Vascular Insulin Resistance: A Potential Link Between Cardiovascular and Metabolic Diseases

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The physiologic actions of insulin in the vasculature serve to couple regulation of metabolic and hemodynamic homeostasis. Insulin activation of the phosphatidylinositol-3-kinase (PI3K) pathway promotes glucose uptake in insulin-responsive tissues and nitric oxide (NO) production in the endothelium. NO induces vasodilation and inhibits platelet aggregation and vascular smooth muscle cell growth. In contrast, insulin activation of the mitogen-activated protein kinase (MAPK) leads to vasoconstriction and pathologic vascular cellular growth. In states of insulin resistance, insulin activation of PI3K is selectively impaired, whereas the MAPK pathway is spared and activated normally. In the endothelium, selective impairment of insulin-mediated NO production may contribute to the development of hypertension, endothelial dysfunction, atherogenesis, and insulin resistance. This article reviews experimental and clinical data elucidating the physiologic and pathophysiologic role of insulin in the vasculature and the mechanisms contributing to the development of vascular and metabolic diseases.

Introduction

In addition to metabolic effects, insulin exerts important biologic actions in the vasculature to stimulate nitric oxide (NO) production from the endothelium via activation of the phosphatidylinositol-3-kinase (PI3K) signaling pathway. Insulin-mediated NO production induces vasorelaxation and increases capillary recruitment and blood flow in the skeletal muscle, which contribute to augmentation of glucose disposal. In physiologic conditions, constitutive stimulation of NO production by insulin may play an important role in the maintenance of vascular health and homeostasis. In states of insulin resistance, insulin activation of the PI3K pathway is selectively impaired and compensatory hyperinsulinemia may activate the vascular mitogen-activated protein kinase (MAPK) pathway, which causes vasoconstriction and promotes atherogenesis.

In the context of the vascular system, insulin resistance manifests as impaired endothelial dysfunction, vasodilation, microvessel disease (ie, retinopathy and nephropathy), and enhanced vascular inflammation and atherosclerotic lesion formation. Therefore, impairment of the vascular insulin-signaling pathway (vascular insulin resistance) may be a triggering factor in the initiation of cardiovascular disease in insulin resistance syndromes such as obesity and type 2 diabetes. Despite intensive research, the cellular mechanisms responsible for vascular insulin resistance remain incompletely understood. This review focuses on recent experimental and clinical data elucidating the physiologic and pathophysiologic role of insulin in the vasculature, and the mechanisms underlying the development of vascular insulin resistance and its potential link with cardiometabolic disease.

Vascular Actions of Insulin

Insulin is an anabolic hormone that plays an essential role in maintaining glucose and lipid homeostasis through its metabolic effects on classic insulin-responsive tissues, including the liver, adipose tissue, and skeletal muscle. In addition, insulin exerts important biologic effects on the vasculature that contribute to either vascular protection or injury, depending on the cell type and pathophysiologic state. The vascular protective effects of insulin—which include vasodilation, inhibition of vascular smooth muscle cell (VSMC) migration and proliferation, attenuation of inflammatory cell infiltration into the vascular

wall, and inhibition of platelet aggregation—are mediated mainly by stimulation of nitric oxide (NO) production in the endothelium [1••,2•]. On the other hand, insulin promotes a host of deleterious vascular effects by stimulating the actions of various growth factors acting through the mitogen-activated protein kinase (MAPK) signaling pathway, which produce vasoconstriction and pro-atherogenic effects [3,4]. Accumulating evidence from human and animal studies suggests a reciprocal relationship between vascular and metabolic actions of insulin and a potential link between insulin and cardiovascular disease [2•].

Vasodilator effects

Insulin has been shown to induce vasodilation in arteries and veins and to induce increased microcirculatory flow, via capillary recruitment, through stimulation of endothelial NO production [2•,5]. Insulin infusion at higher physiologic concentrations under euglycemic glucose clamp conditions causes a dose-dependent increase in blood flow of skeletal muscle. Furthermore, insulin differentially modulates the vascular tree in a time and dose-dependent manner to increase microvascular and total limb blood flow [2•]. Initially, dilation of terminal arterioles increases the number of perfused capillaries, leading to capillary recruitment within a few minutes. This is followed by relaxation of larger resistance vessels, which increases overall limb blood flow. A direct vasodilator effect of insulin was also observed in aortic preparations in vitro, and this relaxation has been shown to be impaired in type 2 diabetic mice [6]. Animal and human studies have demonstrated that vasodilation leading to increased blood flow in the skeletal muscle is a major physiologic consequence of insulin-stimulated endothelial NO production, which may contribute to glucose disposal [6]. In addition to its vasodilator action through stimulation of NO production, insulin has been reported to stimulate calcium efflux from VSMCs by activating the plasma membrane Ca^{2+}-adenosine triphosphatase (ATPase), which attenuates agonist-induced vasoconstriction and the increases in intracellular free Ca^{2+} in VSMCs.

Vasoconstrictor effects

The NO-dependent vasodilator effects of insulin are antagonized by vasoconstrictor effects of insulin mediated by activation of the sympathetic nervous system and stimulation of secretion of the vasoconstrictor endothelin (ET)-1 in the vascular endothelium [7,8]. In healthy humans, acute physiologic and pharmacologic concentrations of insulin increase venous plasma catecholamine concentration and sympathetic outflow in the skeletal muscle [7,9]. In anesthetized dogs, injection of physiologic concentrations of insulin into the carotid artery increased arterial pressure, which was abolished by ganglionic blockade, suggesting that this effect was mediated by sympathetic nervous system activation [7]. Another biologic action of insulin that may impact hemodynamic homeostasis is stimulation of ET-1 release from the endothelium. It has been demonstrated that insulin stimulation of forearm blood flow is potentiated by ET-1 receptor blockade [10]. Consistent with the MAPK dependence of insulin-stimulated secretion of ET-1 in the vascular endothelium, MAPK inhibition has been shown to block the vasoconstrictor effects of insulin in rat skeletal muscle arterioles [10]. Thus, insulin exerts opposing hemodynamic actions with negligible net effect on blood pressure in normal individuals. However, in states of insulin resistance such as obesity and type 2 diabetes, there is impairment in insulin-stimulated NO production and activation of the sympathetic system due to chronic hyperinsulinemia, which shifts the balance in favor of vasoconstriction and may promote hypertension [1••].

Anti-inflammatory and atheroprotective effects

It has been demonstrated that insulin at physiologic concentrations has anti-inflammatory and antiatherogenic effects [11]. The underlying mechanisms may involve stimulation of NO production in the vascular endothelium. NO is an important cardiovascular protective molecule. NO induces vasorelaxation and inhibits vascular smooth muscle growth and proliferation [12]. The endothelium is the first organ that insulin encounters after it is secreted into the circulation. Therefore, constitutive stimulation of NO production by insulin may play a crucial role in the maintenance of vascular health under physiologic conditions. Indeed, recent evidence shows that insulin exerts vasodilatory, antiplatelet, and anti-inflammatory effects at the cellular level in vitro and in vivo [1••,13]. It has been shown that physiologic concentrations of insulin inhibit the binding activity of the pro-inflammatory transcription factor nuclear factor (NF)-κB and the mRNA expression of the pro-inflammatory chemokine monocyte chemoattractant protein (MCP)-1 in human aortic endothelial cells through NO-dependent mechanisms [14]. Moreover, infusion of low-dose insulin with 5% dextrose to obese subjects significantly reduced reactive oxygen species (ROS) generation and NF-κB binding activity in mononuclear cells and decreased plasma concentrations of soluble intercellular adhesion molecule (ICAM)-1, MCP-1, and plasminogen activator inhibitor (PAI)-1 [15]. Neither glucose nor saline infusion without insulin reduced the aforementioned pro-inflammatory markers [14]. In apo E–deficient mice, insulin administration was reported to reduce the number and size of atherosclerotic lesions [16]. In patients with acute myocardial infarction, a low-dose insulin infusion that did not alter plasma glucose concentrations markedly improved clinical outcomes [17,18]. This was accompanied by a significant reduction in plasma C-reactive protein (CRP), an index of systemic inflammation. Collectively, these results support the notion that insulin exerts anti-inflammatory and antiatherogenic effects [14]. In addition, because hyperglycemia is pro-inflammatory

and is associated with marked increases in morbidity and mortality in various conditions, insulin may also exert its anti-inflammatory and antiatherogenic effects through glycemic control [13].

Pro-inflammatory and pro-atherogenic effects

Insulin is a growth factor that regulates several proto-oncogene transcription factors, including c-fos and MAPK [4]. In cultured arterial smooth muscle cells, insulin stimulates VSMC proliferation and migration; these effects are principally mediated through activation of the MAPK pathway [19]. Evidence exists that insulin-like growth factor-1 and proinsulin participate along with insulin in the stimulation of vascular growth and atherosclerosis. The growth-stimulating effects of insulin may contribute to increased cardiovascular risk. Diabetic and obese subjects are at a greater risk of developing atherosclerosis than the rest of the population. Several epidemiologic studies suggest that hyperinsulinemia, which characterizes both obese and type 2 diabetic subjects, may be involved in atherosclerosis [20]. Evidence from human and animal studies has demonstrated that compensatory hyperinsulinemia resulting from insulin resistance stimulates increased endothelial expression of PAI-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin via the MAPK pathway, which may contribute to accelerated atherosclerosis [21]. As described earlier, insulin also promotes release of the vasoconstrictor and pro-atherogenic factor ET-1 from the vascular endothelium.

Vascular Insulin-Signaling Pathways

Insulin signaling in endothelial cells

In the vascular endothelium, insulin stimulates two major signaling transduction cascades: PI3K and MAPK [1••]. Insulin stimulation of NO production through activation of the PI3K pathway leads to vasodilation and increased blood flow, and subsequent augmentation of glucose disposal in skeletal muscle [2•]. The biochemical signaling pathway that regulates endothelial NO production has been elucidated. Insulin signaling is initiated by circulating insulin binding to its receptor. The insulin receptor is a heterotetrameric tyrosine kinase that, after binding insulin, undergoes a rapid tyrosine autophosphorylation, which activates the receptor kinase and allows transient interaction with insulin receptor substrate (IRS). IRS has three subtypes: IRS-1, IRS-2, and IRS-3. IRS-1 is a major substrate for insulin receptor tyrosine kinase and a necessary mediator of insulin-stimulated PI3K and NO production in the endothelium. Tyrosine phosphorylated IRS-1 binds to the p85 regulatory subunit of PI3K, resulting in PI3K activation, which subsequently stimulates phosphorylation of Akt at serine 473 and endothelial nitric oxide synthase (eNOS) at serine 1177, leading to increased eNOS activity and NO production.

In the vascular endothelium, the regulation of NO production by the insulin-signaling pathway is completely distinct and independent from classic calcium-dependent mechanisms used by G protein–coupled receptors such as acetylcholine receptor [2•,5]. Pretreatment of cells with the calcium chelator BAPTA (1,2-bis[o-aminophenoxy]ethane-N,N,N′,N′-tetraacetic acid) does not inhibit the ability of insulin to stimulate phosphorylation of eNOS or enhance eNOS activity. Consistent with this notion, our laboratory recently showed that insulin-stimulated eNOS phosphorylation and vasodilation was impaired in aging rats, whereas acetylcholine-stimulated NO vasodilation was intact. Interestingly, the vascular insulin-signaling pathway that regulates endothelial NO production exhibits striking parallels with the metabolic insulin-signaling pathway in classic insulin-responsive tissues.

Insulin also stimulates the MAPK pathway in the vascular endothelium, which mediates cellular growth and migration and the production of prothrombotic and profibrotic factors [20]. Insulin stimulation of ET-1 secretion and endothelial expression of cellular adhesion molecules (eg, VCAM-1, MCP-1, and E-selectin) is MAPK-dependent but not PI3K-dependent. The insulin level necessary for stimulation of MAPK and PI3K may differ [20]. Fasting plasma insulin levels in a normal insulin-sensitive individual are usually in the low picomolar range (50–150 pM). At this range, insulin constitutively stimulates the PI3K pathway, which participates in regulating the metabolic effects of insulin and maintaining vascular tone. In insulin-resistant states, it has been demonstrated that the insulin-stimulated PI3K pathway is selectively impaired. In humans and animals, selective impairment of PI3K signaling leads to preferential action through signaling pathways that are less impaired (eg, MAPK), tipping the balance of insulin's effects so that they favor abnormal vasoreactivity (hypertension) and vascular growth (stiffening or hypertrophy), which are implicated in the development and progression of macro- and microvascular complications [20]. In addition, fasting insulin levels may reach the nanomolar range. These high levels of insulin stimulate the MAPK pathway, which exerts detrimental effects on the vascular wall by inducing endothelial dysfunction and fostering atherosclerosis. Thus, plasma insulin levels may be a factor controlling the balance between signaling through the PI3K and MAPK pathways.

Insulin signaling in VSMC

It has been demonstrated that insulin receptors are present in human, rat, and bovine VSMC [20]. The insulin-signaling pathway in VSMC is similar to that in endothelial cells: insulin binds to the insulin receptor, leading to tyrosine autophosphorylation, and subsequent phosphorylation/activation of the downstream molecules PI3K and Akt. Insulin stimulates NO production and glucose transport in VSMC

via the PI3K pathway. NO synthesis by VSMC is mainly regulated by inducible NO synthase (iNOS), NO activates the enzyme-soluble guanylate cyclase to generate the second messenger cyclic guanosine monophosphate (cGMP) and induce vasorelaxation. Recently, it was reported that insulin induction of vasorelaxation via Akt-mediated iNOS expression in VSMC plays a role in regulating vascular tone [20]. In addition to stimulating iNOS, insulin inhibits VSMC contractility by attenuating agonist-induced increases in cytosolic calcium through voltage-sensitive calcium channels and stimulating the activity of myosin light-chain phosphatase (MLCP). Because either a PI3K inhibitor or small interfering RNA against Akt abrogated insulin stimulation of MLCP activity, it is likely that insulin inhibits agonist-induced contractility through the PI3K/Akt signaling pathway in VSMC.

Insulin fosters VSMC proliferation and migration, which is inhibited by the MAPK inhibitor PD98059 but not the PI3K inhibitor wortmannin [4]. Insulin may interact with other pro-atherogenic growth factors to promote atherosclerotic processes in insulin resistance states. It is now well established that activation of the renin-angiotensin (Ang) system, especially Ang II and Ang II type 1 receptor (AT1R), has significant pro-inflammatory and proatherogenic actions on the vessel wall, leading to initiation and progression of atherosclerosis [22]. In cultured VSMC, insulin stimulates expression of angiotensinogen and AT1R via activation of the MAPK pathway [23,24]. On the other hand, Ang II interferes with insulin signaling through increased serine phosphorylation of IRS1 [25,26]. Serine phosphorylation of IRS-1 inhibits tyrosine phosphorylation of IRS-1 and results in inactivation of the PI3K pathway [25,26]. In insulin-resistant states, activation of Ang II may impair insulin stimulation of the PI3K pathway. Moreover, Ang II and compensatory hyperinsulinemia may synergistically stimulate MAPK and promote cardiovascular disease [20].

Vascular Insulin Resistance: Implications for Cardiovascular Disease

In the context of the vascular system, insulin resistance manifests as impaired vasodilation, microvessel disease (ie, retinopathy and nephropathy), and enhanced vascular inflammation and atherosclerotic lesion formation. Evidence exists that constitutive production of NO by the endothelium maintains the vasculature in a state of vasodilation and that insulin stimulation of the PI3K pathway may participate in basal NO release [12,27–29]. Interestingly, activation of the PI3K pathway is also responsible for the metabolic action of insulin in skeletal muscle, adipose tissue, and vascular smooth muscle, leading to recruitment of the glucose transporter GLUT-4 to the cell surface, resulting in increased glucose uptake [30]. Thus, impairment of insulin action in the vascular endothelium may be a link between hypertension and metabolic dysfunction in obesity and type 2 diabetes [8,31–33]. Indeed, obese individuals with insulin resistance and patients with type 2 diabetes have impaired insulin-stimulated activation of PI3K [34,35]. In these patients, endothelium-dependent relaxation in response to insulin as well as acetylcholine is often blunted [2•,36]. However, the metabolic and hemodynamic actions of insulin do not completely overlap, because eNOS inhibition abolishes vasodilation but reduces glucose uptake by only 30% to 40% [37]. In addition, induction of endothelial dysfunction with subsequent impairment of insulin-induced increases in total limb blood flow do not decrease insulin-mediated glucose uptake [38]. Studies in which glucose uptake has been measured during hyperinsulinemia, and total limb blood flow has been manipulated with vasodilators (eg, adenosine, bradykinin, and sodium nitroprusside), have shown that total limb blood flow could be increased in either normal or insulin-resistant individuals, without a concomitant increase in insulin-mediated glucose uptake [39]. These findings have been attributed to the fact that various vasoactive agents may change total blood flow, but have distinct effects on the distribution of perfusion within the microcirculation [40].

Recent experimental studies from our laboratory using an aging rat model demonstrated that vascular insulin resistance in aging was independent of metabolic insulin sensitivity and was associated with impaired activation of PI3K and eNOS by insulin, but intact activation of the Ca^{2+}-calmodulin pathway by acetylcholine [33]. We surmised that these findings in aged rats may be due to early abnormalities of the PI3K pathway, which may explain, at least in part, the increased susceptibility of the aging population to vascular injury induced by cardiovascular risk factors. In addition, the novel observation of a dissociation between the development of vascular insulin resistance and endothelial dysfunction implies that decreased vasorelaxation to insulin may contribute to the increase in blood pressure that occurs with age and may be a harbinger for future development of endothelial dysfunction.

Selective impairment of insulin signaling through the PI3K pathway in vascular tissues could be pathophysiologically important in the development of cardiovascular disease (Fig. 1). In vascular endothelial cells, PI3K activation is necessary to promote increased expression and activity of eNOS in response to insulin. PI3K is also a key signaling molecule mediating metabolic actions of insulin in adipose tissue and skeletal muscle. Thus, abnormalities in the PI3K-dependent pathway that are shared among different tissues may provide one molecular explanation for the frequent associations of vascular disease and insulin resistance. Besides vasodilatory actions, stimulation of NO production by insulin may also affect vascular remodeling, such as inhibiting VSMC proliferation and migration and inhibiting platelet aggregation and leuko-

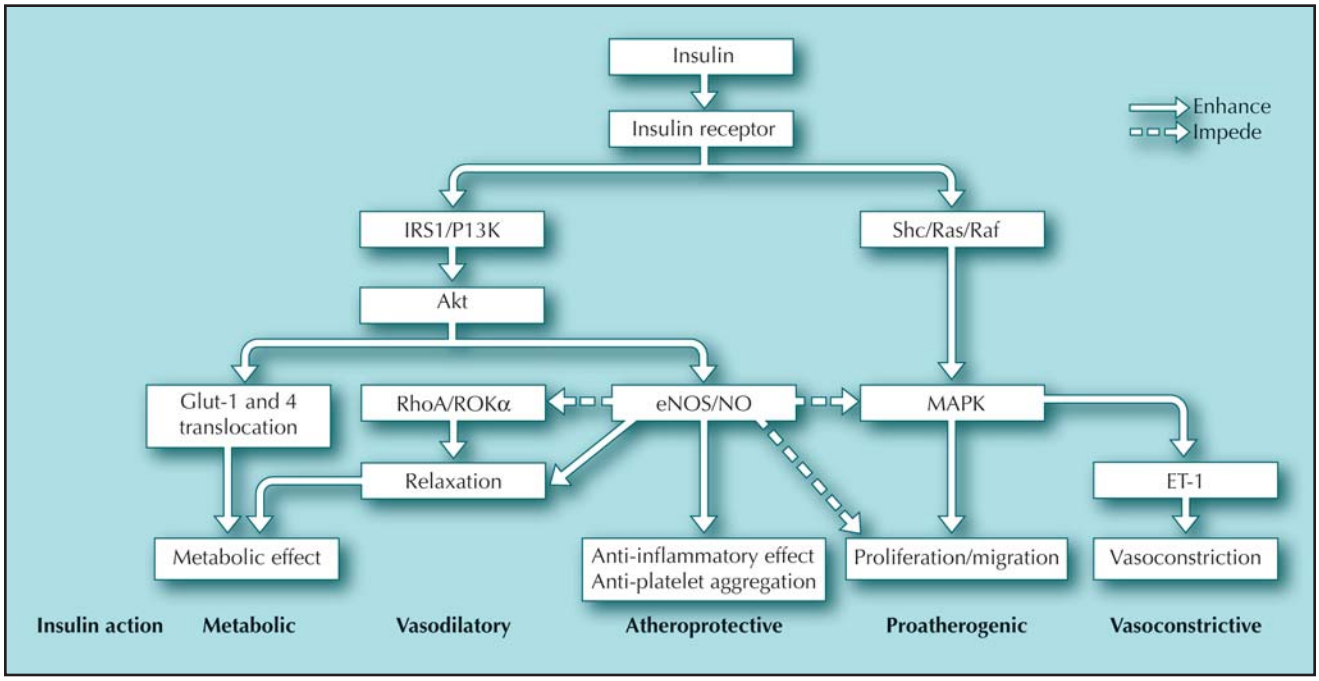

Figure 1. Insulin actions and insulin-signaling pathways in the vasculature. Insulin, after binding its receptor, stimulates two signaling cascades: IRS1/PI3K/Akt phosphorylation and mitogen-activated protein kinase (MAPK) activation. Downstream events of phospho-Akt include 1) stimulation of Glut-1 (vascular smooth muscle cells [VSMC]) or Glut-4 (skeletal muscle, liver, and fat tissues) translocation into membrane, which mediates insulin metabolic effects, 2) leading to endothelial nitric oxide synthase (eNOS) phosphorylation and nitric oxide (NO) production, which induces vasorelaxation, anti-inflammatory, and antiatherogenic effects. Insulin activation of MAPK promotes VSMC proliferation/migration and release of endothelin (ET)-1, which induce pro-atherogenic and vasoconstriction effects. IRS1—insulin receptor substance 1; PI3K—phosphatidylinositol 3-kinase; RhoA—Rho kinase A; ROKα—Rho-associated kinase α.

cyte adhesion to endothelial cells. Thus, the impairment in PI3K activation by insulin in vascular tissues may contribute to the loss of insulin's effect on NO production, which enhances the atherogenic potential of the insulin-resistant state. Furthermore, inhibition of vasodilator effects of insulin in resistance vessels may lead to impairment of muscle blood flow and increased peripheral resistance. In resistance arteries of skeletal muscle, NO-dependent vasodilator effects of insulin are antagonized by insulin-mediated vasoconstriction via ET-1 and MAPK [41–43]. In contrast with insulin-induced vasodilation, the vasoconstrictive effects of insulin remain intact during conditions of insulin resistance. In humans and animals, selective impairment of PI3K signaling leads to preferential action through the MAPK pathway, tipping the balance of insulin's effects so that they favor abnormal vasoreactivity and vascular growth, which are implicated in the development and progression of macro- and microvascular complications. Activation of MAPK-dependent pathways by insulin, including those affecting the sympathetic nervous and renin-angiotensin systems, and increased ET-1 synthesis might also serve to increase vascular tone and foster hypertension [39,40]. Physiologic factors that cause such a selective impairment of insulin-mediated vasoreactivity have not been fully elucidated but may involve ROS stimulation [26]. Recent studies have demonstrated that in vascular cells, ROS activated by Ang II increased serine (human Ser 307, rodent 612) phosphorylation of IRS-1. Serine phosphorylation of IRS-1 inhibits insulin stimulation of IRS-1, results in dissociation of IRS-1 from PI3K, and inhibits PI3-K activation [25,26]. Clinical and experimental studies have demonstrated that angiotensin-converting enzyme inhibitors, AT1 receptor blockers, and antioxidants improve endothelium-dependent vasodilation, arterial structure, and insulin sensitivity in diabetic and hypertensive patients and animals, highlighting an important role of Ang II and ROS in induction of vascular diseases and impaired insulin sensitivity [44–46].

There is a strong clustering of markers of endothelial damage in persons predisposed to salt-sensitive hypertension who concomitantly have insulin resistance and microalbuminuria [47,48]. Clinical studies have demonstrated that salt sensitivity of blood pressure is an independent risk factor for increased cardiovascular morbidity and mortality in normotensive and hypertensive individuals [49]. Salt-sensitive hypertensive patients account for about 50% of hypertensives and have a higher incidence of left ventricular hypertrophy, endothelial dysfunction, hyperlipidemia, and microalbuminuria compared with salt-resistant hypertensive patients [47,48]. In addition, an association between insulin resistance and salt sensitivity has been reported in nondiabetic, nonobese, essential hypertensive subjects and in young, healthy, normotensive subjects [47,48,50,51]. Together,

these findings indicate that salt-sensitive patients display a cluster of cardiovascular risk factors.

The Dahl salt-sensitive (DS) rat is an animal model of salt sensitivity that manifests insulin resistance [52]. We have shown that hypertensive DS rats have impaired endothelium-dependent relaxation and increased vascular superoxide production, suggesting a role for ROS in endothelial dysfunction associated with hypertension [22,53]. We and others also showed that DS rats, despite low plasma renin, have increased local activation of Ang II and upregulation of proatherogenic molecules, which are linked to decreased NO bioavailability [53,54]. Experimentally, Ang II infusion induces endothelial dysfunction via increased vascular oxidative stress [55]. Recent studies supported the notion that insulin resistance is related to increased action of Ang II caused, at least in part, by upregulation of AT1 receptor expression, leading to activation of NAD(P)H oxidase, increased ROS production, and endothelial dysfunction [56]. This may occur in the presence of a low renin state, is usually related to decreased NO bioactivity, and can be partially independent of blood pressure level [54,56]. The DS model of hypertension exemplifies the importance of the interaction between NO, Ang II, and ROS in endothelial dysfunction, which occurs in addition to, but independent of, blood pressure. Indeed, we demonstrated in DS rats that either AT1 receptor blockade with candesartan or specific inhibition of NAD(P)H oxidase with the cell-permeable peptide gp91ds-tat prevented the increase in vascular ROS generation and the upregulation of proatherogenic molecule expression, and normalized endothelial function, independently of blood pressure [22]. Moreover, our recent studies strongly suggested that insulin-mediated aortic vasodilation is impaired in hypertensive DS rats and is normalized by either AT1 receptor blockade or inhibition of ROS production [57].

Conclusions

Almost 25% of US adults have been diagnosed with the metabolic syndrome. Individuals with the metabolic syndrome have an increased risk of coronary artery disease that translates into 2.6-fold increase in cardiovascular mortality [58]. Insulin resistance, endothelial dysfunction, and hypertension are the syndrome's central features. Impaired insulin-mediated vasorelaxation may be synergistic with the vascular effects of hypertension, hyperglycemia, and dyslipidemia. Thus, targeting insulin resistance might be as important as, and synergistic with, blood pressure, lipid, and glycemic control for the prevention of cardiovascular disease in insulin-resistant states. To develop novel effective therapies, further elucidation of the mechanisms underlying the vascular dysfunction associated with insulin resistance is warranted.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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