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Diabetic nephropathy: protective factors and a new therapeutic paradigm☆

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ABSTRACT

Diabetic nephropathy (DN) is the most common cause of chronic kidney disease (CKD) and its number has been increasing. CKD is a worldwide threat to health but the precise mechanism of this problem is not fully appreciated. It is believed that hyperglycemia is one of the most important metabolic factors in the development of DN. Multiple molecular mechanisms have been proposed to mediate hyperglycemia's adverse effects on kidney.

To identify targets for therapeutic intervention, most studies have focused on understanding how abnormal levels of such metabolities cause DN. However, there have been few reports regarding endogenous renal protective factors. Thus, recognition of the importance of this could be providing a new perspective for understanding the development of DN and a new therapeutic paradigm to combat DN.

1. Introduction

Diabetes nephropathy (DN) is the most important cause of chronic kidney disease (CKD) in the world that often leads to requirements for dialysis or renal replacement therapy. There have been many advances in the management of DN (The Diabetes Control & Complications Trial Research Group, 1993; UK Prospective Diabetes Study (UKPDS) Group, 1998). It is well known that activation of the renin–angiotensin system contributes to the development of DN and angiotensin-converting enzyme inhibitors (ACEI) or AT1 receptor blockers (ARB) could attenuate DN. However, recent studies suggest these drugs delay but cannot stop the progression of DN (Brenner et al., 2001; Lewis et al., 2001).

Despite a reasonable understanding of the pathogenesis and pathology of DN, only few studies revealed the importance of endogenous protective factors or the inhibitory effects of hyperglycemia. This review will focus on the evidence supporting the importance of endogenous protective factors that prevent the progression of DN.

2. Endogenous protective factors

2.1. Insulin

Insulin has many vasotropic actions including survival factors for vascular endothelial cells including glomeruli. Hyperglycemia can selectively inhibit insulin's anti-atherosclerotic or anti-glomerulosclerotic actions, while hyperinsulinemia, as observed in insulin-resistant type 2 diabetes, can enhance insulin's pro-atherosclerotic diseases (Rask-Madsen & King, 2007). Insulin resistance in vascular tissue is associated with endothelial dysfunction, leading to cardiovascular diseases including atherosclerosis and DN in animal models (Mima et al., 2011; Rask-Madsen & King, 2007). However, hyperinsulinemia itself does not affect atherosclerosis (Rask-Madsen et al., 2012). Insulin can stimulate the production of nitric oxide (NO), which results in vasodilatation and inhibit smooth muscle cell growth and migration, and podocyte apoptosis. Impaired insulin's action has recognized in the endothelial and mesangial cells in diabetic glomeruli, presumably through the activation of protein kinase C (PKC)β2 isoform (Mima et al., 2011).

Insulin-induced NO production has been reported to be mediated through insulin receptor-mediated activation of the insulin receptor substrate (IRS)/PI3K/Akt/endothelial NO synthase (eNOS) (Kuboki et al., 2000; Montagnani, Chen, Barr, & Quon, 2001). Rask-Madsen et al. clearly demonstrated the importance of vascular insulin signaling in

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endothelial insulin receptor knock-out mice (Rask-Madsen et al., 2010). In diabetes and insulin resistance states, the IRS1/Akt/eNOS pathway is selectively inhibited, but another major pathway of insulin signaling, mitogen-activated protein kinase (MAPK), is not inhibited (Jiang et al., 1999; Mima et al., 2011). Interestingly, this selective insulin resistance has also been shown in skeletal muscle from obesity and type 2 diabetes patients (Cusi et al., 2000), and in the vasculature, myocardium of Zucker fatty rats, which are the animal models of insulin resistance (He et al., 2006). Insulin-stimulated endothelin-1 (ET-1) expression might be preserved in insulin resistance (Oliver et al., 1991), since ET-1 expression is dependent on nuclear factors fos/jun downstream of MAPK signaling (Lee et al., 1991). Further, recent studies clearly show that PKCβ specific inhibitor, ruboxistaurin (RBX) improved insulin signaling on NO production in the vasculature, myocardium and glomeruli of streptozotocin-induced STZ rats and Zucker fatty rats (Mima et al., 2011; Naruse et al., 2006).

Other reports indicated that PKCβ directly inhibited insulin signaling. That is, phorbol 12-myristate 13-acetate (PMA) inhibits IRS2/PI3K activity (Kuboki et al., 2000) or IRS1 tyrosine phosphorylation (Motley et al., 2002). Mutations of IRS1 decreased insulin-induced eNOS activity through IRS1/PI3K/Akt (Federici et al., 2004). Further, we have shown that high glucose inhibited phosphorylation of Akt, eNOS and glycogen synthase kinase (GSK)3α, decreased IRS1 protein expression and increased association with ubiquitination in glomerular endothelial cells (Mima et al., 2011). Studies using mice overexpressing PKCβ2 in endothelial cells (EC-PKCβ2) showed impaired insulin signaling in renal cortex and diabetic EC-PKCβ2 exhibited more albuminuria and increasing extracellular matrix (Mima, Hiraoka-Yamomoto, et al., 2012). Also, overexpression of IRS1 or RBX reversed the inhibitory effects of high glucose (Mima et al., 2011). Thus, inhibition of PKCβ activity or increasing IRS1 activity in glomerular endothelial cell could be a new therapeutic paradigm.

Recent study using mice deleted insulin receptor specifically from podocytes showed severe albuminuria, increasing podocyte apoptosis and deposition of components of the basal membrane (Welsh et al., 2010). This finding strongly supports the importance of insulin signaling as a renoprotective factor.

2.2. HO-1

It is reported that heme oxygenase-1 (HO-1), a potent antioxidant enzyme that can interrupt major mechanisms of vascular injury, is normally upregulated in response to inflammation and oxidative stress. Studies using mice deleted HO-1 gene showed increases of monocyte chemoattractant protein-1 (MCP-1) expression and nuclear factor-κB (NF-κB) activation (Seldon et al., 2007; Tracz et al., 2008). Recently, Geraldes et al. showed that insulin significantly increase protein levels of HO-1 and insulin treatment prevented oxidative stress induced-NF-κB and caspase-8 activation and apoptosis via IRS1/PI3K/Akt2/HO-1 pathway in pericytes (Geraldes et al., 2008). Induction of HO-1 improves hyperglycemia, and reduces podocyte apoptosis and glomerular injury (Elmarakby, Faulkner, Baban, Saleh, & Sullivan, 2012; Lee et al., 2009; Ptilovanciv et al., 2013). Therefore, increasing HO-1 activity through improving insulin sensitivity in glomeruli could decrease the risk for DN.

2.3. VEGF-A

Vascular endothelial growth factor (VEGF)-A belongs to a family of growth factors that include VEGF-B, -C, -D, and –E, and platelet-derived growth factor (PDGF) (Carmeliet et al., 1996; Ferrara & Gerber, 2001; Gerber et al., 1999). Among them, VEGF-A plays a significant role in angiogenesis and vascular permeability. VEGF-A is one of the most important growth factor that responds to hypoxia under normal physiological levels (Ferrara, 2004). Activity of VEGF-A is the ability to promote growth of vascular endothelial cells. VEGF-A promotes angiogenesis, inducing confluent microvascular endothelial cells to invade collagen gel (Nicosia, Nicosia, & Smith, 1994). VEGF-A is also a survival factor for endothelial cells (Alon et al., 1995; Gerber, Dixit, & Ferrara, 1998). VEGF-A prevents endothelial cell apoptosis induced by serum starvation and such activity is mediated by PI3K/Akt pathway (Fujio & Walsh, 1999; Gerber, McMurtrey, et al., 1998). VEGF-A also increases the expression of the anti-apoptotic proteins Bcl-2 (Gerber, Dixit, et al., 1998) or survivin (Tran et al., 2002). Further, VEGF-A increased phosphorylation of Akt and eNOS that prevent endothelial cell apoptosis (Mima, Kitada, et al., 2012).

Increases in levels of VEGF-A are recognized in podocytes and mesangial cells in DN (Chen & Ziyadeh, 2008). There are several reports regarding inhibition of VEGF-A results in amelioration of proteinuria and reduction in mesangial expansion in the early stage of DN in rodent models (Ku et al., 2008; Sung et al., 2006). In contrast, some groups showed treatment with VEGF-A antibodies did not improve DN in diabetic rats (Schrijvers et al., 2005). Further, several patients treated with anti-VEGF agent showed proteinuria, hypertension, and renal failure (Eremina et al., 2008). Supporting these phenomena, recent studies have suggested that VEGF-A might be a renoprotective factor, since VEGF-A null mice show proteinuria, glomerulosclerosis and renal failure (Eremina et al., 2003). Also, during fetal development, one of the cell types producing the largest amounts of VEGF-A is the podocytes. Different from many other cells, podocytes continue to express VEGF-A when they are fully differentiated, though absolute levels of expression decrease (Sison et al., 2010).

Recently, our study showed that diabetes can cause podocyte apoptosis partly due to increased PKCδ/p38MAPK activation and the expression of Src homology-2 domain-containing phosphatase-1 (SHP-1) to cause impairment of VEGF signaling (Mima, Kitada, et al., 2012). Thus, fine balance in the regulation of VEGF-A activity seems to be important for preventing DN. However, further studies will be needed to conclude whether VEGF-A is truly an endogenous protective factor for DN or not.

2.4. Glucagon like peptide-1 and DPP-4 inhibitors

GLP-1 is an incretin hormone which can augment glucose-dependent insulin release and promote preservation of β cells (Drucker, 2006). Analysis of GLP-1 receptor (GLP-1R) revealed its expression in endothelial cells and kidney (Bullock, Heller, & Habener, 1996; Erdogdu, Nathanson, Sjoholm, Nystrom, & Zhang, 2010). It is reported that GLP-1 has multiple vasotropic actions in addition to its effects to insulin secretion. For example, its analog, exendin-4, has been shown to improve left ventricular function after myocardial infarction or ischemia (Nikolaidis et al., 2004; Nystrom et al., 2004). In endothelial cells, GLP-1 might inhibit the expression of tumor necrosis factor-α (TNF-α) and vascular cell adhesion molecule-1 (VCAM-1) (Kodera et al., 2011; Liu, Dear, Knudsen, & Simpson, 2009). Recently, we have shown that GLP-1 is partly mediating its protective actions via its own receptor by the activation of protein kinase A (PKA). The elevation of cAMP levels increased the phosphorylation at phospho-c-Raf (Ser259) that may inhibit phospho-c-Raf (Ser338)/phospho-Erk1/2 which are activated by Ang II to induce its inflammatory action such as plasminogen activator inhibitor-1 (PAI-1), CD68 and CXCL2 expression. Further, we clearly indicated PKCβ activation induced by hyperglycemia or free fatty acids can inhibit GLP-1's protective actions and enhance inflammatory effects on the endothelium by two mechanisms; PKCβ enhances Ang II's action and decreases GLP-1R by its ubiquitination (Mima, Hiraoka-Yamomoto, et al., 2012).

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