

# The Effects of Insulin Resistance and Inflammation on Renal Proximal Tubule Sodium Transport and Hypertension

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## ABSTRACT

Insulin resistance, closely linked to inflammation, is recognized as a key factor in the onset and aggravation of diabetes, cardio-renal syndrome, hypertension, and obesity. In the renal proximal tubule, insulin resistance may increase renal sodium reabsorption, leading to hypertension, edema and sometimes heart failure. Recently some anti-diabetic agents have been shown to have effects on the transporters in renal proximal tubule. Because renal proximal tubule mediates about 70% of sodium reabsorption, it is quite important to clarify the function of renal proximal tubule under insulin resistance and inflammation.

**Keywords:** Insulin; Inflammation; TNF- $\alpha$ ; Proximal Tubule; Insulin Resistance; PPAR $\gamma$ ; Thiazolidinediones

## 1. Introduction

The relationship between inflammation and diabetes had been described long ago by the fact that anti-inflammatory drugs such as salicylates decrease blood glucose level [1]. About more than a century ago sodium salicylate was known to reduce or totally eliminate the diabetic symptoms [2,3]. Only recently the relationship between inflammation and insulin resistance began to be investigated vigorously, when Hotamisligil *et al.* [4] found that a proinflammatory factor tumor necrosis factor (TNF)- $\alpha$  could induce insulin resistance. Karasik *et al.* [5] reported that TNF- $\alpha$  suppressed insulin-induced tyrosine phosphorylation of insulin receptor and its substrates, resulting in attenuated insulin effect and insulin resistance.

To date there seems to be mainly two ways from inflammation to insulin resistance [1]. One is c-Jun N-terminal protein kinases (JNK) pathway [6,7], which, through the activator protein 1 (AP-1) transcription factor in the nucleus, enhances the transcription of inflammatory genes. JNK pathway also induces serine phosphorylation of insulin-related substrate (IRS-1) [8-11]. Phosphorylated IRS-1 itself induces insulin resistance by direct blocking of insulin signaling pathway through IRS-1 [10,11]. Recently Davis *et al.* showed that obesity-in-

duced insulin resistance and inflammation are promoted by JNK in macrophage [12]. They produced mice with selective JNK deficiency in macrophages, which showed improved insulin sensitivity under high-fat diet.

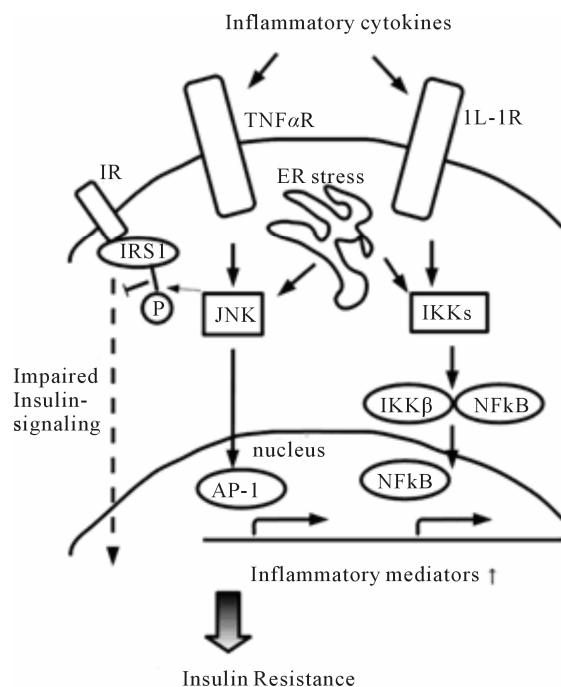
The other is via I $\kappa$ B kinase- $\beta$  (IKK $\beta$ )/NF $\kappa$ B pathway [13]. The signals from proinflammatory factors such as TNF- $\alpha$  and interleukin (IL)-1, via IKK $\beta$  complex, activate NF $\kappa$ B complex. Then NF $\kappa$ B works as a transcription factor [1]. NF $\kappa$ B is a primary regulator of inflammatory response [14] and requires IKK $\beta$  for its activation [15]. IKK $\beta$  has been shown to link inflammation to obesity-induced insulin resistance [16]. IKK $\beta$ /NF $\kappa$ B pathway is triggered by PI3K/AKT signaling [17-19].

These pathways inducing insulin resistance are triggered by such factors as TNF- $\alpha$ , IL-1, endoplasmic reticulum (ER) stress, oxidative stress, and lipids [1]. The details of the pathways from these factors to the emergence and aggravation of insulin resistance still remain to be clarified. **Figure 1** summarizes the main pathways from inflammation to insulin resistance.

## 2. TNF- $\alpha$ and Sodium Reabsorption in Nephron

TNF- $\alpha$  was originally discovered as an anti-tumor factor [20,21]. At first TNF- $\alpha$  was thought to be produced only by immune cells [22,23]. Now epithelial cells and endo-

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**Figure 1. The major pathways from inflammation to insulin resistance. This figure focuses on the two main pathways dependent on JNK or IKK.**

thelial cells have been also found to produce TNF- $\alpha$  [24]. TNF- $\alpha$  is generated by tubular epithelial cells and mesangial cells in the kidney [25-27].

The receptors of TNF- $\alpha$  consist of two major subtypes; TNF $\alpha$ R1 (p55) and TNF $\alpha$ R2 (p75) [28,29]. In the kidney TNF $\alpha$ R1 is predominantly expressed in renal vessels and glomeruli, while TNF $\alpha$ R2 is expressed mainly in renal tubules [30].

The role of these two receptors is not clear, although TNF $\alpha$ R1 may mediate the cytotoxic and inflammatory responses of TNF- $\alpha$ , while TNF $\alpha$ R2 may mediate protective effects of this cytokine [31,32]. For example, in cardiomyocytes TNF $\alpha$ R1 mediates ischemic injury, whereas TNF $\alpha$ R2 mediates cardioprotective effects of TNF- $\alpha$  [33, 34]. In the kidney TNF $\alpha$ R1 is supposed to mediate acute renal vasoconstriction and natriuresis in response to high dose of TNF- $\alpha$  [35].

Using TNF $\alpha$ R1 or TNF $\alpha$ R2 knockout (KO) mice Majid and colleagues showed that these receptors play different roles in renal hemodynamic and natriuretic responses to high dose of TNF- $\alpha$  infusion [35]. After TNF- $\alpha$  infusion, the mean arterial pressure slightly decreased from the baseline but renal vascular resistance increased in WT mice. In both KO mice the blood pressure also decreased, while urinary Na<sup>+</sup> excretion increased in WT and TNF $\alpha$ R2 KO mice but did not change in TNF $\alpha$ R1 KO mice. These results indicate that TNF $\alpha$ R1 mediates the natriuretic response to high-dose TNF- $\alpha$ .

By contrast, the chronic inflammatory effects of

lower-dose TNF- $\alpha$  in the kidney was shown to be mediated by TNF $\alpha$ R2 [36]. Gesek and colleagues showed that chronic TNF- $\alpha$  exposure induced sodium retention by activating ENaC in diabetic rats [37]. They also reported that chronic exposure to low-dose TNF- $\alpha$  stimulates Na<sup>+</sup> uptake in isolated rat distal tubule cells [38]. In LLC-PK1 cells, the model of renal proximal tubule (PT) cells, TNF- $\alpha$  stimulates Na<sup>+</sup>-K<sup>+</sup>-ATPase [39]. TNF $\alpha$ R1<sup>-/-</sup> mice showed enhanced tubular Na<sup>+</sup> reabsorption in response to chronic angiotensin II infusion, suggesting that upregulation of TNF $\alpha$ R2 could contribute to this renal response [40]. TNF- $\alpha$  might be one of the therapeutic targets in hypertension and its complications.

### 3. IRS-1, Insulin Resistance and Renal Proximal Transport

PT plays important roles in the regulation of acid-base and electrolytes homeostasis [41-43]. As for acid-base homeostasis, the Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotransporter NBCe1 in the basolateral side and the Na<sup>+</sup>/H<sup>+</sup> exchanger NHE3 in the apical side of the PT are mainly involved in Na<sup>+</sup> coupled HCO<sub>3</sub><sup>-</sup> reabsorption. Na<sup>+</sup>-K<sup>+</sup>-ATPase gives a driving force for Na<sup>+</sup> reabsorption. Insulin is known to be uptaken into proximal tubule [44-46]. Insulin enhances sodium reabsorption from PT [47,48] by stimulating NHE3 [49], Na<sup>+</sup>-K<sup>+</sup>-ATPase [50-52], and NBCe1 [53].

By using IRS-1 and IRS-2 knockout mice we have clarified [54] that the stimulation of proximal transport by insulin is mediated by IRS-2, not by IRS-1. Signal transduction via Akt, which is thought to mediate the effect of insulin in proximal tubule, is preserved in IRS-1 KO mice but attenuated in IRS-2 KO mice. In insulin resistance signal transduction via IRS-1 is frequently attenuated [55-58]. IRS-2 dependent stimulation of sodium absorption from PT may play an important role in the occurrence of hypertension in insulin resistant status. We recently confirmed that the stimulatory effect of insulin on Na<sup>+</sup> absorption from PT is preserved in rats and human species with insulin resistance ("Stimulatory Effect of Insulin on Renal Proximal Na Transport Is Preserved in Insulin Resistance" 2012 Annual Meeting of American Society of Nephrology).

These results strongly suggest that in insulin resistance the stimulatory effect of insulin on PT transport is preserved via IRS-2. While defects in IRS-1 dependent signaling in insulin resistance may induce impaired vasodilation [59], IRS-2 dependent sodium retention from the kidney may play an important role in the onset and aggravation of hypertension in diabetes.

### 4. Insulin Resistance and Distal Tubules Transporters and Kinases

Insulin also acts on distal tubule, where Na<sup>+</sup>-Cl<sup>-</sup> cotransporter (NCC) is located in the luminal side. NCC is

regulated by with-no-lysine (WNK) kinase oxidative stress-responsive kinase-1 (OSR1)/STE20/SPS1-related proline-alanine-rich kinase (SPAK) system [60].

WNK was originally discovered as a serine-threonine kinase with an atypical lysine alignment [61]. WNK has five subtypes, WNK1, WNK2, WNK3, WNK4 and transcript variant of WNK1, KS-WNK [62]. The mutations in WNK kinases cause Gordon syndrome (also known as familial hyperkalemic hypertension, FHH or pseudohypoaldosteronism type II, PHAII) [63].

At first WNK4 was thought to suppress the NCC activity by reducing its expression in the plasma membrane [63-67]. WNK1 was shown to suppress WNK4 but not directly inhibit NCC [65,67]. On the other hand, disruption of WNK4 gene was shown to decrease phosphorylation of NCC, inducing enhanced  $\text{Na}^+$  excretion and lower blood pressure [68]. Furthermore, overexpression of WNK4 was recently shown to induce PHAII phenotypes, suggesting that WNK4 might actually stimulate the NCC activity [69].

NCC was recently shown to be regulated by insulin via WNKs. In cultured mouse distal tubule cells (mpkDCT cells), insulin increased SPAK and NCC phosphorylation. In mpkDCT cultured cells and mouse kidney, insulin induced OSR1/SPAK phosphorylation and consequent NCC phosphorylation. The insulin-induced NCC phosphorylation was lost in SPAK knockout mice [70]. In hypertensive and hyperinsulinemic db/db mice, WNK-OSR1/SPAK-NCC is phosphorylated by PI3K/Akt signaling pathway [71]. Moreover, NCC is functionally activated by insulin [72].

These results suggest that the insulin/WNK-OSR1/SPAK-NCC system may play an important role in  $\text{Na}^+$  retention and hypertension, and may be another therapeutic target in hypertension associated with insulin resistance.

## 5. PPAR $\gamma$ , Thiazolidinediones and Kidney

Peroxisome-proliferator-activated receptors (PPARs) were first discovered in 1990s. PPARs belong to the nuclear-receptor superfamily and regulate gene expression in response to binding of the ligands such as fatty acids and oxysterols [73]. PPAR variants include PPAR $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ , among them PPAR $\gamma$  is implicated in the onset of insulin resistance. It is expressed most abundantly in adipose tissue and liver but also exists in pancreatic  $\beta$  cells, vascular endothelial cells and macrophages. PPAR $\gamma$  is a target of thiazolidinediones (TZDs), an insulin sensitizing drug.

Although TZDs are quite effective in improving insulin resistance, they have notorious side effects such as fluid retention leading to heart failure [74,75], and an elevated risk of bladder cancer [76]. The side effect of fluid retention is quite important because diabetic pa-

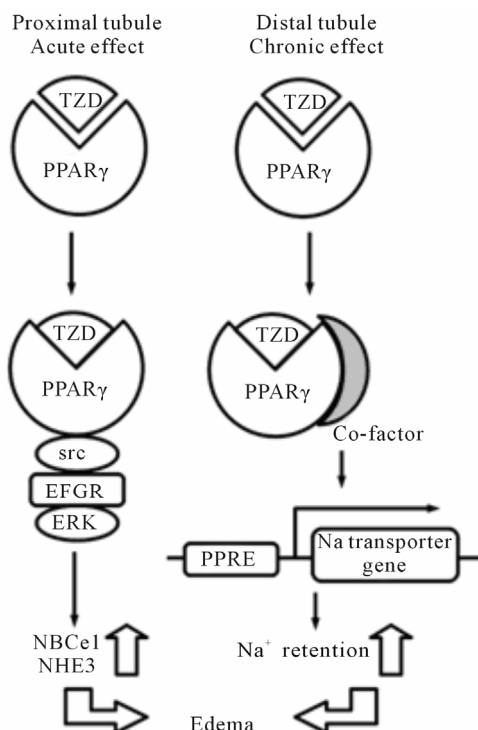
tients are under the risk of heart failure. The mechanism of TZDs-induced fluid retention has been in dispute for a while. The fluid retention effect of TZDs was shown to be dependent on PPAR $\gamma$  in collecting ducts. In particular, the epithelial  $\text{Na}^+$  channel (ENaC) in collecting ducts was first thought to be the main cause of TZDs-induced fluid retention [77,78]. In addition, TZDs were shown to enhance ENaC $\alpha$  subunit expression through the glucocorticoid inducible kinase SGK1 [79]. On the contrary, the other studies showed that TZDs did not alter ENaC expression and activity [80,81]. Though amiloride, an ENaC inhibitor, prevented TZDs-induced volume expansion in mice [78], it failed to prevent volume expansion induced by GI262570, a non-TZD PPAR $\gamma$  agonist in rats [82]. In mice lacking ENaC $\alpha$  subunit selectively in collecting ducts, TZDs-induced fluid retention was not attenuated [83]. This strongly suggests that ENaC stimulation is not responsible for TZDs-induced fluid retention. On the other hand, some reports suggested that PT transport is stimulated by TZDs both in human [84] and rabbit [85].

We hypothesized that PT may be another important target of TZDs and have proved that TZDs significantly stimulate PT transport within several minutes [86]. This rapid stimulation is dependent on PPAR $\gamma$ -Src-EGFR-ERK pathway in rabbit, rat and human PTs. However, this rapid stimulation was not observed in mouse PTs, because of constitutive activation of Src/EGFR. The truncated construct representing the ligand-binding domain of PPAR $\gamma$  was also able to mediate the similar signaling, suggesting that the TZDs-induced PT transport stimulation is independent of transcriptional activity of PPAR $\gamma$ . Our work may help to develop new TZDs with fewer side effects. Recently another study showed that TZDs do not increase the ENaC activity and its mRNA expression in the kidney [87], confirming that ENaC is not a main target of TZDs. The actual target of TZDs on distal  $\text{Na}^+$  transport remains to be determined. **Figure 2** shows the proposed mechanisms by which TZDs induce  $\text{Na}^+$  and fluid retention.

## 6. PPAR $\gamma$ , TZDs, Insulin Resistance and Inflammation

As described above, insulin resistance is closely related to inflammation. Expansion of adipocyte induces inflammatory reactions such as proliferation of macrophage and release of inflammatory cytokines like TNF- $\alpha$  and IL-1, triggering the onset of insulin resistance [88].

Patients with dominant negative mutations of PPAR $\gamma$  have severe insulin resistance, diabetes and even hypertension [89]. On the other hand, human PPAR $\gamma$  polymorphism Pro12Ala leads to improved insulin sensitivity and glucose tolerance [90]. Moreover, in mice, increased PPAR $\gamma$  activity prevented insulin resistance due to obesity



**Figure 2. The proposed mechanisms by which TZDs induce  $\text{Na}^+$  and fluid retention. TZDs may induce acute stimulation of PT transport by non-genomic mechanism, while they induce chronic stimulation of distal transport by activation of undefined Na transporter(s).**

obesity [91], while lack of  $\text{PPAR}\gamma$  in fat, muscle, or liver predispose mice to developing insulin resistance [92-95]. Therefore,  $\text{PPAR}\gamma$  plays important roles in glucose homeostasis [96].

TZDs can reduce blood glucose by improving insulin resistance [97]. Upon binding to TZDs,  $\text{PPAR}\gamma$  makes heterodimers with retinoid-X receptors (RXRs). This complex binds to specific DNA sequence known as peroxisome proliferator response elements (PPREs) on the promoters of  $\text{PPAR}\gamma$  target genes. These genes are transactivated after binding of  $\text{PPAR}\gamma/\text{RXR}$  complex. Some of these genes are involved in metabolic homeostasis [98]. Moreover,  $\text{PPAR}\gamma$  also regulates inflammatory response genes [99]. TZDs might prevent the onset of insulin resistance and improve glucose tolerance, by either improving metabolic homeostasis or preventing inflammation.

Several studies showed that TZDs exert renoprotective effects [100] and anti-inflammatory effects [101] in the kidney. Moreover, Troglitazone and other  $\text{PPAR}\gamma$  agonists inhibit inflammation-related chemokine expression in human tubular epithelial cells HK2 [102]. TZDs might have direct anti-inflammatory effects and ameliorate insulin resistance in PTs. Future studies are required to clarify the detailed mechanisms underlying the renoprotective effects of TZDs.

## 7. Conclusions and Prospectives

We have discussed the relationship between insulin resistance and inflammation in the context of the onset of hypertension. Insulin resistance, caused by inflammation mainly in adipose tissue, is implicated in unfavorable effects on various organs including kidney, resulting in increasing mortality and morbidity in all over the world.

In the kidney, insulin-induced  $\text{Na}^+$  retention may be causally linked to hypertension. In PT, IRS-2 dependent  $\text{Na}^+$  reabsorption may be enhanced, even in insulin resistance with defective IRS-1 signaling. In the distal tubule, a WNK-SPAK/OSR1-NCC system may be also activated by insulin.

TZDs can significantly improve insulin sensitivity. However, TZDs-induced fluid retention is a serious problem in diabetes treatment. The development of medications that improve insulin resistance without inducing the serious side effects is expected.

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