Review Article

The Renin-Angiotensin System in the Pathophysiology of Type 2 Diabetes

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Key Words

Renin-angiotensin system • Insulin secretion • Insulin resistance • Skeletal muscle • Adipose tissue

Abstract

Increased activation of the renin-angiotensin system (RAS) has been related to cardiovascular disease and type 2 diabetes mellitus. Most randomized clinical trials have demonstrated that RAS blockade reduces the incidence of type 2 diabetes, which has been explained by improved insulin secretion and insulin sensitivity. In this review, an overview of the mechanisms that may underlie the association between the RAS and type 2 diabetes will be provided, with focus on skeletal muscle and adipose tissue function. This will include discussion of several human studies performed in our laboratory to investigate the metabolic and hemodynamic effects of the RAS, combining in vivo measurements of whole-body and tissue metabolism with molecular and immunohistochemical approaches. Available data suggest that the detrimental effects of the RAS on insulin secretion are mediated by a reduction in pancreatic blood flow and induction of islet fibrosis, oxidative stress as well as inflammation, whereas both impaired skeletal muscle function and adipose tissue dysfunction may underlie RAS-induced insulin resistance. Thus, although future studies in humans are warranted, current evidence supports that targeting the RAS in intervention studies may improve metabolic and cardiovascular function in conditions of insulin resistance like obesity and type 2 diabetes.

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Introduction

Two key features in the pathogenesis of type 2 diabetes are insulin resistance (a decreased ability of insulin to stimulate peripheral glucose uptake) [1] and beta-cell failure (inability of the pancreatic beta-cells to adequately secrete insulin) [2]. Although it is well established that abdominal obesity is a major risk factor for chronic diseases, the mechanisms underlying obesity-related type 2 diabetes are not yet fully understood. However, progress has been made regarding the identification of underlying mechanisms as well as approaches to prevent, delay, or treat type 2 diabetes over the past few years.

Obesity is characterized by increased activation of the renin-angiotensin system (RAS), as has been reviewed extensively [3, 4]. Interestingly, the RAS has been linked to obesity-related chronic diseases. More specific, the RAS has been established as a major determinant of cardiovascular disease [5–7]. In addition, multiple lines of evidence suggest that increased activation of the RAS is involved in the development of type 2 diabetes [3, 8–10]. In agreement with the latter, a meta-analysis of comparative outcome trials [11] has shown that RAS blockade, using either angiotensin (Ang) II type 1 receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi), reduced the incidence of new-onset type 2 diabetes by 22% in high-risk populations. More recently, the prospective NAVIGATOR trial [12] has also shown that treatment with the ARB valsartan (median follow-up 5 years), in addition to lifestyle modification, reduced type 2 diabetes incidence by 14% in subjects with impaired glucose homeostasis. However, the prospective DREAM trial [13] showed somewhat conflicting results. In this trial, ACEi treatment (median follow-up 3 years) non-significantly reduced the incidence of type 2 diabetes by 9% compared with placebo in subjects with impaired glucose homeostasis but without cardiovascular disease. However, ACEi treatment significantly increased regression to normoglycemia and reduced 2-hour glucose concentrations compared with placebo [13]. Importantly, differences in study design, population, and treatment duration may underlie the less convincing effects of ACEi on the onset of type 2 diabetes in the DREAM trial. Nevertheless, most randomized clinical trials indicate that RAS blockade may protect against the development of type 2 diabetes in humans. The beneficial effects of RAS blockade in the prevention of type 2 diabetes have been explained both by improved insulin sensitivity and insulin secretion [3, 8, 9].

In this review, an overview of the mechanisms that underlie the relation between disproportionate activation of the RAS and type 2 diabetes will be provided, with focus on mechanisms related to insulin sensitivity. This will include the discussion of several human studies performed in our laboratory, in which whole-body and tissue physiology were studied in vivo in humans, using techniques like arterio-venous balance measurements across adipose tissue (AT) and skeletal muscle, tissue blood flow measurements, microdialysis and hyperinsulinemic-euglycemic and hyperglycemic clamps, in combination with molecular and immunohistochemical approaches to examine the metabolic and hemodynamic effects of Ang II – the main effector molecule of the RAS – and RAS blockade.

The Renin-Angiotensin System and Beta-Cell Function

Obesity and physical inactivity are major risk factors for the development of insulin resistance and type 2 diabetes. The decline in insulin sensitivity imposes progressive stress on the compromised beta-cell. At a certain stage, insulin secretion becomes insufficient to maintain normoglycemia, and glucose concentrations start to rise into the prediabetic range, resulting in impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) [14]. Beta-cell failure is a prerequisite in the development for type 2 diabetes, and a deterio-

ration of beta-cell function as well as loss of functional beta-cell mass are important determinants of disease progression [2, 15].

Evidence suggests that the RAS may contribute to an impaired insulin secretion [9, 16, 17]. In rodents, Ang II decreased pancreatic islet blood flow, which could lead to a reduced insulin release by the beta-cells [9, 17], whereas RAS blockade enhanced pancreatic blood flow [18, 19]. In addition to the systemic RAS, which is known for its classical effects on blood pressure, electrolyte and fluid homeostasis [20, 21], RAS components have been identified in many tissues, including the kidney, heart, brain, nerve fibers, reproductive organs, blood vessels, liver, skeletal muscle, AT, and pancreas [3]. Thus, it may well be that the pancreatic RAS also directly affects beta-cell function and mass. Indeed, in vitro and in vivo studies performed in rodents have shown that the RAS induced islet fibrosis, oxidative stress, inflammation, and impaired insulin secretion, whereas RAS blockade with an ACEi or ARB improved islet morphology and function and increased glucose tolerance [22–28].

Notwithstanding the extensive data derived from animal studies, evidence in humans is limited. Incubation of isolated human pancreatic islets with an ACEi counteracted several of the deleterious effects of high-glucose exposure, including reduction of insulin secretion and increased oxidative stress [29]. In vivo, it has been demonstrated that treatment with the ARB candesartan (8 mg daily for 3 months) or ACEi captopril (mean dose 81 ± 12 mg daily for 4 months) increased early-phase insulin secretion in patients with essential hypertension and impaired glucose tolerance [30, 31], although treatment with the ARB valsartan (80 mg twice daily) for 6 weeks [32] or the ACEi ramipril (up to 15 mg daily) for 3 years [33] did not improve beta-cell function. In addition to other methodological issues, the dosage used and treatment duration may explain these conflicting findings. Very recently, we have performed a randomized, placebo-controlled, double-blind study to investigate the effects of long-term treatment with the ARB valsartan (320 mg daily) on beta-cell function in subjects with impaired glucose metabolism. We demonstrated that valsartan treatment for 26 weeks improved both first-phase and second-phase insulin secretion, assessed by a hyperglycemic-clamp, compared with placebo [34]. Collectively, available data indicate that the pancreatic islet RAS may, at least in part, be responsible for impaired insulin secretion, and RAS blockade may be a promising strategy to enhance insulin secretion in subjects at high risk of developing type 2 diabetes.

The Renin-Angiotensin System and Insulin Sensitivity

Although several clinical studies have shown beneficial effects of RAS blockade on insulin sensitivity in humans [30, 35–43], conflicting data have also been reported [44–53]. Unfortunately, many of these investigations are based on uncontrolled study designs and surrogate markers of insulin sensitivity, and are potentially confounded by the use of additional medication. Therefore, we performed a double-blind, placebo-controlled, randomized trial to examine the effects of ACE inhibitor treatment on insulin sensitivity, as assessed by a hyperinsulinemic-euglycemic clamp, in obese insulin resistant subjects. We demonstrated that treatment with the ACE inhibitor ramipril (5 mg daily) for 2 weeks had no significant effects on whole-body insulin sensitivity [54]. Our findings are consistent with evidence from other well-designed trials in nondiabetic hypertensive patients [53] and in type 2 diabetic patients with hypertension [47, 48], showing no beneficial effect of short-term ACE inhibitor treatment on insulin sensitivity. Thus, in humans, evidence for beneficial effects of short-term RAS blockade on insulin sensitivity is controversial. However, dosage and treatment duration may be important factors determining study outcome. This is supported by recent findings from our group, demonstrating that treatment with the ARB valsartan

(320 mg daily) for 26 weeks significantly improved insulin sensitivity compared with placebo in subjects with impaired glucose metabolism [34].

As stated above, RAS components are present in a variety of tissues playing a major role in the etiology of insulin resistance and type 2 diabetes. We discussed several years ago that the RAS may exert detrimental effects in skeletal muscle and AT, which in turn may contribute to insulin resistance [3]. Thus, the beneficial effects of long-term RAS blockade on insulin sensitivity may be mediated by improved skeletal muscle and AT function. In the following paragraphs, an up-to-date overview of studies that have investigated the effects of the RAS on skeletal muscle and AT function in relation to insulin sensitivity will be provided.

The Renin-Angiotensin System and Skeletal Muscle Function

Skeletal muscle is a major tissue in the etiology of insulin resistance, as it accounts for more than 80% of insulin-stimulated glucose disposal [55]. The RAS may induce impairments in skeletal muscle metabolism through effects on tissue perfusion, skeletal muscle insulin signaling and mitochondrial function.

Skeletal Muscle Blood Flow

The vascular system controls the delivery of nutrients and hormones to skeletal muscle. Therefore, skeletal muscle blood flow may regulate tissue metabolism and contractile performance. In addition to total blood flow, expansion of the endothelial surface area available for exchange of nutrients through the recruitment of additional microvasculature within the muscle may enhance nutrient delivery to the tissue and may be an important factor that determines skeletal muscle glucose uptake [56]. Indeed, it has been demonstrated that impaired insulin-mediated capillary recruitment, as seen in obesity and insulin resistance [57, 58], may contribute to reduced glucose uptake in vivo [59–62].

Since the RAS is one of the major mechanisms regulating vascular tone [20, 21], we hypothesized that Ang II may reduce skeletal muscle blood flow in humans, which in turn may contribute to reduced glucose uptake. Indeed, we found that local administration of Ang II into the gastrocnemius muscle by microdialysis markedly decreased local blood flow in lean and obese subjects [63]. In line, chronic RAS blockade increased postprandial forearm blood flow in subjects with type 2 diabetes [64], and both acute and chronic RAS blockade prevented or improved skeletal muscle microvascular dysfunction in rats [65–67]. However, we did not find an increase in basal and insulin-stimulated total forearm blood flow after 2 weeks ACEi treatment in obese insulin resistant subjects [54]. It should be mentioned that we did not assess capillary recruitment in the latter study. To summarize, the majority of available data suggest that the RAS is involved in the regulation of skeletal muscle blood flow (total blood flow and/or capillary recruitment), although the quantitative contribution of RAS-induced impairments in skeletal muscle blood flow to overall insulin and glucose homeostasis in states of insulin resistance remains to be established.

Skeletal Muscle Insulin Signaling

Evidence from cell experiments and animal studies indicate that the RAS may directly impair insulin signaling. It has been shown that the heterozygous TG(mREN2)27 rat, harboring the mouse transgene for renin, was characterized by increased Ang II concentrations and insulin resistance, which could be attributed to specific defects in the insulin-signaling pathway in skeletal muscle [68]. In agreement with these findings, both acute and chronic RAS blockade increased protein expression of glucose-transporter 4 (GLUT4) and decreased insulin resistance in obese Zucker rats [8]. Bradykinin accumulation caused by

ACE inhibitor treatment may also contribute to the beneficial effects on glucose metabolism. For example, it has been demonstrated that bradykinin increased basal and insulin-stimulated glucose uptake in skeletal muscle of insulin resistant obese Zucker rats [69, 70], possibly by improving post-receptor insulin signaling and enhancing GLUT4 translocation to the cell membrane [70].

Furthermore, it has been shown that Ang II infusion induced insulin resistance in rats, which could, however, not been attributed to impairment in early steps of insulin signaling [71]. Rather, increased oxidative stress, possibly through impaired insulin signaling located downstream from phosphatidylinositol (PI) 3 kinase activation, seems to be involved in Ang II-induced insulin resistance [71]. In line, in vivo treatment with the ARB valsartan reduced oxidative stress, NF- κ B activation and TNF- α expression in skeletal muscle of the TG(mREN2)27 rat [72]. In the same study, Ang II treatment of L6 myotubes induced NF- κ B activation and TNF- α production and decreased insulin-stimulated Akt activation and GLUT4 translocation, effects that were markedly diminished by the ARB valsartan [72].

Blockade of RAS via direct inhibition of the rate-limiting enzyme renin, thereby reducing the conversion of angiotensinogen to Ang I, leading to decreased Ang II concentrations, may provide more potent RAS blockade compared with ACEi or ARBs. The effects of direct renin inhibition, or inhibition of aldosterone effects using mineralocorticoid receptor blockade, on glucose metabolism and the onset of type 2 diabetes may be different from treatment with ACEi and/or ARBs. Direct renin inhibition and mineralocorticoid receptor blockade has been shown to improve insulin sensitivity and skeletal muscle glucose uptake in obese Zucker rats [73], transgenic (mRen2)27 rats [74, 75], and diabetic mice [76, 77]. At the moment, however, no clinical data is available yet regarding the effect of these drugs on glucose metabolism in humans. Thus, additional outcome trials are needed to establish the role of these novel classes of antihypertensive drugs, alone or in combination with ACEi or ARBs, in the prevention of type 2 diabetes.

In summary, several lines of evidence suggest that the RAS may contribute to impaired insulin signaling in skeletal muscle, either directly or via induction of oxidative stress and NF- κ B activation in this tissue. Until now, however, human studies examining the effects of Ang II and RAS blockade on skeletal muscle insulin signaling have not been performed.

Mitochondrial Function

Mitochondrial dysfunction in skeletal muscle has been suggested to underlie the development of insulin resistance and type 2 diabetes, although it should be explicitly mentioned that a number of recent studies question whether reduced mitochondrial function is a primary factor in the pathophysiology of these disorders [78]. Increased skeletal muscle mitochondrial reactive oxygen species (ROS) have been implicated in mitochondrial dysfunction and insulin resistance [79–81]. Interestingly, it has been shown that Ang II increased mitochondrial ROS, decreased the expression of genes involved in mitochondrial biogenesis, and reduced mitochondrial content and membrane potential in C2C12 myocytes, whereas RAS blockade reversed these effects [82]. Furthermore, chronic Ang II infusion in mice reduced muscle mitochondrial content, increased intramuscular triacylglycerol (TAG) content and deteriorated glycemic control. RAS blockade was able to partially reverse the reduction in mitochondrial content, which was associated with an increased fat oxidation, a decreased intramuscular TAG content, and an improved glucose tolerance [82]. Nevertheless, data in humans are scarce. We have shown that 2 weeks ACEi treatment had no effect on whole-body substrate oxidation and intramuscular TAG content [54]. Clearly, more human in vitro studies and long-term clinical trials are needed to examine the importance of the RAS in skeletal muscle metabolism. Currently, we are investigating the effects of long-term RAS blockade on skeletal muscle fatty acid handling in subjects with impaired glucose

metabolism, using a dual stable isotope approach in combination with measurements of arterio-venous concentration differences across forearm muscle and forearm blood flow, enabling differentiation between the metabolic fate of dietary versus endogenous fatty acids. In addition, skeletal muscle biopsies will allow assessment of RAS blockade-induced effects on intramuscular lipid metabolism.

The Renin-Angiotensin System and Adipose Tissue Function

Converging evidences suggest that AT dysfunction, rather than abdominal fat mass per se, plays a crucial role in the development and progression of insulin resistance and type 2 diabetes [83]. Adipocyte hypertrophy, macrophage infiltration, inflammation, and an impaired AT blood flow (ATBF) are important aspects of AT dysfunction that are associated with insulin resistance, as reviewed [83].

In humans, different RAS components have been identified in AT [84–89]. We have measured arterio-venous concentration differences of Ang II and its precursor, angiotensinogen (AGT), across abdominal subcutaneous AT in combination with measurements of ATBF in lean and obese subjects under baseline conditions and during beta-adrenergic stimulation, and have shown that locally produced Ang II in AT was not secreted into the circulation in these subjects [90]. However, AGT was released from AT during beta-adrenergic stimulation in obese subjects, which may have contributed to increased plasma Ang II concentrations [90]. Together, these data suggest that the RAS in AT may exert autocrine, paracrine, and endocrine effects. Indeed, substantial evidence suggests that disturbances in the RAS may impair AT function via multiple mechanisms, which together may contribute to the development of insulin resistance, as discussed below.

Adipocyte Size

Hypertrophic adipocytes in obese and prediabetic individuals as well as in patients with type 2 diabetes have been observed by many investigators [91–94]. In fact, enlargement of abdominal subcutaneous adipocyte size appears to be an independent determinant of insulin resistance and type 2 diabetes [94, 95]. A reduced buffering capacity for lipid storage in hypertrophic adipocytes, leading to lipid overflow in the circulation and ectopic fat deposition, as well as increased production of pro-inflammatory cytokines by enlarged adipocytes seem to underlie the association between adipocyte size and insulin resistance [83, 96].

The enlargement of adipocytes may represent a failure in the recruitment of new adipocytes due to impaired differentiation, which is a precipitating factor in the etiology type 2 diabetes [93, 94]. Cell experiments and studies in rodents indicate that the Ang II may inhibit adipocyte differentiation, which may contribute to enlargement of existing adipocytes. Conversely, RAS blockade has been found to reduce adipocyte size [97–101]. In line, we have recently shown that long-term ARB treatment markedly decreased abdominal subcutaneous adipocyte size, with a shift towards a higher frequency of small adipocytes, compared with placebo in subjects with impaired glucose metabolism [102]. Interestingly, it has been demonstrated that some ARBs show partial peroxisome proliferator-activated receptor-gamma (PPAR γ) agonistic activity in vitro, which may contribute to increased adipocyte differentiation [103, 104]. Telmisartan is the most potent and only ARB to show activation of PPAR γ at concentrations achievable in the plasma with normal oral dosing [104]. However, studies in subjects with the metabolic syndrome or diabetes comparing telmisartan with different comparators, including other ARBs, could not demonstrate a consistent superiority regarding improvement of glucose metabolism by telmisartan [105].

Important processes in the regulation of adipocyte size, in addition to adipocyte differentiation, include the storage and release of fatty acids. Ang II stimulation increased lipid synthesis and storage in 3T3-L1 and human adipocytes [106]. Moreover, recent in vitro experiments have demonstrated that Ang II decreased, whereas RAS blockade increased gene/protein expression and activity of lipoprotein lipase, an enzyme that increases TAG clearance by AT [98]. Furthermore, we [63] and others [107, 108] have shown that local Ang II administration in abdominal subcutaneous AT by microdialysis decreased AT lipolysis in vivo in humans. We confirmed and extended these findings by demonstrating that Ang II modestly but dose-dependently reduced lipolysis in human isolated adipocytes, an effect that was completely abolished by Ang II type 1 receptor blockade [109]. These Ang II-induced effects may, theoretically, contribute to adipocyte enlargement. However, conflicting data with respect to RAS effects on AT lipolysis have also been reported [110–112]. Taken together, the RAS may affect adipocyte size through effects on adipocyte differentiation and AT lipid metabolism, thereby potentially modulating the lipid storage capacity of adipocytes, the inflammatory phenotype of AT and, as a consequence, insulin sensitivity.

Adipose Tissue Inflammation

AT macrophage infiltration and inflammation are important hallmarks of obesity, insulin resistance, and type 2 diabetes [83]. Adipocyte size is an important determinant of adipokine expression and secretion, with a shift toward dominance of proinflammatory adipokine secretion by large adipocytes [83].

Interestingly, it has been demonstrated that Ang II increased, whereas RAS blockade decreased AT gene expression of inflammatory markers, thereby affecting glucose homeostasis in rodents [23, 25, 99–101, 113, 114]. As mentioned above, we have recently found that treatment with the ARB valsartan for 26 weeks reduced abdominal subcutaneous adipocyte size compared with placebo in subjects with impaired glucose metabolism [102]. This may lead to beneficial alterations in AT gene expression and secretion of inflammatory cell markers. Indeed, we have recently demonstrated that the valsartan-induced decrease in adipocyte size was associated with reduced expression of macrophage infiltration markers in human AT [102]. The reduction in AT gene expression of inflammatory cell markers after RAS blockade may in turn translate into alterations in circulating adipokines. Indeed, several studies have shown that ARB treatment increased circulating adiponectin concentrations [115–119]. In contrast, ARB treatment had no effects on circulating leptin, TNF- α and adiponectin, despite increased insulin sensitivity [120]. These apparently conflicting findings may be explained by differences in study population, since in several of these positive studies patients with essential hypertension, the metabolic syndrome, and/or increased systemic inflammation participated. Taken together, Ang II seems to contribute to AT inflammation, at least in rodents. As such, long-term RAS blockade may improve AT inflammation, thereby enhancing insulin sensitivity. More human studies are needed to examine the effects of RAS blockade on AT inflammation and circulating concentrations of adipokines that have been linked to insulin sensitivity.

Adipose Tissue Blood Flow

We and others have shown that both fasting ATBF and the postprandial increase in ATBF are decreased in obese, insulin resistant, and type 2 diabetic subjects [90, 91, 121–124]. Interestingly, an impaired ATBF response to nutrient intake is closely associated with insulin resistance [91, 122, 123].

One of the explanations for this relationship may be that a decreased ATBF negatively affects the AT lipid buffering capacity via a reduction of TAG clearance [125] and increased re-esterification of non-esterified fatty acids [126], resulting in an excessive flux of lipids

toward non-ATs (ectopic fat storage) and, as a consequence, insulin resistance [83]. Alternatively, it has been postulated that an impaired ATBF may lead to a relative oxygen deficit in certain parts of AT ('AT hypoxia') [83, 127]. Indeed, we have demonstrated for the first time that ATBF is an important regulator of AT PO₂ in humans [91]. Experiments in 3T3-L1 [128–130] and human adipocytes [131] suggest that low oxygen availability (1% O₂) may adversely affect the expression of adipokines, with a shift towards a pro-inflammatory phenotype. However, in marked contrast with previous studies in obese mice [129, 132] and humans [133, 134], we have very recently demonstrated that obese individuals exhibited increased AT PO₂ despite lower ATBF, which was accompanied by insulin resistance and AT inflammation [91]. Clearly, more studies in humans are needed to examine the role of AT PO₂ in metabolic disease.

Using both microdialysis and microinfusion approaches, we have demonstrated that Ang II decreases ATBF [63, 121] and that local blockade of the Ang II type 1 receptor in abdominal subcutaneous AT markedly increases ATBF in humans [121]. Furthermore, we have shown that treatment with the ARB valsartan for 26 weeks increased both fasting and postprandial ATBF compared with placebo [102], which may have contributed to the valsartan-induced increase in insulin sensitivity [34].

Conclusions

Several in vitro, animal, and clinical studies have demonstrated that the RAS may contribute to impaired insulin secretion and insulin resistance, thereby increasing the risk for type 2 diabetes. Detrimental effects of the RAS on insulin secretion seem to be mediated by a reduction in pancreatic blood flow and induction of islet fibrosis, oxidative stress, and inflammation, whereas both impaired skeletal muscle function (disturbances in skeletal muscle blood flow, insulin signaling, and mitochondrial function) and AT dysfunction (adipocyte hyperthrophy, inflammation, and impairments in ATBF and lipid metabolism) may underlie RAS-induced insulin resistance. Thus, the reduced incidence of new-onset type 2 diabetes following long-term treatment with ACEi or ARBs in high-risk individuals seems to involve beneficial effects on the pancreas, skeletal muscle, and AT. Collectively, the studies described in this review support that targeting the RAS in intervention studies improves metabolic and cardiovascular function in conditions of insulin resistance like obesity and type 2 diabetes. However, more clinical studies in humans at high risk of developing type 2 diabetes are warranted.

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Disclosure Statement

The author declared no conflicts of interest.

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