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The Renin Angiotensin Aldosterone System in Hypertension: Roles of Insulin Resistance and Oxidative Stress

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Despite major advances in the understanding of the pathogenesis and treatment of hypertension (HTN) and other components of the cardiometabolic syndrome (CMS), these entities continue to contribute to major morbidity and mortality from cardiovascular disease (CVD) and chronic kidney disease (CKD). There is an increasing prevalence of HTN in the United States, and this disease currently affects 29% of the population or approximately 65 million persons.¹ In the adult United States population, the prevalence of overweight and obesity is reported to be 66%, and that of the CMS between 35% and 40%.² Approximately 28 million persons in the United States have CKD defined as either proteinuria or estimated glomerular filtration rate of less than 60. HTN, CMS, and diabetes all play important roles in this increase in CKD.

It is estimated that at least 50% of hypertensive patients are insulin resistant, and insulin resistance is one fundamental abnormality in the pathogenesis of the CMS.^{3,4} In this context, patients with HTN have higher fasting and postprandial insulin levels, independent of body mass index or body fat distribution.⁵ Moreover, both insulin resistance and HTN are implicated in the pathophysiology of CKD and CVD. Studies in humans demonstrate that improving insulin resistance, with insulin sensitizers, has a positive effect on blood pressure control.

Several pathophysiologic factors are involved in the relationship between HTN and the other components of the CMS, including inappropriate activation of the renin angiotensin aldosterone system (RAAS), oxidative stress, and inflammation. Other factors include impaired insulin-mediated vasodilatation, enhanced sympathetic nervous system (SNS) activation, and abnormal sodium handling by the kidney. The purpose of this article is to present the current state of knowledge, focusing on the role of insulin resistance and RAAS-mediated oxidative stress on endothelial dysfunction and the pathogenesis of HTN.

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RENAL SODIUM HANDLING

Several abnormalities in renal handling of sodium have been demonstrated in both HTN and the CMS. Initially, it was demonstrated that insulin enhances sodium reabsorption in the diluting segment of the distal nephron, in part, through increased expression of sodium transporters, such as the epithelial sodium channel, with consequent decrease in sodium excretion.^{6,7} This effect could potentially contribute to the genesis of hypertension under hyperinsulinemic conditions secondary to selective insulin resistance of nonrenal tissues. In opposition to this hypothesis, using a murine model of selective knockout of the insulin receptor in the renal tubule epithelial cells, it was reported that the absence of insulin action results in impaired natriuresis and increased blood pressure, findings that were correlated with reduced renal nitric oxide (NO) production.⁸ This novel evidence can explain how decreased NO production would lead to renal vasoconstriction and increased sodium reabsorption with resultant HTN in conditions of insulin resistance. The significance of these contradictory results is not clear yet, and further studies are needed to clarify the significance of insulin signaling in sodium and water metabolism.

SYMPATHETIC NERVOUS SYSTEM ACTIVATION

Clinical studies have shown that individuals with CMS have increased SNS activity, and this increased activity is correlated with insulin resistance.⁹ A number of mechanisms are involved in the activation of the SNS in the CMS. In states of insulin resistance compensatory hyperinsulinemia can cause enhanced sympathetic output in humans through ventromedial hypothalamus mechanisms.^{10,11} Additionally leptin, which is elevated in obesity, increases sympathetic nerve activation.¹² The role of leptin in the control of sympathetic tone and blood pressure is supported by the observation that humans with leptin deficiency exhibit sympathetic system dysfunction and postural hypotension.¹³ More recently, investigators showed in an animal model of obesity that leptin actions to increase renal sympathetic system activity are mediated by phosphoinositol 3-kinase (PI3K) activation.¹⁴ The PI3K enzyme is involved in many of the metabolic actions of insulin.¹⁵

RAAS also interacts, in a positive feedback fashion, with the SNS (Fig. 1). Injection of angiotensin II (Ang II) in the brain of experimental models causes increased sympathetic output. Additionally, the activation of the RAAS facilitates sympathetic ganglia transmission and inhibits the reuptake of noradrenaline in the nerve terminals.¹⁶ In this context, angiotensin-converting enzyme (ACE) inhibition promotes reuptake of noradrenaline in nerve terminals, perhaps explaining one of the beneficial effects of RAAS blockade.¹⁷ Thus, enhancement of the SNS and the RAAS act in a positive feedback regulatory mechanism in the setting of HTN and the CMS.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

The interaction between the RAAS and the SNS is at least partially responsible for the development of HTN in states of insulin resistance, such as the CMS. Often in the CMS there is an increase in visceral adipose tissue and the increased inflammation and oxidative stress in this tissue leads to increased production of components of the adipose renin angiotensin system.¹⁸ In animal models, overexpression of angiotensinogen (AGT), restricted to adipose tissue, increases total body fat mass. Further, mice that overexpress adipose AGT are also hypertensive.¹⁹ These data provide new evidence that AGT and Ang II produced in adipose tissue have local effects to enhance adipocyte tissue growth and expansion, and systemic effects on blood pressure regulation. These findings contribute to the understanding of the role of adipose tissue in development of HTN and other components of the CMS.²⁰

Ang II exerts many of its detrimental effects through its interaction with the Ang II type 1 receptor (AT₁R). AT₁R activation in the zona glomerulosa of the adrenal cortex stimulates the production of mineralocorticoids. Furthermore, the activation of AT₁R, in nonadrenal tissues, results in a myriad of intracellular events including production of reactive oxygen species (ROS), which contribute to reduced insulin metabolic signaling, and proliferative and inflammatory responses. These AT₁R-mediated signals can cause impaired vascular insulin metabolic signaling and endothelial dysfunction, with secondary increases in blood pressure.²¹

Aldosterone is also increased in conditions of increased adiposity and insulin resistance.²² Indeed, human and rodent adipose tissue is capable of secreting potent mineralocorticoid-releasing factors.²³ Aldosterone increases blood pressure both by its classic actions, mainly sodium retention and plasma volume expansion, and through nongenomic mineralocorticoid receptor (MR) mediated actions.¹⁵

OXIDATIVE STRESS

One mechanism by which an activated RAAS increases insulin resistance is through increased generation of reactive oxygen species ROS. These charged products are involved in the regulation of normal cell signaling and cell growth, proliferation, and expansion of the extracellular matrix. ROS can be produced in different vascular cell types, including endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), by activation of xanthine oxidase, nitric oxide synthase, the mitochondrial respiratory chain, and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymatic complex, resulting in increased production of superoxide (O₂⁻) (Fig. 2). These ROS can, in turn, directly inflict tissue injury or can contribute to the production of additional ROS by converting NO into peroxynitrate, which is also injurious to tissues. This results in less bioavailable NO and consequently impaired endothelial function.²⁴

Xanthine oxidase (XO), a hypoxia-inducible enzyme, is also expressed in vascular endothelial and VSMCs, and catalyzes the production of O₂⁻. Rodents overexpressing the human renin and AGT genes have increased activity of XO in concert with endothelial dysfunction and HTN. In this model HTN is reversible with antioxidant therapy.²⁵ In salt-fed spontaneously hypertensive rats (SHR), renal XO activity is increased, and chronic treatment with allopurinol reduces its activity, suggesting a role for this enzyme in HTN-related kidney dysfunction.²⁶ Additional studies employing this XO inhibitor in hyperuricemic individuals with CKD was associated with reduced uric acid levels, and preserved kidney function.²⁷

The nitric oxide synthase enzymes, in particular endothelial nitric oxide synthase enzymes (eNOS), are another important source of ROS. In physiologic conditions, eNOS transfers electrons from a heme group in the oxygenase domain to L-arginine, which results in production of L-citrulline and NO. Under conditions of decreased availability of 5,6,7,8-tetrahydrobiopterin (a cofactor in NO production) or the substrate L-arginine, eNOS switches from this coupled state to an uncoupled state, in which electrons from the heme group reduce oxygen, resulting in production of O₂⁻.²⁸ This uncoupling of eNOS appears to play an important role in endothelial dysfunction and the development of HTN in conditions of insulin resistance, such as the CMS.

ROS are also produced in mitochondria, and during enhanced oxidative phosphorylation this production is increased.²⁹ Most of electron transport is coupled to production of ATP, but approximately 1% to 2% of electrons can be derived to production of O₂⁻, which is scavenged by manganese O₂⁻ dismutase (SOD), a mechanism that can be overwhelmed in pathologic conditions.²⁸ Oxidative stress can adversely affect mitochondrial DNA, and studies in both humans and atherosclerosis-prone rodents have correlated the extent of mitochondrial DNA

injury to vascular damage and atherosclerosis.³⁰ Excessive mitochondrial generation of ROS contributes to development of insulin resistance, diabetes, CVD, and CKD.²⁹

A major source of ROS is the membrane-bound vascular-derived NADPH oxidase enzymatic system. Key components of this highly regulated system are the membrane-bound subunits p22^{phox} and Nox2, the cytosolic subunits p47^{phox}, p67^{phox}, p40^{phox} and the small guanosine triphosphate-binding protein Rac1/Rac2.^{31,32} Activation of the complex involves the interaction between cytosolic subunits p47^{phox} and p67^{phox}, followed by their translocation to the plasma membrane along with prenylated Rac1,³³ where they interact with plasma membrane-bound subunits.³⁴ In vascular tissue, the NADPH oxidase enzymatic complex can be acutely and chronically activated in response to a variety of stimuli, including Ang II and aldosterone, even at low concentrations.³⁵

In normal rats, infusion of noradrenaline or Ang II increased blood pressure to similar extent. However, only Ang II-induced hypertension was associated with increased vascular production of O₂⁻.³⁶ Further, antioxidant treatment with liposomal-encapsulated SOD resulted in significantly reduced blood pressure in Ang II-infused animals, but not in those treated with norepinephrine. Additionally, SOD treatment was associated with enhanced endothelium-dependent vasodilatation and hypotensive responses to acetylcholine. Other models of hypertension, such as the SHR, the stroke-prone SHR, the Dahl salt-sensitive rat, and the transgenic Ren2 rat, also display increased NADPH oxidase-driven production of ROS. In these models, antioxidant treatment results in improvement of endothelial function and HTN.³⁷

From a clinical standpoint, patients with HTN or CVD often exhibit increased oxidative stress. For example, the plasma oxidized-reduced glutathione ratio and malon-dialdehyde levels are significantly higher, and the activity of SOD, catalase, and glutathione peroxidase significantly lower, in blood and mononuclear peripheral cells of hypertensive patients relative to their normotensive counterparts.³⁸ Finally, NADPH oxidase-driven production of O₂⁻ is abnormally enhanced in mononuclear cells, from hypertensive individuals, stimulated with Ang II and ET (endothelin)-1.³⁹

Many of the vascular maladaptive effects of the RAAS are mediated through Ang II and aldosterone activation of NADPH oxidase system in vascular tissue (see Fig. 2).⁵ In addition, Ang II and aldosterone can directly activate NADPH oxidase through stimulation of Rac1 activity and translocation to the membrane in VSMCs or through activation of p47^{phox}.²⁸ On the other hand, treatment of hypertensive rats with an hydroxymethylglutaryl-CoA reductase inhibitor results in less activation of vascular NADPH oxidase subunits and reduced generation of ROS, in concert with improved endothelial function and blood pressure.⁴⁰ Direct inhibition of NADPH oxidase in a mouse model of Ang II-induced hypertension, by blocking the interaction of p47^{phox} and gp91^{phox} or the employment of p47^{phox} knockout methodology results in blunting of O₂⁻ production.^{41,42} In addition, in rodent models of HTN and increased NADPH activity, use of antioxidants results in improved blood pressure.⁴³

Aldosterone can also activate NADPH oxidase and trigger oxidative stress.⁴⁴ Other mineralocorticoids such as deoxycorticosterone acetate can also induce increased production of O₂⁻ in different experimental models of HTN.⁴⁵ Furthermore, in the transgenic Ren2 rat, which overexpresses the mouse renin gene in numerous tissues, and exhibits significantly increased plasma aldosterone levels; MR inhibition can reduce cardiac, renal, skeletal muscle, pancreas and vascular NADPH oxidase-ROS generation. This reduction in ROS occurs in concert with improved insulin metabolic signaling and regression of tissue structure abnormalities.³² MR activation increases skeletal muscle NADPH oxidase activity, in part by way of activation of membrane-bound Nox2 and p22^{phox} as well as the cytosolic p47^{phox}

subunits. The resulting oxidative stress leads to systemic insulin resistance, impaired intracellular insulin signaling, and defective insulin-stimulated glucose transport in skeletal muscle. These changes are reversed by in vivo treatment with a MR inhibitor, at a dose that does not reduce blood pressure.³²

ROLE OF OXIDATIVE STRESS IN INSULIN RESISTANCE

Binding of insulin to its receptor triggers signaling through the PI3K/protein kinase B (Akt) cascade, which results in glucose transporter-4 (GLUT4) translocation to the plasma membrane and facilitated glucose uptake. In addition, Akt phosphorylates and activates eNOS resulting in NO production and vasodilatation.⁴⁶ Therefore, insulin resistance states exhibit impaired insulin-mediated vasodilatation.⁴⁶

On the other hand, data from experimental animal models have shown that insulin can stimulate vasoconstriction through production of ET-1, a process that requires intact mitogen-activated protein kinase (MAPK) signaling.⁴⁷ It has been proposed that in insulin-resistant states while the PI3K/Akt pathway signaling is impaired with consequent decreased production of NO, the MAPK pathway is stimulated by hyperinsulinemia resulting in elevated ET-1 production.⁴⁸ Nevertheless, a recent study examining obese patients did not confirm a role for hyperinsulinemia in ET-1-mediated vasoconstriction in states of insulin resistance.⁴⁹ Thus, the potential role of increased ET-1 in the CMS is still unclear.

The impact of ROS and oxidative stress on insulin metabolic signaling and systemic insulin sensitivity is a field of intense research. The main tissues involved in the pathophysiology of insulin resistance are skeletal muscle and adipose tissue. However, decreased insulin metabolic signaling in vascular tissue can also contribute to endothelial dysfunction, HTN, and atherosclerosis. Increased oxidative stress and resulting impairment in insulin metabolic signaling may play a key role in the pathogenesis of HTN, CMS, and CVD.⁵⁰

In vitro and in vivo studies have demonstrated an association between increased ROS production and insulin resistance. Prolonged exposure of adipose cells to oxidative stress results in decreased insulin-stimulated glucose transport, lipogenesis, and activity of glycogen synthase, consistent with impaired insulin action.⁵¹ In cultured skeletal muscle cells overexpressing GLUT4, pretreatment with the antioxidant α -lipoic acid is protective against oxidative stress-induced impaired insulin-stimulated glucose uptake.⁵² Adipocytes obtained from high-fat diet-induced insulin resistance display increased production of ROS and stimulation of the protein kinase C delta, a serine/threonine kinase implicated in impaired cellular insulin metabolic signaling.⁵³ This, in turn, results in blunted insulin-stimulated glucose uptake and severely decreased expression/activation of GLUT4 and facilitated glucose transport. Other studies conducted in vitro and in animal models have reported a beneficial effect of antioxidants on insulin sensitivity.

Some studies in humans with insulin resistance report similar beneficial effects of vitamin C, E, or glutathione on insulin metabolic signaling.⁵⁰ Oxidative stress is strongly associated with increased adiposity and impaired insulin sensitivity in humans, suggesting a role for ROS in the generation of obesity-related insulin resistance.⁵⁴ Conversely, it has been demonstrated in humans that insulin resistance is associated with reduced endogenous intracellular antioxidant mechanisms.⁵⁵

The mechanisms implicated in oxidative stress-mediated insulin resistance remain to be fully elucidated, but several experimental studies support a role for activation of redox-sensitive serine (Ser) kinases, including Janus kinase.⁵⁶ Activation of these Ser kinases promotes Ser phosphorylation of substrates, including the insulin receptor and the docking proteins insulin receptor substrate (IRS)-1 or 2. This increased Ser phosphorylation of IRS-1 results in

decreased engagement of IRS-1 with PI3K and impaired downstream insulin metabolic signaling. In addition, increases in inflammatory molecule NK-kB, a key mediator of inflammation, is triggered by activation of the Ser kinase IKK- β , a process that is reversed by salicylates.⁵⁷ In this context, treatment with high doses of aspirin results in increased insulin sensitivity, reduced hepatic glucose output, and improved glucose homeostasis in patients with type 2 diabetes (T2DM).⁵⁸

RENIN ANGIOTENSIN ALDOSTERONE SYSTEMS BLOCKADE IN THE CARDIOMETABOLIC SYNDROME: BEYOND BLOOD PRESSURE NUMBERS

There is increasing evidence for the beneficial effects of RAAS inhibition on metabolic signaling, CVD, and CKD in patients with insulin resistance or overt T2DM. ACE inhibitors and ANG II-receptor blockers (ARBs) have been studied extensively in HTN, congestive heart failure, coronary artery disease, and CKD and are recommended to prevent CVD and nephropathy in patients with T2DM.^{59,60} In addition, some of these studies have also suggested reduced incidence of new-onset T2DM, through secondary outcomes and post hoc analysis. In the Heart Outcomes Prevention Evaluation, a double-blind, randomized, placebo-controlled trial assessing the use of ramipril in preventing cardiovascular death in high-risk patients, the incidence of new-onset diabetes was 34% lower in the ramipril-treated group relative to placebo.⁶¹ In the Captopril Prevention Project, a prospective, randomized trial comparing cardiovascular morbidity and mortality in hypertensive patients using an ACE inhibitor or conventional antihypertensive treatment, the prevalence of new-onset T2DM in the captopril-treated arm was significantly lower.⁶² In the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity study,⁶³ candesartan reduced the onset of diabetes by 19% compared with placebo when used in patients with chronic heart failure. Other studies that have demonstrated reduction in incidence of new-onset diabetes with the use of ACE inhibitors and ANG II-receptor blockers include the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial,⁶⁴ Studies Of Left Ventricular Dysfunction,⁶⁵ and Losartan Intervention For Endpoint Reduction in Hypertension Study.⁶⁶ Possible mechanisms responsible for the reduced incidence of diabetes in these trials include improvement in insulin-mediated glucose uptake, enhanced endothelial function, increased NO activity, reduced inflammatory response, and increased bradykinin levels.

The only prospective randomized double-blind clinical trial to specifically address the role of ACE inhibition on development of T2DM is the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication.⁶⁷ This study randomly assigned 5269 participants without CVD but with impaired fasting glycemia or impaired glucose tolerance to receive ramipril or placebo (and rosiglitazone or placebo in another arm of the study) for a median of 3 years. Use of ramipril was not associated with a significant reduction in the incidence of T2DM. However, treatment with ramipril resulted in significantly increased regression to normoglycemia, relative to placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; $P < .05$), and reduced markers of hepatosteatosis suggesting a beneficial effect of RAAS blockade on glucose homeostasis.

MR blockade may improve insulin metabolic signaling,³² and positively affect CVD outcomes, as demonstrated in the clinical trials: Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). The RALES was a double-blind trial that included patients who had severe heart failure and left ventricular ejection fraction below 35%. Participants were randomized to receive 25 mg of spironolactone or placebo plus conventional treatment with an ACE I, a loop diuretic, and in most cases digoxin. In this trial, there was 30% reduction in the relative risk of death in spironolactone group.⁶⁸ In the EPHESUS trial, a multicenter, randomized, double-blind, placebo-controlled trial, there was a significant reduction in CVD mortality (relative risk, 0.83; 95% CI, 0.72 to 0.94; $P = .005$) and the rate of death from cardiovascular causes or

hospitalization for cardiovascular events (relative risk, 0.87; 95% CI, 0.79 to 0.95; $P = .002$) among patients assigned to eplerenone.⁶⁹

The mechanisms by which MR blockade provides myocardial protection include reduction of coronary vascular inflammation and the risk of subsequent development of interstitial myocardial fibrosis, reduced oxidative stress, improved endothelial dysfunction, attenuated platelet aggregation, decreased activation of matrix metalloproteinases, and improved ventricular remodeling. In addition, MR antagonism results in decreased NADPH oxidase activity and oxidative stress, in concert with improved insulin-stimulated glucose uptake, and attenuated whole-body insulin resistance in the setting of an active RAAS.³² MR blockade may also improve insulin metabolic signaling.³²

As the CMS is a strong predictor for development of T2DM, the metabolic effects related to the use of antihypertensive medications should be taken into account.⁷⁰ In this regard, antihypertensive therapy with thiazide diuretics and β -blockers have been implicated in the development of new-onset diabetes as well as in the worsening of glycemic control in known diabetic patients.⁷¹ A recent systematic review of 22 clinical trials, with 143,153 participants, reported that the association of different anti-hypertensives with new-onset diabetes was lower with ARB and ACE I and higher with β -blockers and diuretics.⁷² Interestingly, a meta-analysis by Zillich and colleagues⁷³ that examined studies with thiazide diuretics found an important correlation between the degree of diuretic-induced hypokalemia and increased glycemia; prevention of hypokalemia resulted in a lesser degree of blood glucose elevation. More recently, a small clinical study with 26 centrally obese, hypertensive patients compared the effects of candesartan and hydrochlorothiazide (HCTZ) on insulin resistance or sensitivity, and fat distribution. The authors reported that HCTZ worsens insulin resistance in association with visceral fat redistribution, increased liver fat content, and elevated markers of inflammation when compared with placebo or candesartan. These authors hypothesized that the deleterious effects seen are likely secondary to activation of the RAAS by HCTZ.⁷⁴ The adverse metabolic effects of the β -blockers seem to be related to the type of agent used, rather than to a class effect,⁷⁵ and new vasodilatory agents as carvedilol and nebivolol are expected to have a better metabolic profile.

The recently published Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial⁷⁶ randomized 11,506 hypertensive patients at high risk for CVD events to receive the combination of benazepril-amlodipine or benazepril-hydrochlorothiazide, and reported a similar reduction in blood pressure between the two groups. However, there was a significant difference concerning the occurrence of cardiovascular events that favor the amlodipine-treated group.⁷⁶ The relation between CVD and insulin metabolic effects of these drugs remains to be reported. Nevertheless, it would appear reasonable to suggest an RAAS-blocker agent as first line of therapy for patients with the CMS.

SUMMARY

The relationship between HTN and other components of the CMS is complex. However, there is growing evidence that enhanced activation of the RAAS is a key factor in the development of endothelial dysfunction and HTN. Insulin resistance is induced by activation of the RAAS and resulting increases in ROS. This insulin resistance occurs in cardiovascular tissue and in tissues traditionally considered as targets for the action of insulin, such as muscle and liver. Indeed, there is a mounting body of evidence that the resultant insulin resistance in cardiovascular tissue and kidneys contributes to the development of endothelial dysfunction, HTN, atherosclerosis, CKD, and CVD.⁷⁷

RAAS-associated signaling by way of the AT₁R and MR, triggers tissue activation of the NADPH oxidase enzymatic activation and increased production of ROS. Oxidative stress in cardiovascular tissue is derived from both NADPH oxidase and mitochondrial generation of ROS, and is central to the development of insulin resistance, endothelial dysfunction, HTN, and atherosclerosis.

Pharmacologic blockade of the RAAS not only improves blood pressure, but also has a beneficial impact on inflammation, oxidative stress, insulin sensitivity, and glucose homeostasis. Several strategies are available for RAAS blockade, including ACE inhibitors, ARBs, and MR blockers, which have been proven in the clinical trials to result in improved CVD and CKD outcomes. New research in these areas will allow for a better understanding of the relationship between HTN, insulin resistance, and activation of the RAAS, which could result in newer alternatives for a more comprehensive management of HTN in the setting of the CMS.

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Fig. 1.
Coordinated influence of obesity, insulin resistance, activation of the RAAS and the SNS in the pathophysiology of hypertension in the CMS.

Fig. 2.

(Upper inset) Vascular effects of insulin (INS) or insulin like growth factor (IGF)-1 and counterregulatory effects of AT_1R and MR activation in endothelial cells. Insulin actions on the blood vessel are partially mediated by increased production of NO through phosphorylation and secondary activation of endothelial NO synthase (eNOS). AT_1R activation decreases the availability of NO by way of the induction of insulin resistance, diminishing eNOS mRNA stability, and promoting NADPH oxidase-induced ROS production. Mineralocorticoids also activate NADPH oxidase with secondary $O_2^{\cdot -}$ production and consequent generation of peroxynitrite ($ONOO^-$). Akt, PI3K/protein kinase B; GRE, glucocorticoid response element; Gq, G_q subunit; IRS, insulin receptor substrate; NOX2, catalytic subunit of NADPH oxidase; p22, p47, p40, and p67, subunits of NADPH oxidase; PH, pleckstrin homology domain; PIP, phosphatidylinositol phosphate; PIP₂, phosphatidylinositol bisphosphate; PIP₃, phosphatidylinositol (3,4,5)-trisphosphate; ROK, Rho kinase; SOD, superoxide dismutase.

(Lower inset) Opposing effects of ANG II and aldosterone (Aldo) versus insulin/IGF-1 on VSMCs. Insulin and IGF-1 cause VSMC relaxation, whereas ANG II and mineralocorticoids cause contraction. MBS, myosin-bound serine; MLC, myosin light chain; MLCK, MLC kinase; Na/Ca exch, Na⁺/Ca²⁺ exchanger. (From Cooper SA, Whaley-Connell A, Habibi J, et al. Renin-angiotensin-aldosterone system and oxidative stress in cardiovascular insulin resistance. *Am J Physiol Heart Circ Physiol* 2007;293:2009–23; with permission.)