

Review Article

Insulin Resistance, Obesity, Hypertension, and Renal Sodium Transport

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Sodium transport through various nephron segments is quite important in regulating sodium reabsorption and blood pressure. Among several regulators of this process, insulin acts on almost all the nephron segments and is a strong enhancer of sodium reabsorption. Sodium-proton exchanger type 3 (NHE3) is a main regulator of sodium reabsorption in the luminal side of proximal tubule. In the basolateral side of the proximal tubule, sodium-bicarbonate cotransporter (NBCe1) mediates sodium and bicarbonate exit from tubular cells. In the distal nephron and the connecting tubule, epithelial sodium channel (ENaC) is of great importance to sodium reabsorption. NHE3, NBCe1, and ENaC are all regulated by insulin. Recently with-no-lysine (WNK) kinases, responsible for familial hypertension, stimulating sodium reabsorption in the distal nephron, have been found to be also regulated by insulin. We will discuss the regulation of renal sodium transport by insulin and its roles in the pathogenesis of hypertension in insulin resistance.

1. Introduction

Obesity is frequently accompanied with hypertension [1]. Obesity is, at the same time, closely related to hyperinsulinemia and insulin resistance [2]. While the precise mechanism of hypertension in insulin resistance remains to be clarified, the activation of sympathetic nerve system, the disorders dysregulation of central nerve system including leptin, and the activation of renin-angiotensin system are generally thought to be involved [1]. Although insulin has powerful stimulatory effects on renal sodium transport, it remains controversial whether hyperinsulinemia itself is a cause of hypertension.

Acute studies suggest that hyperinsulinemia may cause sodium retention and increased sympathetic activity, which will be an important cause of hypertension [3]. On the other hand, hyperinsulinemia due to insulinoma or chronic insulin infusion into animals do not significantly elevate blood pressure [4, 5]. Moreover, insulin itself has vasodilatory actions [6], which is dependent on nitric oxide [7]. Thus, the relationship between hyperinsulinemia and hypertension is not obvious.

However, the influence of insulin on blood pressure may be altered in insulin resistance. For example, the insulin-induced vasodilation is impaired due to defects in PI3-kinase signaling in insulin resistance [8, 9]. Moreover, several recent data suggest that the insulin-induced enhancement of renal sodium reabsorption is preserved or even enhanced in insulin resistance [10–12]. For example, Rocchini et al. showed that, in obese subjects with insulin resistance, urinary sodium excretion was decreased by insulin similarly as in nonobese subjects [11]. These considerations support a significant role of insulin-stimulated renal sodium transport in the pathogenesis of hypertension in insulin resistance. This review will focus mainly on the regulation of sodium reabsorption along the nephron segments by insulin and its roles in the blood pressure control. Figure 1 shows the main sodium transporters and regulators discussed in this review.

2. Insulin Acting Sites upon Nephron

It has been known for a long time, that insulin acts upon the whole nephron. Bourdeau et al. showed, using radioisotope technique that insulin is accumulated in the proximal tubule

[13]. Nakamura et al. showed that insulin binds upon various segments of rabbit nephron, among which it binds strongest upon thick ascending limb of Henle's loop and distal convoluted tubule [14]. In rat nephron, Butlen et al. showed that insulin is accumulated strongest in the proximal tubule, second in the pars recta and distal convoluted tubule [15]. The way that insulin arrives at the nephron seems to be by two ways: one is by glomerular clearance, and the other is peritubular clearance [16]. The former is by glomerular filtration and subsequent reabsorption from tubular cells by endocytosis, the latter is diffusion from peritubular capillaries and subsequent binding to the receptor.

3. Insulin and Renal Proximal Absorption

Insulin uptake in the renal proximal tubule has been reported on animals such as rabbits [13], rats [17], and dogs [18]. Importantly, insulin has been known to enhance sodium reabsorption in the proximal tubule [19]. Insulin stimulates not only sodium but also volume absorption in the rabbit proximal convoluted tubule. Regarding these stimulatory effects, insulin acts only from the basolateral side of the tubule, not from the luminal side [20]. Proximal tubules reabsorb about seventy percents of total Na filtered from glomeruli. Though important regulatory mechanisms exist afterwards in the Henle's loop, distal tubule and connecting tubule, the stimulation of Na reabsorption from proximal tubules may well contribute to the increase of total fluid volume in the individual, leading to hypertension.

Gesek and Schoolwerth proved that insulin directly increases the Na^+ - H^+ exchanger type 3 (NHE3) activity in proximal tubules of rats [21]. This is important because NHE3 plays a major role in apical sodium entry in proximal tubules. Although the signaling pathway of insulin-mediated NHE3 activation remains unclear, Akt is known to play a critical role in the phosphoinositide 3-kinase- (PI3K-) mediated translocation of NHE3 into the apical membranes of proximal tubular cells [22–24]. The PI3K pathway has also chronic and posttranscriptional effects on the re-regulation of NHE3 mRNA in the proximal tubule cell [20, 25, 26].

It has been shown that Na-K-ATPase is also a target of insulin, contributing to the increase of Na reabsorption [27, 28]. Feraille et al. have showed that, in rat proximal convoluted tubule, insulin stimulates Na-K-ATPase activity [29]. Insulin is also known to stimulate the basolateral electrogenic Na- HCO_3^- cotransporter (NBCe1), which plays a major role in sodium and bicarbonate exit from proximal tubular cells [30]. Therefore, insulin stimulates all the transporters involved in Na absorption from proximal tubules.

4. Insulin and Other Renal Tubules

4.1. Henle's Loop. Kirchner reported that insulin enhances chloride reabsorption in the Henle's loop of volume-expanded rats [31]. This showed a possibility that insulin may stimulate NaCl reabsorption in Henle's loop. Later, in rabbit kidney, it was shown that insulin directly stimulates NaCl reabsorption in Henle's loop [32]. Moreover, it was

suggested that Na-K-2Cl cotransporter (NKCC2) and Na-K-ATPase are also involved in this stimulation [33]. Tsimaratos et al. have clarified that C-peptide, the cleavage product of proinsulin, stimulates Na-K-ATPase in rat thick ascending limb, which is mediated via protein kinase C (PKC) α pathway [34]. They also showed that C-peptide activates PKC α , which then stimulates the phosphorylation of Na-K-ATPase α -subunit.

As about twenty percents of Na reabsorption is accomplished at Henle's loop, stimulation of Na reabsorption here should have a substantial impact on whole-body Na homeostasis.

4.2. Distal Tubule and Connecting Tubule. In late tubule, including distal and connecting tubules, it is widely known that insulin stimulates the activity of amiloride-sensitive epithelial sodium channel (ENaC) [35]. A study using kidney-derived cell line has shown that the activation of ENaC by insulin results from an increase of ENaC channel density at the membrane [36]. Moreover, insulin is known to stimulate Na-K-ATPase in this segment [37, 38]. Consistent with these findings, DeFronzo et al. found that hyperinsulinemia and hyperglycemia enhance sodium reabsorption from distal tubule [19]. Some studies showed that insulin stimulates sodium transport via a signaling cascade involving PI3K, 3-phosphoinositide-dependent protein kinase (PDK1), and serum/glucocorticoid-kinase 1 (Sgk1) [39, 40]. In distal tubule, there are other transporters and kinases that are affected by insulin, such as with-no-lysine (WNK) kinases and sodium-chloride cotransporter (NCC), which we will discuss later.

Distal and connecting tubules regulate only about ten percents of total Na reabsorption in the nephron, but this process cannot be ignored as the final regulation of Na reabsorption.

5. IRS1/2, Hyperinsulinemia, Insulin Resistance, and Hypertension

Insulin receptor substrate (IRS) 1 was originally found through an attempt to find out the signal transduction system of insulin [41, 42]. $\text{IRS1}^{-/-}$ mice, however, survived with only a mild insulin resistance, which led to the identification of IRS2 [43]. The structures of IRS1 and IRS2 are quite similar to each other [44], but the signaling pathway is different [45]. IRS1 and IRS2 knockout mice develop mental retardation and insulin resistance [46, 47]. IRS-1 and IRS-2 differ in the tissue expression, the mechanism of insulin resistance, and the association of β -cell hyperplasia [48]. Some IRSs have been found later but IRS1 and IRS2 are the most important among the IRS family.

Our group compared the effects of insulin on proximal tubule absorption in wild-type, $\text{IRS1}^{-/-}$ and $\text{IRS2}^{-/-}$ mice [49]. In wild-type mice, insulin significantly stimulated Na-coupled HCO_3^- absorption from proximal tubule. In $\text{IRS1}^{-/-}$ mice, the stimulation of HCO_3^- absorption by insulin was preserved, but it was significantly attenuated in $\text{IRS2}^{-/-}$ mice. Moreover, the Akt phosphorylation induced

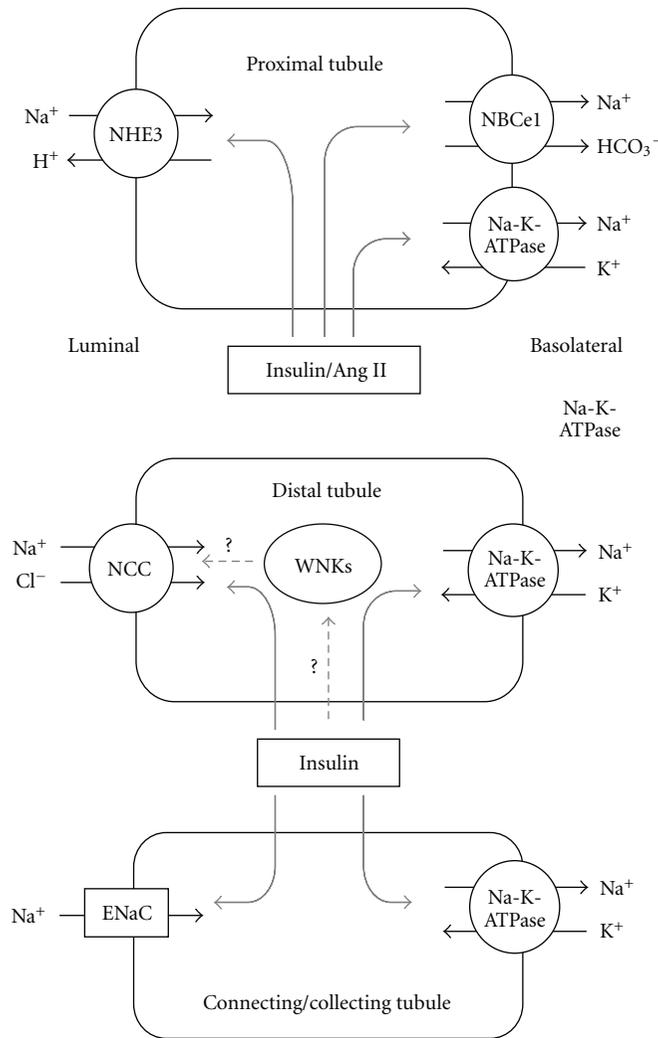


FIGURE 1: The main sodium transporters and regulators in the proximal tubule and distal and connecting/collecting tubules. In the proximal tubule, insulin and Ang II stimulate NHE3 at the luminal side, NBCe1, and Na-K-ATPase at the basolateral side. In the distal and connecting/collecting tubules, insulin stimulates ENaC and NCC in the luminal side, Na-K-ATPase at the basolateral side. Insulin may also indirectly stimulate NCC via WNK kinases.

by insulin stimulation, which mimicked the effect of insulin on proximal absorption, was preserved in IRS1^{-/-} mice but significantly attenuated in IRS2^{-/-} mice. Consistent with a major role of IRS2 in the insulin-mediated transport stimulation in proximal tubules, the tyrosine phosphorylation of IRS2 by insulin was more prominent than that of IRS1. Importantly, signaling defects specific to IRS1 has been often reported in insulin resistance [50–53]. Thus, sodium retention through IRS1-independent way, facilitated by hyperinsulinemia, could be an important factor in the pathogenesis of hypertension in insulin resistance.

6. Tumor Necrosis Factor (TNF) α and Renal Sodium Absorption

TNFα is a pleiotropic 157-amino acid peptide cytokine. It is committed in various physiological reactions, such

as inflammation, proliferation, cell differentiation, and cell death including cell apoptosis [54, 55]. TNFα binds to TNF receptor (TNFR), which has two subtypes, called TNFR1 and TNFR2.

It has been proposed for a long that TNFα causes insulin resistance [56, 57]. Uysal et al. reported that mice lacking TNFα function do not develop obesity-induced insulin resistance [58]. However, TNFα alone may be insufficient to induce insulin resistance [59].

Interestingly, there are controversial papers about the effect of TNFα on sodium reabsorption. In C2BBel cells, derived from human intestinal epithelial cell line, TNFα was reported to reduce NHE3 expression via transcriptional regulation [60, 61]. TNFα seems to reduce Sp1/Sp3 complex to bind to NHE3 promoter DNA via cAMP/PKA way. Relatively high concentrations, though within the physiological levels, of TNFα are also known to increase urine volume and

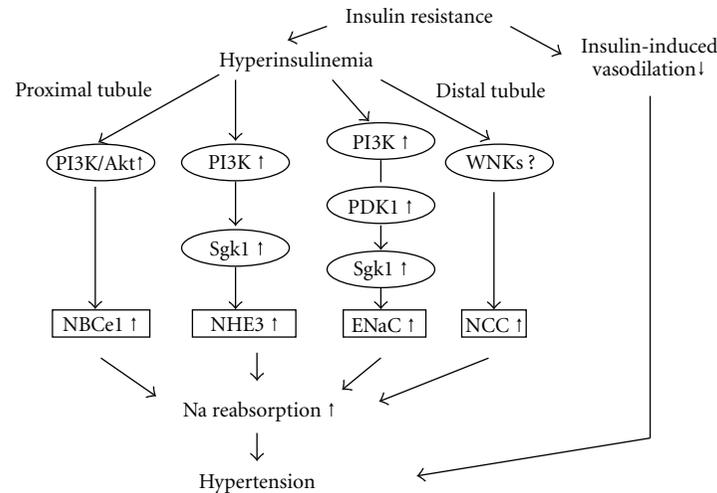


FIGURE 2: Mechanism of hypertension in insulin resistance. In insulin resistance, insulin-induced vasodilation is impaired. However, insulin induced sodium reabsorption through various nephron segments seems to be preserved or enhanced.

sodium excretion [62]. On the contrary, $\text{TNF}\alpha$ was reported to enhance sodium absorption from distal tubule in diabetic rats [63, 64]. The stimulation of sodium uptake by $\text{TNF}\alpha$ was blocked by amiloride, an inhibitor of ENaC, and PD98059, an inhibitor of ERK. It seems that $\text{TNF}\alpha$ acts on sodium status in a biphasic way: toward sodium excretion at high concentrations [65] and sodium retention at low concentrations. The effect of $\text{TNF}\alpha$ on renal sodium reabsorption in the nondiabetic condition, however, remains to be clarified.

7. Angiotensin II and Insulin Resistance

Angiotensin II (Ang II) is important for its potent ability to raise blood pressure. In addition to the vascular effects, Ang II stimulates sodium absorption from the proximal tubule, acting on several transporters carrying sodium [66]. Renin-angiotensin system (RAS) is activated in insulin-resistant state [67, 68]. RAS activation, on the other hand, has been related to impaired insulin signaling and systemic insulin resistance in various tissues and organs [69]. RAS and insulin resistance are, therefore, believed to be closely related. Moreover, numerous clinical evidences with RAS inhibitors, such as ACE inhibitors and ARBs, show that the inhibition of RAS contributes to amelioration of insulin resistance, prevention of hypertension, and damage of tissues and organs.

Interestingly, Ang II is known to regulate proximal tubule transport in a biphasic way: stimulation by low (picomolar to nanomolar) concentrations and inhibition by high (nanomolar to micromolar) concentrations. Studies using Ang II type 1A receptor (AT1A) KO mice revealed that these effects of Ang II are mediated by AT1A [70, 71]. Interestingly, the ERK pathway mediates the stimulatory effect but not the inhibitory effect of Ang II in proximal tubules [72]. It is unknown whether the stimulatory effect of Ang II on proximal tubule transport is enhanced in insulin resistance.

On the other hand, hyperglycemic state was shown to stimulate Ang II expression in the proximal tubule derived cells [73]. This is mediated by p44/42 MAPK signal transduction system. Taken together, Ang II might act to enhance sodium reabsorption from proximal tubule in both acute and chronic phases of insulin resistance.

8. Kidney and WNK, Hypertension, and Insulin

WNK kinase was originally found as a kind of serine-threonine kinase with an atypical lysine placement [74]. Notably, mutations in WNK kinases cause Gordon's syndrome (pseudohypoaldosteronism type II (PHAII) or familial hyperkalemic hypertension (FHH)) [75]. This finding has led to investigating the regulation of WNK kinases and their effects on renal transporters, such as NCC (sodium chloride cotransporter) and NKCC (sodium-potassium-chloride cotransporter), in the context of blood pressure homeostasis.

WNKs have five subtypes: WNK1, WNK2, WNK3, and WNK4, and a transcriptional variant of WNK1, KS-WNK1 [76]. In the distal tubule cells, NCC reabsorbs sodium and chloride at the apical membrane. WNK4 reduces NCC amount at the plasma membrane at least in some conditions [75, 77–80]. On the other hand, WNK4 is reported to enhance the NCC activity through its phosphorylation [81]. WNK1 does not affect NCC activity itself but suppresses WNK4 activity [78, 79]. KS-WNK1, which does not have kinase domain of WNK1, inhibits the WNK1 action on WNK4 [82, 83]. WNK3 stimulates NCC activity in its active form, but exerts a negative effect in its inactive form [84, 85]. In contrast to these distinct effects of individual WNKs on NCC, Heise et al. recently showed that WNKs 1, 3, and 4 all stimulate ENaC through serum glucocorticoid-induced kinase (SGK) 1, and that these stimulatory effects of WNKs are mediated by their N-terminal sequences without kinase activity [86]. These results suggest that WNKs regulate NCC and ENaC through different mechanisms.

TABLE 1: Effects of insulin on renal transporters, channels, or regulators.

	Transporter/channel	Effects of insulin
Proximal	NBCe1	Stimulation
	NHE	Stimulation
	Na-K-ATPase	Stimulation
Henle	NKCC	Stimulation
	Na-K-ATPase	Stimulation
	ENaC	Stimulation
Distal	NCC	Stimulation
	Na-K-ATPase	Stimulation
	WNK4	?
	WNK1	?
CNT	ENaC	Stimulation

Recently, there are some reports suggesting that insulin has influence on the activity of WNKs, which may have a role in the pathogenesis of salt-sensitive hypertension. For WNK1, Vitari et al. showed that WNK1 is a substrate of protein kinase B/Akt, a serine-threonine kinase known to be downstream of insulin signaling. This finding suggests that insulin may affect blood pressure by regulating WNK1 [87]. For WNK4, Sohara et al. have revealed that the WNK4 mutation (R1185C) induces excess phosphorylation of WNK4 S1190, which is a target phosphorylation site by insulin. They have also clarified that the phosphorylation of WNK4 S1190-OSR1/SPAK-NCC cascade is increased in the mice with hyperinsulinemia. These findings suggest that insulin regulates Na reabsorption from the distal tubule through WNKs and is involved in the pathogenesis of salt-sensitive hypertension [88]. Ellison et al. showed that the WNK4-NCC pathway as well as the abundance of WNK4 was altered in the rat model of insulin resistance [89]. Huang and Kuo reported that insulin reduced the renal cortical WNK4 expression [90]. This would indirectly enhance NCC and ENaC [91]. Now, the interaction between WNK kinases and insulin is intensively investigated, so it is expected that, in the near future, the regulatory system of insulin and distal to connecting tubules will be much more clarified.

Table 1 is a summary of insulin action on the regulators of sodium transport in the nephron segment. Insulin acts mostly as an enhancer of sodium reabsorption. The effects of insulin on WNKs require further investigations. Figure 2 is a scheme about how insulin triggers the signal transduction downstream and leads to hypertension.

9. Conclusion

We have discussed the renal actions of insulin. Sodium transport along nephron segments is a key for regulating blood pressure and sodium metabolism, with great influence on cardiovascular management. There are several regulators along each segment of the nephron. Among them, insulin and its signal transduction system have outstanding features and important roles from the view of hypertension associated

with insulin resistance. Moreover, WNKs seem to be important mediators of insulin actions on the distal nephron.

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