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# Insulin resistance and hypertension: new insights

Manoocher Soleimani  [Open Archive](#) • DOI: <https://doi.org/10.1038/ki.2014.392> PlumX Metrics

Insulin resistance is associated with hypertension. Nakamura *et al.* demonstrate in rodents and humans with insulin resistance that while the stimulatory effect of insulin on glucose uptake in adipocytes, mediated via insulin receptor substrate 1 (IRS1), was severely diminished, its effect on salt reabsorption in the kidney proximal tubule, mediated via IRS2, was preserved. Compensatory hyperinsulinemia in individuals with insulin resistance may enhance salt absorption in the proximal tubule, resulting in a state of salt overload and hypertension.

Insulin resistance, or diminished insulin sensitivity, is a key feature of metabolic syndrome, linking obesity, impaired glucose intolerance, dyslipidemia, and hypertension.<sup>1</sup> Diminished insulin sensitivity leads to compensatory hyperinsulinemia in order to maintain normoglycemia through the uptake of glucose in skeletal muscles and adipocytes. The insulin resistance is thought to be secondary to the downregulation, or inactivation, of insulin signaling, which encompasses the insulin receptor (IR) and 'docking proteins,' such as insulin receptor substrates (IRSs).<sup>1,2</sup>

Insulin plays a fundamental role in the control of blood sugar by stimulating the facilitative transport of glucose across adipocytes and skeletal muscle fibers subsequent to the activation of IRS.<sup>1,2</sup> Studies into the mechanism of blood sugar control over the

past three decades have shown that insulin stimulates the translocation of glucose transporters from intracellular membrane compartments to the plasma membrane, increasing the rate of sugar uptake. While more than one facilitative glucose transporter (GLUT) is expressed in adipocytes and skeletal fibers, published studies indicate that GLUT4 is the main transporter responsible for the uptake of glucose in these tissues.<sup>1,2</sup>

Insulin binds and activates the insulin receptor tyrosine kinase (IR), culminating in the phosphorylation of IRS1, IRS2, IRS3, and IRS4, which, through binding with several signaling partners, including phosphoinositide 3-kinase (PI3K), activate the Akt/protein kinase B and the protein kinase C- $\zeta$  cascades and play major roles in insulin function.<sup>1,2</sup> IRS subtypes display tissue-specific distribution and distinct signaling pathways, with IRS1 mediating the effect of insulin on glucose uptake in adipocytes and skeletal muscle and IRS2 primarily mediating the effect of insulin on kidney tubules.<sup>1, 2, 3.</sup>

The interaction between insulin resistance and hypertension can be viewed either as a non-causal association (two independent processes) or as reflecting a cause-and-effect relationship (insulin resistance as a cause of hypertension). In the non-causal association, both insulin resistance and hypertension may represent two independent consequences of the same cellular disorder, that is, an increase in intracellular free calcium, which can result in both vasoconstriction and impaired insulin action.<sup>3,4</sup> Furthermore, it is plausible to consider insulin resistance as a molecular marker of multiple metabolic abnormalities frequently associated with hypertension. Alternatively, hyperinsulinemia can be viewed as a major player in the genesis of hypertension via several mechanisms. These include increased sodium reabsorption in the kidney tubules, activation of the sympathetic nervous system, and alteration in vascular



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insulin resistance in the pathogenesis of hyperglycemia and dyslipidemia is reasonably well studied, less is known about the role of insulin resistance in the pathogenesis of hypertension in metabolic syndrome and other diseases, such as type 2 diabetes

mellitus and obesity.

The ability of the kidney tubules to regulate the reabsorption of sodium is essential for maintaining the vascular volume and systemic blood pressure. Insulin acts on multiple nephron segments to stimulate salt reabsorption. In the proximal tubule, insulin is known to stimulate the Na<sup>+</sup>/H<sup>+</sup> exchanger type 3 (NHE3) on the apical membrane, and the sodium-bicarbonate cotransporter (NBCe1) on the basolateral membrane, to increase the reabsorption of sodium and bicarbonate.<sup>4</sup> The stimulatory effect of insulin on NHE3 is likely mediated via Akt, since this pathway is known to play a critical role in the PI3K-mediated translocation of NHE3 into the apical membranes of proximal tubular cells.<sup>4</sup> Insulin also stimulates the Na-K-ATPase, contributing to the increased sodium reabsorption in the proximal tubule.<sup>4</sup> In brief, insulin activates the sodium-absorbing machinery in the proximal tubule.

Insulin enhances salt reabsorption in the thick ascending limb of Henle (TALH) and the distal nephron. In the TALH, insulin directly stimulates NaCl reabsorption, likely via the activation of Na-K-2Cl cotransporters (NKCC2) and Na-K-ATPase.<sup>5</sup> In the distal nephron and the connecting tubule, insulin activates the epithelial sodium channel (ENaC), likely via an increase of ENaC channel density at the membrane.<sup>4</sup> As in the proximal tubule and TALH, insulin activates Na-K-ATPase in the distal nephron. More recent data demonstrate the stimulatory effect of insulin on with-no-lysine (WNK) kinases, suggesting increased sodium reabsorption in the distal nephron via the sodium-chloride cotransporter NCC.<sup>4</sup>

Insulin receptor substrate 1 (IRS1) was identified as the main signal transduction system for insulin in muscle fibers and adipocytes. IRS1 knockout (KO) mice, however, survived with a mild insulin resistance, which led to the identification of IRS2.<sup>1., 2., 3.</sup> Despite similarities in the structures of IRS1 and IRS2, they differ in their tissue expression and signaling pathways.<sup>1., 2., 3., 4.,6</sup> Previous studies by Seki and colleagues demonstrated that the stimulatory effect of insulin on salt reabsorption in the kidney requires the presence of IRS2 but not IRS1.<sup>7</sup> Studies in microperfused proximal tubules of wild-type and genetically engineered IRS1 KO and IRS2 KO mice demonstrated that physiologic concentrations of insulin significantly increased net HCO<sub>3</sub><sup>-</sup> reabsorption in wild-type and

IRS1 KO mice, but failed to do so in IRS2 KO mice.<sup>7</sup> The stimulation of bicarbonate by insulin in wild-type and IRS1 KO mice was shown to be mediated via the PI3K pathway. Similarly, insulin-induced Akt phosphorylation was preserved in IRS1 KO mice but was markedly attenuated in IRS2 KO mice.<sup>7</sup> These results indicate that IRS2 plays a major role in the stimulation of salt absorption in the proximal tubule by insulin.

Hyperinsulinemia *per se*, and in the absence of insulin resistance, as observed in patients with insulinoma, is not associated with hypertension. However, the hyperinsulinemia that is present in the setting of type 2 diabetes mellitus, obesity, or metabolic syndrome can lead to hypertension. While published results may suggest that the facilitative role of hyperinsulinemia in the genesis of hypertension is predominantly observed in association with insulin resistance, it remains unsettled whether the effect of insulin on salt absorption can lead to hypertension in the absence of insulin resistance.

Studies in lean and obese individuals demonstrate that the insulin-induced vasodilation via PI3K signaling is impaired in individuals with insulin resistance.<sup>3,4</sup> Moreover, renal sodium reabsorption seems to be preserved or even enhanced in insulin resistance. In obese subjects with insulin resistance, urinary sodium excretion was decreased by insulin, indicating that the ability of insulin to stimulate salt absorption was preserved.<sup>8</sup> Coupled together, these considerations support a significant role for insulin-stimulated salt reabsorption and impaired vasodilation in the pathogenesis of hypertension in insulin resistance. [Figure 1](#) depicts the main kidney sodium transporters in various nephron segments and their regulation by insulin.

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**Figure 1** Effect of insulin on salt transporters in the proximal tubule, thick ascending limb of Henle, distal convoluted tubule, and collecting duct.

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The studies by Seki and colleagues in this issue of *Kidney International* (Nakamura *et*

al.<sup>6</sup>) tested the hypothesis that the stimulatory role of insulin in salt absorption in the proximal tubule is preserved in a model of insulin resistance in rats and in humans with metabolic syndrome. They further tested the possibility that the impaired effect of insulin on glucose uptake in adipocytes and its stimulatory effect on salt absorption in the kidney proximal tubule are due to the differential regulation of IRS1 and IRS2 in adipocytes and the proximal tubule, respectively. They used sodium-bicarbonate cotransporter (NBCe1) activity as a surrogate marker for salt absorption in the proximal tubule. They show that insulin stimulates NBCe1 activity in control (normal) rats and that this effect is mediated via IRS2. They further show that the stimulation of NBCe1 by insulin (mediated via IRS2) is preserved, whereas the stimulation of glucose uptake in adipocytes (mediated via IRS1) is blunted, in the Otsuka Long–Evans Tokushima Fatty (OLETF) rat, a spontaneous long-term hyperglycemic rat with insulin resistance.<sup>6</sup> They show a similar profile of NBCe1 activation by insulin in kidneys from humans with insulin resistance. They conclude that the preserved stimulation of proximal tubule transport through the insulin/IRS2/PI3K pathway may play an important role in the pathogenesis of hypertension associated with metabolic syndrome.<sup>6</sup>

The preservation of insulin-mediated salt absorption in the kidney is suggestive of the presence of salt-sensitive hypertension in conditions associated with insulin resistance. If so, shall we recommend that individuals with metabolic syndrome, obesity, or type 2 diabetes mellitus limit their salt intake even before the onset of hypertension? Naturally, the best approach to control hypertension in states associated with insulin resistance is to reverse the cause of resistance, that is, through weight loss, the use of insulin-sensitizing agents, or an assuagement of IRS dysregulation. Alternatively, the use of diuretics that specifically inhibit salt reabsorption in the proximal tubule may look appealing in individuals with hypertension due to insulin resistance. A classic example of the latter would be carbonic anhydrase inhibitors, such as acetazolamide. This option is specifically appealing if it is combined with thiazide derivatives, such as hydrochlorothiazide, which has been shown to prevent the generation of metabolic acidosis from acetazolamide monotherapy while enhancing its diuretic potency.<sup>9</sup> The best approach to treating patients with insulin resistance and hypertension requires long-term studies aimed at addressing the risk factors (insulin resistance, hypertension,

and so on) and optimizing clinical outcomes.

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**Figure 1** Effect of insulin...

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