glucose transporter (GLUT) 4 to the cell membrane.²⁸⁻³⁰ The mechanism through which Ang II decreases insulin-dependent GLUT-4 translocation involves activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the formation of reactive oxygen species.^{31,32} Conversely, ACE inhibitors and ARBs increase GLUT 4 translocation to the membrane and improve skeletal muscle glucose uptake in animal models.^{33,34} ARBs can also increase GLUT4 translocation and improve insulin sensitivity in cultured adipocytes and rodent models.³⁵⁻³⁷ Renin inhibition also improves insulin sensitivity and muscle glucose uptake in transgenic rats which harbor and express murine renin in extra-renal tissues (TG(mRen2)27 rats (Ren2)).³⁸ The direct renin inhibitor aliskiren improves insulin resistance, as determined by an insulin tolerance test, in the db/db mouse model.³⁹

Studies provide conflicting data as to the role of nitric oxide (NO) in the pathogenesis of insulin resistance during activation of the RAAS. On the one hand, increased NO and cyclic guanosine monophosphate (cGMP) have been reported to contribute the favorable effects of ACE inhibition and Ang II receptor blockade on muscle glucose uptake.^{34,40} For example, treatment of diabetic mice with an ACE inhibitor decreased circulating glucose and insulin concentrations and increased skeletal muscle glucose uptake through a bradykinin B₂receptor- and NO synthase (NOS)-dependent pathway.^{34,41} Likewise, NOS inhibition prevented the favorable effects of the ARB valsartan on muscle glucose uptake.⁴⁰ On the other hand, Csibi *et al.* have reported that Ang II induces of tyrosine nitration of Akt, resulting in inhibition of Akt phosphorylation and decreased translocation of GLUT 4, an effect that could be blocked by NOS inhibition.⁴²

Recent data suggest that Ang II may cause insulin resistance in part through aldosterone, or at least mineralocorticoid receptor (MR)-dependent, effects. For example, the aldosterone inhibitor spironolactone decreased oxidative stress and increased insulin-induced muscle glucose uptake in the Ren2 rat.⁴³ Likewise, aldosterone induces oxidative stress, inflammation and insulin resistance in rodent adipocytes, effects that are blocked by eplerenone, an MR inhibitor.⁴⁴ Aldosterone induces oxidative stress, degradation of insulin receptor substrates 1 and 2, and insulin resistance in cultured 3T3-L1 cells; in this case, the effect is blocked by a glucocorticoid receptor (GR) antagonist, but not by an MR antagonist.⁴⁵ Aldosterone inhibits uncoupling protein-1 and induces insulin resistance in brown adipocytes as well.⁴⁶ In a recent study in humans, however, Urbanet *et al.* reported no effect of physiological or supraphysiological concentrations of aldosterone on insulin sensitivity in visceral adipose tissue *ex vivo*, whereas pharmacological concentration of aldosterone decreased insulin sensitivity through a GR-dependent but MR-independent mechanism.⁴⁷ Thus, pharmacological strategies to decrease aldosterone formation may be expected to improve insulin sensitivity.

The renin-angiotensin-aldosterone system and β -cell function

Many studies of the role of the RAAS in modulating glucose homeostasis have focused on insulin sensitivity, but the importance of adequate insulin secretion by the pancreas has recently gained attention. Although obesity and the metabolic syndrome are characterized by insulin resistance, the maintenance of glucose homeostasis in this setting requires increased secretion and/or decreased insulin clearance to maintain effective insulin concentrations.⁴⁸ Studies in insulin-resistant populations indicate that the progression from normal to impaired glucose tolerance, and from impaired glucose tolerance to T2DM is characterized by declining β -cell function (or, inappropriate insulin secretion).⁴⁹ In this setting, insulin concentrations are increased compared to insulin-sensitive subjects, but are inappropriate in the setting of insulin resistance because they fail to meet the demands of insulin resistant tissues and cannot maintain normoglycemia. Results from two independent genome-wide association studies support the hypothesis that insulin secretory capacity is important in T2DM pathogenesis.^{50,51} These studies demonstrated that genes involved in pancreatic islet development and function are associated with increased T2DM risk. Although genetic and dietary components determine insulin secretory capacity, many other factors remain unexplored, and an expanded understanding should lead to additional targeted interventions.⁴⁸

Evidence suggests that the RAAS affects insulin secretion, and pharmacologic inhibition could reduce diabetes risk by preserving beta cell function. Ang II may impair insulin secretion indirectly by producing vasoconstriction and reducing islet blood flow. This effect has been demonstrated during pancreatic perfusion studies in rats.⁵² Similarly, Ang II infusion in humans decreases the amplitude of basal insulin oscillation and impairs glucose tolerance and insulin response during an oral glucose tolerance test.⁵³

Just as there is a vascular RAAS, many components of the RAAS are expressed in the endocrine pancreas, further supporting a role in regulation of insulin secretion (Figure 3).⁵² Renin and ACE have been localized to the vasculature and microvasculature of the pancreatic islet. In the islet, β -cells express angiotensinogen, and AT₁ and AT₂ receptors. Islet α -cells also express angiotensinogen and the δ cell expresses the AT₂ receptor. The MR is expressed in both mouse and human islets and appears to localize primarily in δ -cells and PP-cells of the pancreas.⁵⁴

Chronic exposure to high glucose concentrations or to high fat increases AT₁ receptor expression as well as oxidative stress, inflammation and apoptosis in β -cells, in isolated

islets, and in the intact pancreas.⁵⁴⁻⁵⁶ These changes are accompanied by decreased insulin content. Exposure to an ACE inhibitor or ARB reverses these effects.^{55,56} Direct renin inhibition increased pancreatic β -cell area, insulin secretion, and glucose tolerance in the genetically obese, diabetic KK-A(y) mice.⁵⁷ These data suggest that RAAS blockade could improve glucose homeostasis by improving the insulin secretory response.

Although the effects of RAAS blockade on insulin secretion in humans have not been studied extensively, recent studies are encouraging. In subjects with impaired fasting glucose or impaired glucose tolerance, treatment with valsartan for 26 weeks modestly increased glucose-stimulated insulin secretion, as measured via hyperglycemic clamp, and improved insulin sensitivity, measured by euglycemic clamp.⁵⁸ There was no effect of the ARB on glucose-independent insulin secretion, assessed by L-arginine stimulation.⁵⁸ Similarly, treatment with valsartan for 16 weeks reduced glucose excursion and increased insulin response during glucose tolerance tests in obese, hypertensive subjects. The benefits of RAAS blockade may be due to effects on both peripheral insulin sensitivity and insulin secretion, and further studies are needed to better define these responses and durability of the effect.

Aldosterone decreases insulin secretion *in vitro* and *in vivo*

A recent study using hyperglycemic clamps in aldosterone synthase-deficient mice suggests that endogenous aldosterone suppresses glucose-stimulated insulin secretion *in vivo*.⁵⁴ Aldosterone also decreases glucose- and IMBX-stimulated insulin secretion from cultured or perfused islets and from MIN6 cells, a β -cell line.⁵⁴ Several lines of evidence suggest that aldosterone decreases glucose-stimulated insulin secretion through an MR-independent mechanism. First, aldosterone decreased insulin secretion from the MIN6 β -cell line, which minimally express MR.⁵⁴ Second, the effect of aldosterone was not blocked by spironolactone, eplerenone, or the water soluble MR antagonist RU-28318; nor was the effect blocked by GR antagonism.⁵⁴

During treatment with an MR antagonist, plasma renin activity, Ang II, and aldosterone concentrations all increased, due to loss of feedback inhibition and induction of aldosterone synthesizing enzymes.⁵⁹ If aldosterone decreases insulin secretion through an MR-independent mechanism, then increased aldosterone concentrations during MR antagonism could result in impaired β -cell function and hyperglycemia in patients with the metabolic syndrome. Consistent with an MR-independent effect of aldosterone on insulin secretion, in patients with an aldosterone-producing adenoma, surgical excision of the adenoma reduced circulating glucose concentrations, whereas pharmacological treatment with spironolactone did not.⁶⁰ In one randomized, placebo-controlled, crossover study in 50 patients with T2DM and resistant hypertension, spironolactone improved blood pressure but increased circulating Ang II concentrations and significantly worsened glycemic control.⁶¹ Among patients with heart failure, treatment with spironolactone resulted in increased hemoglobin A1C and cortisol concentrations and decreased adiponectin, whereas these findings were not seen in the eplerenone-treated group.⁶² In a recent observational study, the incidence of diabetes was increased in spironolactone-treated patients compared to patients treated with the ARB losartan.⁶³ Additional prospective clinical studies are needed to elucidate the effect of MR antagonism on glucose metabolism and insulin secretion.

Concluding remarks

Ang II and aldosterone promote oxidative stress and interfere with insulin signaling, to decrease glucose uptake in insulin-sensitive cells via AT_1 receptor- and mineralocorticoid receptor-dependent mechanism, respectively. Pharmacologic strategies to reduce the production of Ang II and aldosterone or to block these two receptors improve insulin

sensitivity both *in vitro* and in animal models. Increasing evidence suggests that Ang II and aldosterone also decrease pancreatic β -cell function. In particular, Ang II contributes to glucose and lipid induced oxidative stress, inflammation, and apoptosis via the AT₁ receptor. Aldosterone decreases insulin secretion without decreasing insulin content of β -cells, through a mineralocorticoid receptor-*independent* mechanism that also involves oxidative stress. AT₁ receptor blockade improves insulin secretion in animal models and in humans. Strategies to reduce the production of Ang II should have similar effects. By contrast MR antagonism may be expected to decrease insulin secretion because aldosterone concentrations are increased due to lack of feedback inhibition. Thus, the net effect of MR antagonism may depend on the balance between improved insulin sensitivity and worsened insulin secretion.

The extent to which endogenous aldosterone contributes to the observed effects of Ang II on insulin sensitivity and insulin secretion remains an important question. During chronic AT₁ receptor antagonism or ACE inhibition, aldosterone concentrations “escape” back to normal concentrations.⁶⁴ If aldosterone contributes significantly to the effects of Ang II on insulin sensitivity or secretion, this could lead to inconsistent effects of ARBs and ACE inhibitors on the incidence of diabetes. Further strategies to prevent “aldosterone escape” could therefore be beneficial in individuals at high risk for diabetes.

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Figure 1. The renin-angiotensin-aldosterone system

The cascade is initiated by renin secretion, and subsequent conversion of angiotensinogen to angiotensin I (Ang I). Angiotensin II (Ang II) produces vasoconstriction and stimulates adrenal aldosterone secretion via AT₁ receptors. Pharmacologic agents are available to block this pathway at nearly every step in the pathway (highlighted in red). Aliskiren is the only currently available renin inhibitor. Angiotensin I converting enzyme (ACE) inhibitors prevent conversion of Ang I to Ang II. Mineralocorticoid receptor (MR) antagonists (e.g. spironolactone, eplerenone) block the effects of aldosterone in the kidney. Downstream targets of aldosterone include the epithelial sodium channel (ENaC) which is upregulated by the MR and mediates sodium reabsorption in the distal kidney.

Figure 2. Angiotensin II and aldosterone induce insulin resistance

Angiotensin II (Ang II) and aldosterone activate nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase to generate reactive oxygen species (O₂⁻). Activation of redox-sensitive serine kinases such as c-jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK)-1 leads to the phosphorylation of serines in insulin receptor substrate-1 (IRS-1) and decreased interaction with phosphatidylinositol 3-kinase (PI3K). This in turn leads to decreased activation of protein kinase B (Akt) and PKC, decreased translocation of GLUT4 to the membrane and decreased glucose transport. Blockade of the Ang II subtype 1 receptor (AT₁R) or the mineralocorticoid receptor prevents these effects of Ang II and aldosterone, respectively. Direct renin inhibitors and angiotensin-converting enzyme (ACE) inhibitors improve insulin resistance by decreasing the formation of Ang II and aldosterone. ACE inhibitors also increase glucose transport via a nitric oxide-dependent mechanism.

Figure 3. Angiotensin II and aldosterone decrease insulin secretion

Chronic hyperglycemia and free fatty acids increase the expression of the angiotensin II subtype 1 receptor (AT₁R) and uncoupling protein 2, as well as the activity of protein kinase C and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, leading to inflammation, the formation of reactive oxygen species (O₂⁻), β-cell apoptosis and decreased insulin formation and secretion. These effects are reversed by AT₁ receptor blockade (ARB). Aldosterone decreases insulin secretion without affecting the insulin content of β-cells, through a mechanism that also involves reactive oxygen species. This effect is not mediated via the mineralocorticoid receptor. ATP indicates adenosine triphosphate, cAMP cyclic adenosine monophosphate, GLUT2 glucose transporter 2, IBMX 3-isobutyl-1-methylxanthine, PDE phosphodiesterase, PKA protein kinase A, GPCR G-protein coupled receptors.