The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome

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Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. Am J Physiol Heart Circ Physiol 302: H1219–H1230, 2012. First published January 6, 2012; doi:10.1152/ajpheart.00796.2011.—The renin-angiotensin system (RAS) is an important therapeutic target in the treatment of hypertension. Obesity has emerged as a primary contributor to essential hypertension in the United States and clusters with other metabolic disorders (hyperglycemia, hypertension, high triglycerides, low HDL cholesterol) defined within the metabolic syndrome. In addition to hypertension, RAS blockade may also serve as an effective treatment strategy to control impaired glucose and insulin tolerance and dyslipidemias in patients with the metabolic syndrome. Hyperglycemia, insulin resistance, and/or specific cholesterol metabolites have been demonstrated to activate components required for the synthesis [angiotensinogen, renin, angiotensin-converting enzyme (ACE)], degradation (ACE2), or responsiveness (angiotensin II type 1 receptors, Mas receptors) to angiotensin peptides in cell types (e.g., pancreatic islet cells, adipocytes, macrophages) that mediate specific disorders of the metabolic syndrome. An activated local RAS in these cell types may contribute to dysregulated function by promoting oxidative stress, apoptosis, and inflammation. This review will discuss data demonstrating the regulation of components of the RAS by cholesterol and its metabolites, glucose, and/or insulin in cell types implicated in disorders of the metabolic syndrome. In addition, we discuss data supporting a role for an activated local RAS in dyslipidemias and glucose intolerance/insulin resistance and the development of hypertension in the metabolic syndrome. Identification of activated RAS as a common thread contributing to several disorders of the metabolic syndrome makes the use of angiotensin receptor blockers and ACE inhibitors an intriguing and novel option for multisymptom treatment.

obesity; angiotensinogen; hypercholesterolemia; glucose; insulin

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Introduction

The renin-angiotensin system (RAS) is an ever-evolving endocrine system with considerable checks and balances on the production and catabolism of angiotensin peptides most likely due to the manifold effects of angiotensins. To discuss the RAS in the metabolic syndrome requires a brief review of the components required for the synthesis and catabolism of angiotensin II (ANG II), the primary peptide of the system (Fig. 1). Angiotensinogen (AGT) is the only known precursor in the synthesis of ANG II. This large protein (~58 kDa) is produced by several cell types, including hepatocytes, adipocytes, kidney cells (e.g., mesangial cells, proximal tubule epithelial cells), and brain cells (e.g., neurons, glia). The liver is considered the primary source of circulating AGT in normal physiology, but production within other cell types (e.g., adipocytes, kidney cells) may contribute to local or even circulating concentrations of ANG II in pathophysiological conditions such as the metabolic syndrome. Kidney-derived renin cleaves 10 amino acids from the NH2-terminus of AGT to produce angiotensin I (ANG I), a biologically inactive peptide that is rapidly hydrolyzed by angiotensin-converting enzyme (ACE) to the octapeptide, ANG II. Several other angiotensin peptides formed from AGT have biological activity, including angiotensin 2–8 (angiotensin III, ANG III), angiotensin 3–8 (angiotensin IV, ANG IV), and angiotensin-(1–7) [ANG-(1–7)]. Products from degradation of ANG II at the NH2-terminus (ANG III, IV) result from aminopeptidase (A and M) catabolism, whereas ANG-(1–7) is formed primarily from ANG II through the actions of ACE2 at the COOH-terminus. Several of these angiotensin peptides have been implicated in insulin resistance (41, 71, 95) or hypertension (12, 85–86) of the metabolic syndrome. The complexity of the system, including the expression of various components that are regulated distinctly in different cell types, suggests that several different aspects of the meta-
Fig. 1. Components of the renin-angiotensin system (RAS). The precursor peptide, angiotensinogen, is cleaved by renin to form the decapeptide angiotensin I. The catalytic activity of renin increases when bound to the (pro)renin receptor [(P)RR], and furthermore, the otherwise inactive prorenin can become catalytically active when bound to the (P)RR. The dipeptidase angiotensin-converting enzyme (ACE) cleaves angiotensin I to form the octapeptide angiotensin II (ANG II), the central active component of this system. ANG II can be catabolized by angiotensin-converting enzyme 2 (ACE2) into angiotensin-(1–7) [(ANG-(1–7)], another active peptide of this system which typically opposes the actions of ANG II. ANG II can also be cleaved into smaller fragments, such as angiotensin III and angiotensin IV by aminopeptidases A and M, respectively. Most effects of ANG II are mediated by the angiotensin type 1 receptor (AT1R); however, ANG II can also bind to the angiotensin type 2 receptor (AT2R), which generally exhibits opposing effects to those at the AT1R. ANG-(1–7) acts via the Mas receptor and angiotensin IV can bind to the insulin-regulated aminopeptidase receptors (IRAP).

Table 1. IDF and AHA/NHLBI Joint Scientific Statement 2009 (3) states that diagnosis of metabolic syndrome requires three of the following

<table>
<thead>
<tr>
<th>Defining Parameter</th>
<th>Requisite Levels</th>
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<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>It is recommended that IDF cut points be used for non-Europeans, and either IDF or AHA/NHLBI cut points be used for people of European origin until more data are available.†</td>
</tr>
<tr>
<td>Elevated blood pressure*, mmHg</td>
<td>≥130/≥85</td>
</tr>
<tr>
<td>Elevated fasting blood glucose*, mg/dl</td>
<td>≥110</td>
</tr>
<tr>
<td>Elevated triglycerides*, mg/dl</td>
<td>≥150</td>
</tr>
<tr>
<td>Reduced HDL cholesterol*, mg/dl</td>
<td>Men ≤40</td>
</tr>
<tr>
<td></td>
<td>Women ≤50</td>
</tr>
</tbody>
</table>

IDF, International Diabetes Federation; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute. *Drug treatment for indicated parameter is an alternate indicator. †IDF: men ≥ 94 cm, and women ≥ 80 cm; and AHA/NHLBI: men ≥ 102 cm, and women ≥ 88 cm.
sites for interactions between the RAS and dyslipidemias of the metabolic syndrome include the regulation of RAS components in dyslipidemic conditions in cell types that contribute to vascular disease and effects of ANG II to promote oxidation of LDL cholesterol. Other interesting aspects of the RAS in dyslipidemias include the ability of certain angiotensin II type 1 receptor (AT\(_1\)R) antagonists to exert beneficial effects on dyslipidemias. We will summarize data supporting the influence of dyslipidemia on the RAS and vice versa, followed by a brief summary of clinical trial data for RAS inhibition in the treatment of dyslipidemias.

The influence of cholesterol on the RAS. Early studies supported an ability of hypercholesterolemia in the form of LDL cholesterol to increase AT\(_1\)R gene expression on vascular smooth muscle cells (78) and later that oxidized LDL can also increase AT\(_1\)R expression in human coronary artery endothelial cells (68). Follow-up studies demonstrated that AT\(_1\)R expression in aortas of rabbits was increased by hypercholesterolemia and contributed to greater vasoconstrictor responses to ANG II (77). Previous studies from our laboratory demonstrated that LDL receptor-deficient (LDLR\(^{-/-}\)) mice fed a diet enriched in fat and cholesteryl exhibited elevated plasma concentrations of AGT and ANG II compared with age-matched C57BL/6 mice fed standard mouse diet (29). These effects of hypercholesterolemia to stimulate circulating ANG II as well as AT\(_1\)R expression in cell types with established roles in the development of atherosclerosis may contribute to the beneficial effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition to decrease atherosclerotic burden. Improvements in lipid profiles may alleviate RAS contributions to vascular pathologies in multiple ways, as has also been shown that HDL cholesterol protects against diabetes-induced increases in AT\(_1\)R expression in rat aortas (114). These results support the concept that hypercholesterolemia stimulates the expression of several components of the RAS in tissues with pivotal roles in the development of atherosclerosis.

The brain RAS plays a pivotal role in control of blood pressure, and alterations in brain cholesterol metabolism have been linked to the regulation of the brain RAS. Recent studies demonstrated that 27-hydroxycholesterol and 24S-hydroxycholesterol upregulated the expression of AGT, ACE, and AT\(_1\)R in rat primary neurons through a liver X receptor (LXR)-\(\beta\)-dependent mechanism (74). Moreover, rats fed a cholesterol-enriched diet demonstrated an increased expression of ACE and AGT in brain (74). The authors also demonstrated markers of an activated RAS in the cerebrospinal fluid of patients who have an accumulation of 27-hydroxysterol in plasma because of mutations in CYP7B1, the gene for 27-hydroxycholesterol 7-\(\alpha\)-hydroxylase (74). These findings suggest that specific cholesterol metabolites that correlate to plasma levels of cholesterol may contribute to an activated brain RAS and hypertension of the metabolic syndrome.

Mechanisms for the stimulation of the RAS by cholesterol and/or its metabolites are unclear but may involve stimulation of LXR or other cholesterol-sensing nuclear receptors. However, in the case of LXR, since the administration of LXR ligands to LDLR\(^{-/-}\) or apolipoprotein E-deficient (ApoE\(^{-/-}\)) mice markedly decreased atherosclerotic lesion formation (55), an ability of LXR ligands to activate the RAS is not consistent with the antiatherogenic properties of these compounds. Further studies are needed to determine the mechanisms for cholesterol and/or cholesterol metabolites as regulators of components of the RAS and whether this regulation is significant in pathologies of the metabolic syndrome.

The influence of the RAS on cholesterol. In addition to the regulation of the RAS in the setting of dyslipidemia, ANG II exerts several effects that influence cholesterol metabolism. Data from our laboratory demonstrated that deficiency of angiotensin II type 1a receptors (AT\(_1\)aR) in LDLR\(^{-/-}\) mice exhibiting high plasma concentrations of ANG II strikingly reduced atherosclerotic lesion formation through a stimulated RAS (29). In this study, however, there were no changes in serum cholesterol due to AT\(_1\)aR deficiency in LDLR\(^{-/-}\) mice, and in subsequent studies, infusions of ANG II to ApoE\(^{-/-}\) or LDLR\(^{-/-}\) mice had no effect on serum concentrations of cholesterol (18) or on lipoprotein cholesterol distributions (49), suggesting limited influence of the RAS on cholesterol concentrations or distributions. Other data suggest the proatherogenic effects of ANG II are due to its impact on cholesterol modifications and foam cell formation, not on absolute cholesterol concentrations in serum. ANG II has been shown to upregulate the expression of Acyl-CoA:cholesterol acyltransferase-1 (ACAT1; converts free cholesteryl into esters for storage in lipid droplets, thus promoting foam cell formation) in primary cultures of human monocyte-macrophages, which could increase cholesterol content of atherosclerotic lesions (57). Several studies have reported that ANG II increased the oxidation of LDL in macrophage cell lines as well as mouse peritoneal macrophages, possibly through activation of NADPH oxidase (59–60). Interestingly, recent studies demonstrated that the administration of statins to ApoE\(^{-/-}\) mice infused with ANG II reduced atherosclerosis (116). However, the ability of statin administration to reduce ANG II-induced atherosclerosis in this study was also independent of serum cholesterol concentrations. These results suggest that ANG II may influence the atherogenic properties of cholesterol without necessarily changing the blood concentrations. Unfortunately, the majority of clinical trials examining the effects of RAS inhibition on dyslipidemias primarily quantify blood concentrations of LDL, HDL, or TGs (Table 2) rather than changes in cholesterol metabolites (e.g., oxidized LDL) that have been suggested to promote atherosclerosis. Thus the quantification of blood lipid levels following RAS blockade may not be the most important indicator of the effectiveness of these drugs against dyslipidemias of the metabolic syndrome.

The effects of RAS inhibition on cholesterol. Not surprising given the above discussion, clinical studies using RAS antagonists have demonstrated an improvement of cardiovascular risk factors, though with varied effects on lipid profiles (summarized in Table 2). While numerous clinical trials have failed to find significant improvements on blood TG and total cholesterol concentrations, several of these were limited by small population size (<130 patients) and/or short study durations (<4 mo) (43, 51, 63, 109) (Table 2). Data from the Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial, which involved 8,611 patients over the course of 4.8 years, showed that total cholesterol and non-HDL-C levels were reduced with losartan treatment compared with the \(\beta\)-blocker, atenolol (84). The Treat to Target study examined irbesartan treatment in 9,281 patients with, and 4,919 patients...
without the metabolic syndrome over the course of nine months and found that while irbesartan alone significantly reduced TG levels and increased HDL-C levels, the effects were much more pronounced in patients with the metabolic syndrome (61). A similar study examining 3,259 patients with metabolic syndrome found that irbesartan reduced concentrations of LDL-C and TG with more dramatic results in patients with severe insulin resistance (88). Some angiotensin receptor blockers (ARBs), such as telmisartan and eprosartan, have been reported to stimulate peroxisome proliferator-activated receptor-γ (PPARγ) (8, 96) and could thus indirectly influence systemic lipid concentrations, so it is unclear whether the differences in results from clinical trials arise from these ancillary properties of RAS blockade, especially when improvements in TG levels could be a result of improved insulin sensitivity (52, 88). However, in a study directly comparing several ARBs (can-desartan, eprosartan, telmisartan, losartan, irbesartan, and valsar-tan), those with minimal PPARγ-stimulating properties, such as losartan and can-desartan, exerted more pronounced effects to lower LDL cholesterol (64). These results suggest that RAS inhibition, rather than PPARγ agonizing effects, contribute to favorable effects of ARBs on serum lipids.

The RAS as a Modulator of Glucose Homeostasis in the Metabolic Syndrome

Insulin resistance is commonly manifest in patients diagnosed with the metabolic syndrome, though the exact parameter included in definitions of metabolic syndrome vary because insulin resistance can manifest as elevated fasting blood glucose or impaired glucose tolerance. For example, the World Health Organization criteria include the presence of diabetes mellitus, insulin resistance, or impaired fasting glucose or glucose tolerance (4), whereas the International Diabetes Federation and American Heart Association/National Heart, Lung, and Blood Institute criterion is elevated fasting plasma glucose (≥100 mg/dl) (3). The condition of insulin resistance exacerbates other symptoms associated with the metabolic syndrome and is recognized as part of the etiology leading to increased cardiac mortality (92). Accumulating evidence indicates hyperglycemia can increase ANG II synthesis, and elevated ANG II actions may be one mechanism through which insulin resistance exacerbates other aspects of the metabolic syndrome. Interestingly, the role for ANG II in the development of insulin resistance (82, 94) is confirmed by evidence showing that antihypertensive drugs that block the RAS may also act to prevent diabetes.

Regulation of the RAS by hyperglycemia. Prolonged hyperglycemia and tissue insulin resistance resulting in hyperinsulinemia can upregulate components of the RAS as well as enhance the proinflammatory and profibrotic actions mediated by ANG II, which have been linked to macrovascular complications of diabetes (42) as well as diabetic nephropathy (124). High-glucose levels stimulate renin release and increase the expression of (pro)renin receptor, AGT, ACE, and AT1R in rat kidneys (100, 108, 123–124). The angiotensin II type 2 receptor is also upregulated; however, this receptor appears to promote natriuresis and diuresis to counterbalance increases in blood pressure (46, 47). The increased expression of AGT by treatment with high glucose in rat proximal tubule cells is ameliorated by cotreatment with insulin, which acts by modulating proteins bound to the insulin response element within the AGT promoter (24, 122, 123). Similar regulation of AGT by acute changes in glucose and insulin using clamped rats has been observed in liver and adipose tissue (39). Infusion of insulin suppressed AGT gene expression in fat and liver of lean, but not obese, rats. In contrast, glucose infusion increased AGT gene expression in fat and livers of both obese and lean rats. The upregulation of RAS components necessary for the synthesis and actions of ANG II in tissues such as kidney, liver, and adipose tissue by hyperglycemia may contribute to hypertension associated with the metabolic syndrome as well as end-organ damage (e.g., kidney) in type 2 diabetics.

The RAS in the development of insulin resistance. Human, animal, and tissue research has indicated that ANG II can
reduce whole body glucose utilization and insulin sensitivity, increase skeletal muscle and adipose tissue insulin resistance, impair insulin signaling and action, and negatively affect pancreatic function and insulin secretion. Early attempts to implicate the RAS in the regulation of insulin sensitivity focused primarily on the hemodynamic effects of ANG II (15, 54, 110). A reduction of peripheral blood flow in response to ANG II decreased glucose and insulin delivery to skeletal muscle and adipose tissue (94). Conversely, improvements in glucose disposal and insulin sensitivity following ACE inhibition were attributed to a loss of ANG II-mediated vasoconstriction (76, 87, 102). Recent evidence suggests that the RAS influences glucose homeostasis independent of its ability to regulate blood flow. Specifically, Richey et al. (94) demonstrated that ANG II infusion into the interstitial space of skeletal muscle in dogs could result in insulin resistance independent of changes in blood flow (94). Chronic ANG II infusion into insulin-sensitive rats was shown to reduce peripheral glucose use and insulin-induced glucose uptake, as well as impair the ability of insulin to suppress hepatic glucose production (82). In the TG(mREN2)27 rat, a model of ANG II-induced hypertension, significant reductions in tyrosine phosphorylation of the insulin receptor and the insulin receptor substrate 1 in skeletal muscle were consistent with a whole body reduction in insulin-mediated glucose transport (101). ANG II activation of NADPH oxidase and the production of reactive oxygen species in skeletal muscle, which inhibits phosphatidylinositol 3-kinase recruitment of glucose transporter-4 (117), have been suggested as mechanisms contributing to ANG II-mediated inhibition of insulin action. Collectively, these studies suggest that an activated RAS may contribute to insulin resistance of the metabolic syndrome.

The impact of a pancreatic RAS on insulin secretion. In addition to regulation of insulin sensitivity, the discovery of a local RAS in the pancreas opened up the possibility that ANG II could directly influence pancreatic function (Table 3). In 1991, Chappell et al. (23) identified that several components of the RAS are expressed in canine pancreas. Further studies demonstrated, depending on the species examined, the expression of ANG II binding sites (22, 66), ANG II (67), ACE (65), and ACE2 (81) in pancreas. Moreover, hyperglycemia was demonstrated to increase ANG II-positive pancreatic stellate cells (62) and to increase the expression of RAS components (AGT, ACE, AT1R) in human islets (72). Early studies focused on the vasconstrictive actions of ANG II on pancreatic microvasculature because the regulation of blood perfusion into and out of the pancreas is critical for glucose sensing as well as for rapid release of insulin (56). An acute ANG II infusion into isolated mouse pancreas induced a dose-dependent reduction in pancreatic and islet blood flow that was accompanied by reduced glucose-induced insulin secretion (56). Acute inhibition of insulin secretion in the pancreas could be due to ANG II disruption of insulin signaling as well as decreased blood flow. Similar to observations in skeletal muscle, ANG II was demonstrated to induce reactive oxygen species in pancreatic islets from rats via stimulated expression and activation of NADPH oxidase (50). In addition to the promotion of oxidative stress in pancreas, chronic ANG II has been demonstrated to promote expression of monocyte chemoattractant protein-1 in RINm5F β-cells (25), suggesting that ANG II promotes inflammation in islets.

Recent studies suggested a potential role for ACE2 in the regulation of pancreatic insulin synthesis and secretion. ACE2 was identified in pancreatic β-cells from rats (35) and mice (81). In addition, the Mas receptor was demonstrated in mouse endocrine and exocrine pancreas (10), suggesting that pancreas has the ability to respond to ACE2-mediated production of ANG(1–7). Interestingly, mice with whole body deficiency of ACE2 displayed impaired first-phase insulin secretion when stimulated with glucose yet remained sensitive to insulin (81). Notably, adenoviral-mediated overexpression of ACE2 in pancreas of db/db mice increased islet insulin content, reduced β-cell apoptosis, and improved glucose tolerance (9). Since Mas receptor blockade reversed the beneficial effects of ACE2

<table>
<thead>
<tr>
<th>RAS Component/Species</th>
<th>Cell Type/Location</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Renin Human Rat</td>
<td>β-cells, Islets: connective tissue surrounding blood vessels and in reticular fibers AR42J: a pancreatic acinar cell line</td>
<td>(103) (21)</td>
</tr>
<tr>
<td>AGT Canine Rat</td>
<td>Pancreas α-cells</td>
<td>(23) (93)</td>
</tr>
<tr>
<td>ACE Rat</td>
<td>Islets: microvasculature, islet periphery</td>
<td>(106) (53)</td>
</tr>
</tbody>
</table>
| ACE2 Rat Mouse       | Acini and islets Islets | (106) (35) (9)
| AT1R Human Mouse     | β-cells β-cells | (103) (65) |
| AT2R Rat Mouse       | Colocalized with somatostatin-producing cells Islets (β-cells) | (119) (26) |
| Mas receptor Mouse   | Endocrine and exocrine | (10) |

AGT, angiotensinogen; ACE, angiotensin-converting enzyme; AT1R and AT2R, angiotensin II types 1 and 2 receptors, respectively; ACE2, angiotensin-converting enzyme 2.
adenoviral expression in pancreas on glucose homeostasis and first-phase insulin secretion, these results suggested a pivotal role for ANG-(1–7) in the regulation of pancreatic β-cell function. It appears that as for several other responses elicited by these angiotensin peptides, ANG II reduces pancreatic β-cell function, whereas ANG-(1–7) is protective. Therefore, the modulation of the RAS via a shift from the ANG II/AT1R axis to the ANG-(1–7)/Mas receptor axis may have potential as a novel therapy to blunt β-cell failure in patients with the metabolic syndrome.

The effect of RAS inhibition on insulin resistance. Studies in humans show that obese insulin-resistant men exhibit enhanced insulin sensitivity and improved early phase insulin secretion when treated with ARBs (90). Additionally, several large-scale clinical trials have demonstrated that the use of ARBs or ACE inhibitors can significantly reduce the incidence of new-onset diabetes (NOD) in hypertensive patients and/or patients with other symptoms of the metabolic syndrome (6, 11, 75, 121) (Table 4). However, the clinical acceptance of these drugs as treatments for diabetes is not unanimous as the variety of study parameters, end points, and pharmacological agents used in these trials has made it difficult to interpret and compare results.

The Heart Outcomes Prevention Evaluation Trial (HOPE), which concluded that ramipril (an ACE inhibitor) was more effective than placebo primarily in reducing cardiac mortality, myocardial infarction, and stroke (121) was analyzed post hoc for the incidence of NOD and demonstrated a 32% reduction in patients administered ramipril. Several other studies, including Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Captopril Prevention Project (CAPPP), and Studies Of Left Ventricular Dysfunction (SOLVD) trials that assessed the effectiveness of ACE inhibitors against other hypertensive treatments or placebo with a primary end point of cardiac events also reported significant reductions in NOD (6, 79, 115). Moreover, several meta-analyses have concluded that ACE inhibitors and ARBs provide a significant protection against the development of NOD (2, 107).

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial was specifically designed on the heels of the HOPE study to assess the effects of ramipril on the incidence of NOD (11). This study examined 5,269 people with impaired glucose tolerance and/or impaired fasting glucose, but without known cardiovascular disease (CVD), that were randomized to ramipril versus placebo, or rosiglitazone versus placebo for a three-year follow-up. Results from this trial were disappointing in that ramipril treatment for a median of three years was not shown to significantly reduce the incidence of NOD, but it did modestly increase regression to normoglycemia compared with placebo (11). The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial evaluated the effectiveness of the ARB valsartan in 9,306 patients over a median of five years in reducing NOD and reported a 14% reduction in NOD compared with placebo (75). Patients in the NAVIGATOR trial had impaired glucose tolerance and established CVD or risk factors. The DREAM and NAVIGATOR trials are the only large-scale trials thus far designed with the primary end point of NOD, and the results were conflicting. Differences between these studies include type of treatment (ACE inhibitor in DREAM vs. ARB in NAVIGATOR), baseline health status of the study population (no CVD in DREAM, established CVD in NAVIGATOR), and duration (3 yr in DREAM vs. 5 yr in NAVIGATOR). A comparison of the parameters of multiple clinical trials may yield insight into the conditions under which ARBs and ACE inhibitors are effective as an antidiabetic treatment. The trials that reported the highest risk reductions in NOD also had populations with the highest risk for cardiac events at baseline. Since RAS blockade was shown to be effective in reducing cardiac events, presumably these patients had an activated RAS (referring to elevated ANG II levels and/or enhanced ability of receptors to respond to ANG II). The DREAM trial excluded those with significant cardiac risk factors and thus possibly excluded the population that would most likely benefit from blockade of the RAS (i.e., those with an activated RAS). The NAVIGATOR did include patients with cardiovascular risk factors and/or disease, but this trial also included lifestyle modification for all participants, which independently reduces insulin resistance and improves cardiac outcomes and thus could be a confounding factor in the interpretation of the results of this study. Additionally, the increased use of concomitant medication in the NAVIGATOR trial makes it difficult to discern the benefits achieved from

### Table 4. Effects of RAS antagonists on the development of type 2 diabetes

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>Ramipril treatment reduces the risk of NOD in 5,720 patients at risk for cardiovascular events over 4.5 yr (relative risk, 0.66; ramipril vs. placebo treatments).</td>
<td>(121)</td>
</tr>
<tr>
<td>DREAM</td>
<td>Ramipril treatment had no significant effect on the development of NOD; however, it did increase regression to normoglycemia compared with placebo in study of 5,269 patients.</td>
<td>(11)</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>Valsartan treatment reduced the development of NOD by 14% in a study including 9,306 patients with impaired glucose tolerance and other cardiovascular risk factors over 5 yr.</td>
<td>(75)</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Of the 291 nondiabetic patients included in the SOLVD trial, 5.9% of those given enalapril compared with 22.4% of those given placebo developed NOD.</td>
<td>(115)</td>
</tr>
<tr>
<td>CAPPP</td>
<td>Of the 10,413 nondiabetic patients included in the CAPPP trial, there was a 14% reduction in NOD in captopril-treated patients.</td>
<td>(79)</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Patients without diabetes at baseline receiving lisinopril instead of chlorothalidone had reduced fasting glucose and through 2 yr of follow-up had significantly reduced NOD (odds ratio, 0.55).</td>
<td>(6)</td>
</tr>
<tr>
<td>LIFE</td>
<td>Over 4.8 yr, losartan treatment significantly reduced the incidence of NOD compared with atenolol (relative risk, 0.75) in 7,998 hypertensive patients with left ventricular hypertrophy.</td>
<td>(69)</td>
</tr>
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</table>

HOPE, Heart Outcomes Prevention Evaluation Trial; DREAM, Diabetes REduction Assessment with ramipril and rosiglitazone Medication; NAVIGATOR, Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research; SOLVD, Studies Of Left Ventricular Dysfunction; CAPPP, Captopril Prevention Project; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; NOD, new-onset diabetes.
valsartan alone. Interestingly, no trials have reported systemic levels of ANG II in participants, which might identify patients who exhibit an activated RAS. Correlation of systemic levels of ANG II with metabolic parameters, like hypertension, hyperglycemia, and obesity, could identify a pool of patients that would be responsive to RAS blockade and thus have a higher likelihood of delaying NOD.

The Adipose Tissue RAS as a Modulator of Blood Pressure in the Metabolic Syndrome

Both obesity, in the form of increased body mass index or waist circumference (Table 1), and elevated blood pressure are components of the metabolic syndrome and the RAS presents a potential causal link between the two. Notably, adipose tissue is the only tissue in adults that is able to expand indefinitely during the development of obesity and has gained increasing interest in its possible control of blood pressure. Adipocyte hypertrophy is a stimulus for increased production of several adipokines that have been implicated in the control of blood pressure, including components of the RAS. The most compelling data indicating a role for the RAS in the blood pressure component of the metabolic syndrome come from studies demonstrating an activated RAS as a mediator of obesity-associated hypertension. ANG II exerts several effects that regulate blood pressure, including vasoconstriction, stimulation of the sympathetic nervous system, and elaboration of aldosterone to promote sodium and water retention (Fig. 2).

Many of these effects have been demonstrated in experimental models of obesity-hypertension that have characteristics of the metabolic syndrome. The challenge is to understand how the RAS is activated in the setting of the metabolic syndrome and what downstream effectors then contribute to increased blood pressure.

Fig. 2. Interplay between the RAS and the metabolic syndrome. Specific factors of the metabolic syndrome (hypercholesterolemia, hyperglycemia, obesity defined as elevated waist circumference) regulate the expression of components of the RAS that activate ANG II production and responsiveness in specific tissues/cell types. Regulated production, catabolism, or secretion of RAS components from pivotal cell types (smooth muscle cells, endothelial cells, adipocytes, pancreatic islet cells, kidney cells, brain cells) results in angiotensin peptide-mediated mechanisms that then augment or contribute to the development of specific aspects of the metabolic syndrome.
dance decreased as body mass index or adipocyte size increased, secretion of AGT protein from adipose tissue was increased (120). These effects were specific to adipose tissue, as AGT mRNA was not changed in liver or other tissues from mice with diet-induced obesity. The authors suggested that even though mRNA abundance of AGT in individual adipocytes was decreased, the marked increase in adipose tissue mass resulted in greater plasma levels of AGT with obesity.

In addition to AGT, other components of the RAS are expressed in adipocytes and regulated in the metabolic syndrome. Results from our laboratory demonstrated that initial stimulation of ACE2 mRNA abundance in adipose tissue of mice fed a high-fat diet for one week was followed by a reduction in ACE2 enzymatic activity after four months on diet, potentially contributing to high local and systemic levels of ANG II and the development of obesity-hypertension (44). In addition, postnatal overfeeding or high-fat feeding in rats resulted in increased adipose tissue (pro)renin receptor expression (1). Again, the mechanisms for changes in the expression of RAS components in adipose tissue with obesity are unclear. However, in the case of ACE2, results from our studies demonstrated that ACE2 may be shed from hypertrophied adipocytes through cleavage of the extracellular domain by tumor necrosis factor-α convertase [a disintegrin and metalloproteinase 17 (ADAM17)] (44). In addition, recent studies from our laboratory demonstrated that bone marrow deficiency of ACE2 in high-fat-fed mice increased markers of adipose inflammation and impaired glucose tolerance (105), suggesting an interplay between adipocytes and macrophages in regulation of adipose tissue function. It will be of interest to determine whether specific dietary interventions, including changes in the type, amount, or source of dietary fat/cholesterol, can be targeted to blunt activation of the adipocyte RAS.

The role of the adipose tissue RAS in obesity-hypertension. Studies from our laboratory have shown that rats prone to obesity when fed a medium-fat diet become hypertensive associated with an activated RAS compared with rats resistant to the development of obesity when fed the diet (13). Evidence that this effect may be due to the adipose tissue RAS comes from Massiera et al. (73) who created a mouse model of AGT overexpression specifically in adipocytes, under the control of a fatty acid binding protein promoter. In mice with whole body AGT deficiency, transgenic overexpression of AGT only in adipocytes increased plasma AGT levels by 20–30%, demonstrating a contribution of adipocyte-derived AGT to the systemic RAS. Moreover, an overexpression of AGT in adipocytes of AGT-deficient mice normalized the hypotensive phenotype of AGT knockout animals. When AGT was overexpressed in adipocytes of wild-type mice, systolic blood pressure increased. Conversely, recent studies from our laboratory demonstrate that a deficiency of AGT specifically in adipocytes of wild-type mice reduced plasma AGT concentrations and systolic blood pressure (7). These results demonstrate that adipocyte-derived AGT contributes to systemic AGT levels and blood pressure under normal conditions. These results set the stage for further studies examining the role of adipocyte-derived AGT as a source of plasma AGT and hypertension associated with obesity.

The subject of blockers of the RAS as high-efficacy drugs in the treatment of obesity-hypertension has been previously reviewed (16, 21, 32, 37, 53, 58, 93, 97–99, 103, 106, 118, 119). Given the fairly consistent data demonstrating the activation of the RAS in patients with the metabolic syndrome and obesity-related hypertension, the use of RAS inhibitors appears warranted. Moreover, as described in this review, targeted inhibition of the RAS may provide benefits against several aspects of the metabolic syndrome, including dyslipidemias, insulin resistance, and NOD even in the absence of hypertension.

Conclusions

The RAS is regulated by several causative factors within the metabolic syndrome but is also a contributor to the disorders of the metabolic syndrome (Fig. 2). This suggests that the RAS may be a common thread linking these disorders. Key features associated with the metabolic syndrome, including hyperglycemia, hypercholesterolemia, and high-fat environments, regulate the expression of RAS components in cell types (e.g., mesangial cells, macrophages, adipocytes, vascular wall cells) that mediate disorders of the syndrome. Conversely, angiotensin peptides then contribute to organ-specific disorders of the syndrome, including decreased insulin responsiveness in skeletal muscle or adipose tissue, pancreatic β-cell apoptosis and deficits in insulin secretion, macrophage foam cell formation, and increased blood pressure. Each of these effects of an activated RAS in the form of increased local or systemic ANG II has been linked experimentally and clinically to the metabolic syndrome, and drugs inhibiting the RAS have shown benefits against several defining components of the metabolic syndrome. It is tempting to speculate that interference with the RAS at specific sites of the system may be an effective single therapy with an efficacy against multiple disorders of the syndrome. A more precise understanding of the mechanisms for activation of the RAS by components of the metabolic syndrome in specific cell types (e.g., adipocytes) may delineate new therapeutic approaches. For example, nutritional interventions and/or drug therapies that regulate RAS components within specific cell types, such as adipocytes, may identify lifestyle modifications that limit RAS activation in the metabolic syndrome. In addition, the identification of the relative role of the systemic versus local RAS in specific disorders of the syndrome may delineate specific therapies that could be targeted to blunt RAS activation within certain cell types. ACE2 and/or ANG-(1–7) may serve as a novel therapeutic components of the RAS that, if activated, could treat multiple components of the metabolic syndrome (hypertension, diabetes).

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

K.P., R.S., F.Y., and L.A.C. prepared figures; K.P., R.S., F.Y., and L.A.C. edited and revised manuscript; K.P., R.S., F.Y., and L.A.C. approved final version of manuscript; L.A.C. conceived and designed research; L.A.C. performed experiments; L.A.C. analyzed data; L.A.C. interpreted results of experiments.
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