New Drugs and Technologies

Renin-Angiotensin System and Angiotensin Receptor Blockers in the Metabolic Syndrome

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Activation of the renin-angiotensin system (RAS) occurs in many cardiovascular disorders, and its modulation with angiotensin-converting enzyme (ACE) inhibitors is now established therapy for hypertension, left ventricular dysfunction, diabetic nephropathy, and atherosclerosis. More recently, angiotensin type 1 receptor blockers (ARBs) have shown similar promise. Research is currently focused on the role of the RAS in the metabolic syndrome (MetS), a disorder characterized primarily by insulin resistance that has emerged as a major risk factor for cardiovascular disease. Here, we review how cross talk between angiotensin II (AII) and insulin signaling contributes to the pathophysiology of the MetS and raises the potential for therapeutic use of angiotensin antagonists in its management.

Metabolic Syndrome

The MetS, also known as syndrome X, is an intermediate state between normal metabolism and type 2 diabetes mellitus. It is characterized by a constellation of atherogenic risk factors that include dyslipidemia, hypertension, and hyperglycemia; a susceptible genomic substrate; and superimposed proinflammatory and prothrombotic milieu. Although the underlying mechanisms for the MetS have not been entirely elucidated, resistance to the cellular actions of insulin is known to be a cardinal feature. The MetS is prevalent in nearly 20% of the adult US population; the likelihood of developing MetS increases with advancing age, higher body mass index, postmenopausal status, smoking, and physical inactivity.

Insulin Resistance, Hyperinsulinemia, and Atherosclerosis

Important organ systems involved in the MetS include the vasculature, heart, adipose tissue, liver, and skeletal muscle. Hyperinsulinemia and insulin resistance are both implicated in the pathogenesis of hypertension, obesity, type 2 diabetes, and atherosclerosis (Figure).

Insulin

At physiological concentrations, insulin has vasodilator and antiinflammatory actions that are mediated in part through the release of nitric oxide (NO) and inhibition of the transcription factor nuclear factor-κB (NF-κB). Loss of these actions results from altered cellular responses to insulin that are mediated via phosphatidylinositol 3 (PI3) kinase and mitogen-activated protein (MAP) kinase activation that is dependent on tyrosine phosphorylation of insulin receptor substrates 1 and 2 (IRS1 and IRS2). In addition to the well-known metabolic effects of insulin such as glucose transport, glycogen synthesis, and lipid metabolism, the PI3 kinase pathway mediates the vasodilator and antiinflammatory effects of insulin via activation of NO synthase. The MAP kinase pathway promotes the mitogenic effects that lead to cell growth and proliferation. Insulin resistance is characterized by impaired activation of the PI3 kinase pathway, combined with preserved signaling via the MAP kinase pathway, which shifts the balance in favor of the atherogenic actions of insulin, probably by differential signal amplification.

Endothelium and Inflammation

The vascular endothelium plays a pivotal role in the regulation of blood flow, coagulation, and inflammation in the vessel wall. Both the MetS and diabetes promote endothelial cell dysfunction that is accompanied by diminished NO bioavailability resulting from excessive production of reactive oxygen species (ROS) such as superoxide anions (O$_2^-$). O$_2^-$ inactivates NO to form toxic peroxynitrite, which in turn uncouples endothelial NO synthase by oxidizing its cofactor, tetrahydrobiopterin, and switches its function from NO synthesis to O$_2^-$ production. Insulin resistance also induces ROS generation by releasing free fatty acids from adipose tissue via activation of protein kinase C and inhibition of PI3 pathways. The reduction in NO and other endothelium-derived vasodilators is accompanied by increased production of endothelin, vasoconstrictor prostanoids, and AII. The combination of oxidative stress, diminished NO bioavailability, and dyslipidemia leads to upregulation of transcription factors such as NF-κB and activator protein 1, which regulate genes that encode for inflammatory mediators such as tumor necrosis factor (TNF-α) and interleukin (IL)-1.

Diminished bioavailability of NO in experimental models of insulin resistance has now been confirmed clinically. Thus, (1) there is a correlation between insulin sensitivity and basal...
NO production in healthy subjects; (2) insulin-resistant humans have impaired endothelium-dependent vasodilator responses; and (3) endothelial dysfunction is also detectable in healthy first-degree relatives of subjects with type 2 diabetes, who are at increased risk of developing diabetes. The robust association between insulin resistance and endothelial dysfunction has fueled speculation not only that insulin resistance promotes endothelial dysfunction but also that the 2 states may represent manifestations of a common underlying pathology.

**Vascular Smooth Muscle**
Patients with hyperinsulinemia also manifest abnormal vascular smooth muscle function. Type 2 diabetes is characterized by diminished NO-mediated vasodilation, decreased vasoconstriction in response to exogenous endothelin, and increased vasoconstrictor tone mediated by endogenous endothelin. Insulin, through direct trophic effects and by generation of ROS, protein kinase C, and activation of NF-κB, promotes smooth muscle cell growth, migration, and proliferation.

**Coagulation**
Activation of NF-κB promotes synthesis of plasminogen activator inhibitor type 1 (PAI-1), a natural inhibitor of tissue plasminogen activator in atherosclerotic vessels, and leads to impaired fibrinolysis. In patients with the MetS, PAI-1 and fibrinogen levels are elevated; PAI-1 levels correlate with plasma insulin levels and insulin resistance and appear to predict the likelihood of developing diabetes. Platelets of patients with the MetS manifest resistance to the physiological action of insulin (which is inhibition of platelet aggregation via NO release) and increased propensity for aggregation. Overall, alterations in platelet function and the coagulation cascade create a prothrombotic milieu that contributes to atherothrombosis.

**Adipose Tissue and Hyperlipidemia**
In adipose tissue, insulin resistance is associated with decreased uptake and increased release of free fatty acids, which are converted in the liver to triglyceride-rich very-low-density lipoprotein particles. The resulting hypertriglyceride-
emia drives the dyslipidemic triad by promoting the synthesis of small, easily oxidizable dense LDL and enhanced clearance of HDL that is believed to be highly atherogenic. Low HDL may also be a consequence of decreased ATP-binding cassette transporter 1 expression, which mediates reverse cholesterol transport in peripheral cells.

Several components of the RAS such as angiotensinogen, ACE, and angiotensin type 1 (AT1) receptors are present within human adipose tissue. Experimental studies suggest that the adipose RAS is regulated by hormonal and nutritional factors and correlates with the degree of obesity and that AII may modulate adipose tissue blood flow, growth, and metabolism. Thus, an upregulated adipose RAS may have deleterious local and systemic effects in obese individuals and contribute to insulin resistance and hypertension.

Adipose tissue is also a prolific source of cytokines such as TNF-α and IL-6, adiponectin, and resistin, collectively referred to as adipocytokines. Through putative endocrine, paracrine, or autocrine actions, adipocytokines contribute to insulin resistance and mediate the link between abdominal obesity and the MetS. Tissue expression of TNF-α correlates with hyperinsulinemia in obesity, a link that is reversed with weight reduction. The effects of TNF-α are manifold, including (1) modulation of lipid metabolism, (2) inhibition of insulin signaling via a decrease in tyrosine kinase activity in insulin receptors and phosphorylation and activation of IRS1, (3) downregulation of glucose transporter proteins and pancreatic β-cell dysfunction, (4) increased expression of inducible NO synthase, and (5) reduced NO bioavailability and impaired endothelium-dependent dilatation.

Levels of adiponectin, a protein with potential antiatherosclerotic properties, correlate inversely with the degree of insulin resistance, hyperinsulinemia, and C-reactive protein (CRP). Although obesity and type 2 diabetes are associated with lower levels of adiponectin, inhibition of the RAS with ACE inhibitors or ARBs appears to increase plasma adiponectin levels in hypertensive patients. Clinically, waist circumference correlates strongly with CRP and fibrinogen levels, explaining between 15% and 42% of the total variability for CRP levels, an association that is stronger in women. Approximately 30% of circulating IL-6 originates from adipose tissue in healthy subjects.

Among other functions, these cytokines induce an inflammatory response in the vessel wall that is evident in patients as an elevation in circulating levels of CRP and other inflammatory markers that serve as markers of worse prognosis in patients with and without the MetS. Moreover, elevated circulating levels of fibrinogen, CRP, PAI-1, and IL-6 also predict the development of type 2 diabetes. Thus, the pathophysiology of insulin resistance, MetS, and atherosclerotic cardiovascular events may have a common proximal inflammatory basis (Figure).

Hypertension and Atherosclerosis
Blood pressure in obese patients is sensitive to sodium intake. This sensitivity is related to fasting insulin level, which, together with the antinatriuretic effect of insulin, activation of the sympathetic nervous system, and abnormal vascular function, contributes to the development of hypertension. Thus, the combined burden of vascular dysfunction and its resultant abnormal regulation of blood flow, a proinflammatory and procoagulant state, dyslipidemia, and hypertension promotes atherogenesis. In several large, prospective, observational studies, insulin resistance has been shown to predict the incidence of and mortality related to coronary artery disease and stroke.

Interactions Between the Insulin and RAS
The RAS consists primarily of an enzymatic cascade in which angiotensinogen is converted to angiotensin I and subsequently to AII by the actions of renin and ACE, respectively, although alternative caspase-dependent synthetic pathways for AII are also present. In addition to the endocrine system, paracrine RAS activity can be detected within the kidney, adipose tissue, heart, and blood vessels. AII, the major effector peptide of the RAS, regulates vasomotor tone, blood pressure, and cardiovascular structure largely via activation of the G-protein–coupled AT1 receptor. Considerable evidence suggests that AII may also modulate the actions of insulin.

The complex cellular interactions of the RAS and insulin signaling include the shared signal transduction pathways, including the PI3 kinase and MAP kinase pathways, and tyrosine phosphorylation of IRS1 and IRS2, after binding to their respective receptors. Insulin receptor–mediated activation of IRS1 and IRS2 activates the PI3 kinase pathways, whereas their AII-mediated activation inhibits PI3 kinase. Thus, activation of the RAS may inhibit the metabolic actions of insulin via the PI3 kinase pathway but synergistically promote its proliferative effects via the MAP kinase pathway.

Additionally, both hyperglycemia and insulin activate the RAS by increasing the expression of angiotensinogen, AII, and the AT1 receptor, which, in concert, may contribute to the development of hypertension in patients with insulin resistance. Moreover, the RAS has been implicated in the pathogenesis of plaque rupture, with increased ACE and AII activity observed primarily within macrophages within atherosclerotic lesions. AII acting via AT1 receptors is a powerful stimulus for the generation of ROS in the blood vessels from the NAD(P)H oxidases, which become further upregulated in hyperglycemic states. This increased oxidant stress is instrumental in provoking endothelial dysfunction, inflammation, smooth muscle hypertrophy, and vascular remodeling. AII also contributes to plaque formation by promoting macrophage and T-lymphocyte recruitment through the generation of adhesion molecules and cytokines; by inhibiting fibrinolytic activity through increased PAI-1 expression; by inducing arterial wall remodeling mediated by smooth muscle cell growth, migration, and proliferation; and by altering the composition of the extracellular matrix.

RAS-driven oxidative stress also has been proposed as a stimulus for the formation of advanced glycation end products. Advanced glycation end products are compounds formed by nonenzymatic glycation of amino acids on proteins, lipids, and nucleic acid. These molecules act on a cell surface receptor for advanced glycation end products and play a key role in the pathogenesis of vascular injury in
hyperglycemic states mediated in part by NAD(P)H-dependent generation of ROS. In experimental studies, inhibition of the RAS with ACE inhibitors and ARBs is associated with a reduced formation and accumulation of advanced glycation end products.

ACE Inhibition and Insulin Resistance

Realization of RAS activation and cross talk between RAS and insulin signaling has been an impetus for exploring the therapeutic potential of RAS inhibition in the treatment of the MetS. ACE inhibition has been shown to improve insulin sensitivity and glycemic control in diabetic patients and to result in a 14% relative reduction in the incidence of new-onset type 2 diabetes in the Captopril Prevention Project (CAPPP). This observation was confirmed by the Heart Outcomes Prevention Evaluation (HOPE) trial in which ramipril significantly reduced cardiovascular events in addition to a 34% reduction in the incidence of new-onset diabetes and a 16% reduction in diabetic complications. The therapeutic potential of ACE inhibitors in patients with insulin resistance is being investigated in the ongoing Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial. This multicenter, randomized study with a 2×2 factorial design has a primary composite end point of new onset of diabetes mellitus or all-cause mortality. Enrollment of 5629 patients was completed in 2003, and the patients will be followed up for a minimum of 3 years.

The mechanisms by which ACE inhibitors improve insulin sensitivity appear to be due in part to increased glucose uptake in skeletal muscle via enhanced synthesis and translocation of glucose transporter 4 protein to the cell surface, an effect that is promoted by upregulation of tyrosine phosphorylation of IRS-1 and enhanced bradykinin and NO activities.

ARBs and the MetS

Two types of angiotensin receptors have been identified and cloned in humans, AT1 and angiotensin type 2 (AT2). The receptors belong to the superfamily of G-protein-coupled receptors with 7 transmembrane regions but have distinct signal transduction pathways. The AT1 receptor is present in many tissues and organs, including the heart, blood vessels, kidney, and adipocytes, whereas the AT2 receptor is expressed mainly in the fetus and has low levels of expression after birth. Most known physiological and pathophysiological effects of AII appear to be mediated through the AT1 receptor, although the potential physiological effects of AT2 receptor stimulation in adults, which include inhibition of cell growth, possibly via NO and bradykinin generation, and antagonizing AT1-receptor-mediated actions of AII, may play a lesser role.

ARBs competitively bind the AT1 receptor with high affinity and selectivity and slow dissociation. Their safety, efficacy, and tolerability have been established. ARBs offer a reasonable therapeutic alternative for patients with heart failure intolerant of ACE inhibitors. Significant regression of left ventricular hypertrophy in untreated patients with essential hypertension with ARBs raises the possibility that they may be superior to other agents in patients with left ventricular hypertrophy. Indeed, in the Losartan Intervention for Endpoint Reduction (LIFE) trial of patients with hypertension and left ventricular hypertrophy, losartan reduced the composite cardiovascular event rate by 13% and the incidence of new-onset diabetes by 25% compared with atenolol. Similarly, pretreatment with valsartan, compared with amlodipine, was associated with a reduction in the incidence of diabetes in high-risk hypertensive patients in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE). Thus, ARBs appear to be as effective as ACE inhibitors in preventing the development of new-onset diabetes in high-risk patients.

Patients with insulin resistance represent one such high-risk group, and several lines of evidence support the therapeutic role for ARBs in patients with the MetS. First, in the carbohydrate-feeding murine model, increased AII and AT1 receptor density were associated with the development of hypertension and hyperinsulinemia, an effect that was prevented by short- and long-term AT1 receptor blockade. In a mouse genetic model of the MetS, treatment with an ARB inhibited the development of hyperinsulinemia, hypertension, obesity, cardiac hypertrophy, and atherosclerosis. Moreover, the clinical trials with ACE inhibitors and ARBs described above provide convincing evidence that inhibition of the RAS alters glucose metabolism in humans. Finally, endothelial dysfunction, which is predictive of future cardiovascular morbidity and mortality, can be reversed by short- and long-term AT1 receptor blockade. This cardioprotective effect is associated with increased NO bioavailability, reduced oxidative stress, and antiinflammatory modulation of cell surface and circulating adhesion molecules.

The ongoing Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is the largest diabetes prevention study exploring the role of an ARB in patients with impaired glucose tolerance resulting from insulin resistance or in those at high risk for cardiovascular events. In a multicenter, double-blind, 2×2 factorial design trial, >9000 patients with impaired glucose tolerance will be randomized into 1 of 4 arms: placebo, nateglinide 60 mg, valsartan 160 mg, or nateglinide plus valsartan. The primary outcomes are time to progression to diabetes and the composite end point of cardiovascular events. This study will provide vital information about the impact of inhibition of the RAS with ARBs in the treatment of patients with the MetS.

Conclusions

An estimated 20% of the US adult population is afflicted by the MetS. Insulin resistance appears to be a central feature of this syndrome, which is associated with hypertension, hyperlipidemia, hypercoagulability, inflammation, and ultimately atherosclerosis and cardiovascular disease. Prospective studies show that insulin resistance predicts the incidence of and mortality related to coronary artery disease and stroke. There is cross talk between the RAS and insulin signaling at multiple levels, and the RAS appears to be important in atherogenesis, which may make it an appropriate target for intervention. ARBs appear to be equivalent to ACE inhibitors for the treatment of heart failure and may provide superior...
end-organ protection in hypertensives. Consequently, ARBs may be therapeutically effective in the MetS by improving glucose metabolism, reducing inflammation and endothelial dysfunction, and delaying progression to type 2 diabetes, a hypothesis currently being investigated in clinical trials.

References


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