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REVIEW **Open Access**

Role of insulin signaling and its associated signaling in glomerulus for diabetic kidney disease

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Summary. The number of patients with diabetic kidney disease (DKD) has been rising significantly over the last several decades and is one of the most frequent causes of chronic kidney disease (CKD) in the United States. Hyperglycemia accelerates development of DKD, a direct result of increased intracellular glucose availability. Two large clinical studies, the Diabetes Control and Complications Trial in type 1 diabetes and the United Kingdom Prospective Diabetes Study in type 2 diabetes showed that intensive glycemic control delayed the onset and the progression of DKD. On the other hand, it is reported that glycemic control alone is not sufficient to control DKD progression.

Recent data support that insulin signaling and its associated signaling contribute significantly to preserve glomerular function. However, little is known about the key regulators of insulin signaling in glomerular component cells. In this review, we summarize the novel knowledge regarding the reno-protective effects of insulin signaling or its associated signaling in glomerular constituent cells on DKD.

Key words: Diabetic kidney disease (DKD), Insulin signaling, Insulin receptor substrate 1 (IRS1), Vascular endothelial growth factor (VEGF), Pyruvate kinase M2 (PKM2)

Introduction

Diabetes is the most common cause of chronic kidney disease (CKD) and chronic hyperglycemia is a major cause of diabetic kidney disease (DKD) which remains a leading cause of new-onset end-stage renal disease (ESRD), and yet treatment is still very limited. Several studies have shown that there is a causal relationship between the degree of blood glucose control and the development of complications in patients with diabetes (Diabetes Control and Complications Trial Research Group et al., 1993); (UK Prospective Diabetes Study (UKPDS) Group, 1998; Mima et al., 2012a). Two large long-term follow-up studies, the Diabetic Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study in type 2 diabetes, suggested that intensive blood glucose control could delay the onset and the progression of DKD (UK Prospective Diabetes Study (UKPDS) Group, 1998).

In addition to diabetic condition, the activation of the renin angiotensin aldosterone system (RAAS) is thought to play a significant role in developing DKD, as numerous previous studies showing that RAAS blockade by angiotensin converting enzyme inhibitors (ACEI), AT1 receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) delay the progression of DKD (Mima et al., 2006, 2008; Mima, 2022b). However, these agents are not perfect for DKD treatment (Nobakht et al., 2011; Bakris et al., 2020).

The focus of research on the pathogenesis of DKD is on the risk factors or mechanisms by which hyperglycemia causes glomerular and tubular lesions. However, the lack of a treatment based on the mechanism by which hyperglycemia produces harmful metabolites suggests that a change in approach is needed for effective treatment of DKD. DKD results from an imbalance between the increased toxic effects of systemic metabolic abnormalities such as hyperglycemia, hyperlipidemia, and hypertension and the decreased regenerative effects of endogenous protective factors such as insulin signaling or vascular endothelial growth factor (VEGF) signaling (Mima et al., 2012b). Insulin signaling has also been reported to enhance VEGF signaling (Walker et al., 2021). We have reported that hyperglycemia might cause podocyte apoptosis by dual mechanisms of increasing inflammation or oxidative stress, and inhibition of protective growth factor action such as VEGF receptors (Mima et al., 2012b; Mima, 2013a). Furthermore, our previous results indicated that hyperglycemia via advanced glycation end products (AGEs) and oxidants can activate protein

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kinase C (PKC), mitogen-activated protein (MAP) kinase, and oxidases to cause mesangial expansion, leading to glomerulosclerosis (Mima et al., 2011). This pathological change in glomeruli is caused by overexpression of transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF). This process is promoted by angiotensin II and inflammation and reduced by VEGF, insulin signaling, and activated protein C (APC) (Mima et al., 2012a-d; Mima, 2013b). Activation of PKC can also inhibit insulin signaling and VEGF action; hyperglycemia reduces the protective effects of these cytokines, leading to proteinuria, mesangial expansion, and glomerulo-sclerosis (Mima et al., 2012a-d). In this review, we will discuss insulin signaling and VEGF, a signal associated with insulin signaling which can be involved in preventing DKD.

Insulin signaling

In diabetic and insulin-resistant states, insulin's actions in the endothelial cells are inhibited, leading to endothelial dysfunction, then leading to cardiovascular diseases including DKD in animal models. Insulin can stimulate the production of nitric oxide (NO) by the activation of endothelial NO synthase (eNOS), resulting in vasodilatation and antithrombosis, and inhibiting smooth muscle cell growth. Impaired action of insulin has been observed in the glomerular endothelial cells and mesangial cells in DKD, possibly by the activation of the PKCβ2 isoform (Rask-Madsen and King, 2007). Furthermore, insulin receptor substrate 1 (IRS1)/Akt/eNOS is selectively inhibited by diabetes and insulin-resistant states, but another insulin signaling, mitogen-activated protein kinase (MAPK), is not inhibited (Mima et al., 2011). It has been reported that PKCβ specific inhibitor, ruboxistaurin (RBX), reversed insulin signaling on NO production in the myocardium, vasculature, and glomeruli of diabetic rodents (Naruse et al., 2006). Indeed, RBX has been shown to markedly reduce albuminuria in patients with DKD (Tuttle et al., 2015). Studies using mice overexpressing PKCβ2 in endothelial cells (EC-PKCβ2) showed impaired insulin signaling in glomeruli, increasing extracellular matrix and albuminuria (Mima et al., 2012c). Also, phosphodiesterase 5, an exogenous NO donor, might decrease blood pressure (Wolk et al., 2009). However, there are no reports that clearly prove that phosphodiesterase 5 is effective in slowing the progression of DKD. Therefore, inhibition of PKCβ activity or increases IRS1/insulin signaling in glomerular endothelial cell might be a promising treatment for DKD (Mima, 2016).

Mice lacking the gene encoding the insulin receptor specifically from podocytes showed excessive excretion of albuminuria, shortening of the podocyte foot processes, increased deposition of podocyte components, and a higher frequency of podocyte apoptosis (Welsh et al., 2010). This finding also suggests the importance of insulin signaling as a reno-protective factor.

Pyruvate kinase M2

A recent clinical study called the Joslin 50-year Medalist Study examined patients with type 1 diabetes for a long duration (over 50 years) and found that 87% of them did not show clinically significant DKD confirmed by renal pathologic investigation (Keenan et al., 2007; Sun et al., 2011). These studies support the significance of endogenous protective factors which can reduce the toxic effects of diabetic states on the kidney. Examination of the glomeruli of these patients revealed that increased glycolytic flux was important in inhibiting the accumulation of glucose toxic metabolites, improving mitochondrial function, decreasing podocyte apoptosis and mesangial expansion. Activation of pyruvate kinase M2 (PKM2), a key enzyme in the glycolytic system, can normalize renal hemodynamics, mitochondrial dysfunction, and glomerular pathology in a DKD mouse model (Qi et al., 2017). Interestingly, insulin can up-regulate the expression of PKM2 and protect PKM2 from degradation (Liu et al., 2021).

Heme oxygenase-1

Heme oxygenase-1 (HO-1) is a potent anti-oxidant enzyme that has been reported to inhibit a key mechanism of vascular injury, which is usually upregulated in response to inflammation and oxidative stress (Seldon et al., 2007). Recently, we have reported that nuclear factor-κB (NF-κB) activation is recognized in the glomeruli or retina of diabetic and insulin-resistant states (Mima et al., 2012d, 2018). Studies using mice deleted HO-1 gene showed NF-kB activation (Seldon et al., 2007; Tracz et al., 2008). It has been reported that insulin signaling significantly increases protein levels of HO-1 and that insulin treatment prevented oxidative stress induced-NF-κB and caspase-8 activation and pericyte apoptosis through the IRS1/PI3K/Akt2/HO-1 pathway (Geraldes et al., 2008). Activation of HO-1 can improve insulin sensitivity in glomerular tissue and reduce podocyte apoptosis, decreasing the risk for DKD.

Incretin hormones receptor signaling

Glucagon like peptide-1 (GLP-1) is a gut incretin hormone which can augment glucose-dependent insulin responses and promote preservation in β cells (Drucker, 2006). It is reported that GLP-1 receptor (GLP-1R) is present abundantly in the gastrointestinal tract but it has also been reported in endothelial cells and kidney (Bullock et al., 1996; Erdogdu et al., 2010). In endothelial cells, GLP-1 can inhibit the expression of tumor necrosis factor-α (TNF-α) and vascular cell adhesion molecule-1 (VCAM-1) (Kodera et al., 2011). GLP-1 has been reported to have multiple vasotropic actions in addition to its effects on insulin secretion. Exendin-4, a GLP-1 analog, has been shown to improve left ventricular function in ischemic heart disease (Nikolaidis et al., 2004; Nystrom et al., 2004). Our

previous report showed that GLP-1 was mediating its protective actions through GLP-1R by the activation of protein kinase A (PKA). The elevation of cAMP levels increased the phosphorylation at phosphor-c-Raf (Ser259) that can inhibit angiotensin II-induced inflammatory cytokines.

Activation of PKCβ induced by hyperglycemia and fatty acids inhibits the protective effect of GLP-1 and promotes endothelial inflammation by two mechanisms; PKCβ enhances Ang II's action and decreases GLP-1R by ubiquitin proteasome system (Mima et al., 2012c).

Dipeptidyl peptidase-4 (DPP-4) inhibitors can increase active incretin levels by preventing their rapid degradation. Recently, we have shown that a DPP-4 inhibitor, linagliptin, decreased high glucose-induced podocyte apoptosis and found that linagliptin offers protection against DKD through insulin/IRS1 signaling in cultured podocytes; the addition of linagliptin reversed high glucose-induced inhibition of insulin-induced tyrosine phosphorylation of IRS1 (Mima et al., 2020). One possible mechanism of glomerulosclerosis in DKD is endothelial-to-mesenchymal transition (EndMT), which is defined as a complex process in which cells detach from the endothelial layer resulting in endothelial dysfunction and acquiring a myofibroblastic phenotype (Yasuzawa et al., 2021). Interestingly, linagliptin can decrease the expression of TGF-β-induced EndMT in glomerular endothelial cells in DKD (Kanasaki et al., 2014).

VEGF-A

VEGF-A belongs to a family of growth factors including VEGF-B, -C, -D, and -E, and platelet-derived growth factor (PDGF) (Carmeliet et al., 1996; Gerber et al., 1999; Ferrana and Gerber, 2001). Especially, VEGF-A can promote angiogenesis, causing vascular permeability (Nicosia et al., 1994). VEGF-A also is known to prevent endothelial cell apoptosis induced by serum starvation and such activity is mediated by the PI3K/Akt pathway (Gerber et al., 1998; Fujio and Walsh, 1999). VEGF-A is upregulated in the retina, causing

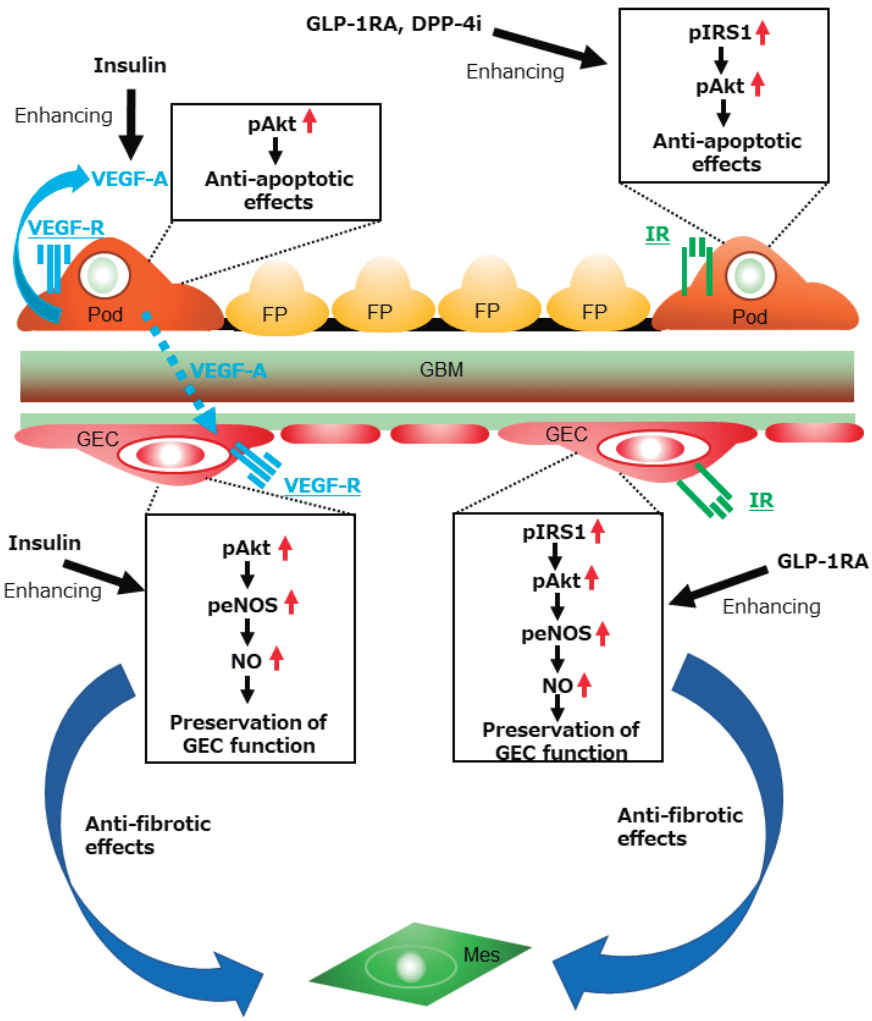

Fig. 1. Proposed mechanisms of insulin signaling and its associated signaling in glomerulus for renoprotection in DKD. VEGF-A, vascular endothelial growth factor-A; VEGF-R, vascular endothelial growth factor receptor; IR, insulin receptor; GLP-1R, glucagonlike peptide-1 receptor; DPP4i, dipeptidyl peptidase-4 inhibitors; pAkt, phosphorylation of Akt; pIRS1, (tyrosine) phosphorylation of insulin substrate-1; peNOS, phosphorylation of endothelial nitric oxide synthase; Pod, podocyte; FP, foot process; GEC, glomerular endothelial cell; Mes, mesangial cell; GBM; glomerular basement membrane.

diabetic proliferative retinopathy, but its expression is abnormally low in the myocardium and peripheral lesions cause poor collateral vessel formation in peripheral tissues (Chou et al., 2002). VEGF-A is also a survival factor for endothelial cells. VEGF-A can increase anti-apoptotic proteins Bcl-2 and survivin (Tran et al., 2002). Our previous report showed that VEGF-A increased phosphorylation of Akt and eNOS preventing endothelial cell apoptosis (Mima et al., 2012b). VEGF-A may have actions in non-endothelial cells; during fetal development, one of the cell types producing the largest amounts of VEGF-A is the podocytes (Eremina et al., 2008). Furthermore, during angiogenesis, VEGF-A interacts with other angiogenic factors, playing a pivotal role in maintaining endothelial cell function and a glomerular tuft, filtration barrier. Unlike many other cells, podocytes continue to express VEGF-A after being fully differentiated, though the absolute amount of expression decreases (Sison et al., 2010). Knock out VEGF-A mice showed a loss of endothelial cell fenestration, endothelial cell necrosis, and loss of podocyte foot process, leading to glomerulosclerosis and renal failure. This suggests that VEGF-A might be a reno-protective factor (Eremina et al., 2008). Unphysiological increases in levels of VEGF-A are recognized in podocytes and mesangial cells in DKD (Chen and Ziyadeh, 2008). Previous reports showed inhibition of VEGF-A ameliorates proteinuria and renal pathology in the early stages of DKD in rodent models (Sung et al., 2006; Ku et al., 2008). However, another group showed that treatment with VEGF-A antibodies did not improve DKD in diabetic rats (Schrijvers et al., 2005). Furthermore, patients treated with anti-VEGF agent showed that treatment with anti-VEGF agent scaused proteinuria, hypertension, and renal failure (Eremina et al., 2008).

We have shown that hyperglycemia can induce podocyte apoptosis, increase PKCδ/p38 mitogen-activated protein kinase (MAPK) activation and the expression of Src homology-2 domain-containing phosphatase-1 (SHP-1) to cause impairment of VEGF signaling (Mima et al., 2012b). A previous study using mice overexpressing IRS1 in endothelial cells (EC-IRS1) showed increases in mRNA VEGF in endothelial cells (Katagiri et al., 2016). Thus, insulin signaling may regulate VEGF expression.

Hypoxia-inducible factor (HIF)-α subunits are degraded under normal oxygen conditions. HIF-prolyl hydroxylase domain inhibitors (HIF-PHIs) are used for the treatment of renal anemia in CKD. HIF can bind to hypoxia response element (HRE) and increase VEGF expression. Furthermore, p300 and CREB-binding (CBP) contribute to HIF-1α-induced activation of the VEGF promoter. Therefore, the fine balance induced by HIF-PHIs in the regulation of VEGF-A seems important for renoprotection (Mima, 2021). Figure 1 shows proposed renoprotecitive mechanisms of insulin signaling and its associated signaling in glomerulus.

Conclusion

It seems that glycemic control is the best prevention of DKD, but DKD develops despite treatment for diabetes. Treatments that inhibit the aldose reductase pathway, advanced glycation end products (AGEs), oxidative stress, PKC, TGFβ-Smads pathway, and the RAAS have been attempted. However, the effect is partial. The effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors on DKD in recent years has been remarkable, but it also has not been sufficient. Thus, novel therapies based on insulin signaling and its associated signaling in glomerulus could be promising for treatment of DKD.

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