Biomedicine & Pharmacotherapy 94 (2017) 176–187

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Original article

The roles of sodium-glucose cotransporter 2 inhibitors in preventing kidney injury in diabetes

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ARTICLE INFO

Article history:
Received 2 June 2017
Received in revised form 19 July 2017
Accepted 19 July 2017

Keywords:
Diabetes mellitus
Sodium-glucose cotransporter 2
Renal function
Diabetic nephropathy

ABSTRACT

Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) worldwide. The early effective treatment of high plasma glucose could delay or prevent the onset of DN. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are new target treatments for ameliorating high plasma glucose and help to maintain glucose homeostasis in diabetic patients. Reduced renal glucose reabsorption by SGLT2 inhibition seems to have high potential to improve glycemic control in diabetes mellitus (DM) not only through glucose lowering but also through glucose-independent effects such as blood pressure-lowering and direct renal effects in diabetes. Of note, the important events in the pathogenesis of glucose-induced renal injury and DN including oxidative stress, inflammation, fibrosis and apoptosis conditions have shown to be ameliorate after the treatment with SGLT2 inhibitors. Interestingly, SGLT2 inhibitors have been reported to reduce albuminuria in DM via an activation of renal tubuloglomerular feedback by increased macula densa sodium and chloride delivery, leading to afferent vasoconstriction and attenuated diabetes-induced renal hyperfiltration. These effects also help to conserve glomerular integrity. Thus, the treatment of diabetes mellitus using SGLT2 inhibitors could be one of the effective approach for the management of diabetic-associated kidney disease like DN. This review summarizes the up to date information and discusses the bidirectional relationship between the SGLT2 inhibitor treatments and the renal functions that are available from both basic research and clinical reports. The details of renal outcomes of SGLT2 inhibitors in DN are also provide in this review.

Contents

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http://dx.doi.org/10.1016/j.biopha.2017.07.095
0753-3322/

1. Introduction

Diabetic nephropathy (DN) is the major complication that can lead to end-stage renal disease (ESRD). The incidence of diabetic nephropathy has been increasing more than double in the past decade and at present it accounts for approximately 50% of all ESRD worldwide [1]. Moreover, co-morbidities like hypertension, obesity, dyslipidemia, and arterial sclerosis have an injurious on the kidney forming complex patterns of nephropathy [2]. DN is characterized by renal functional and structural alterations. Glomerular hyperfiltration, glomerular and renal hypertrophy and increased albuminuria are the common early stage features of renal diabetic changes [3]. Advanced DN or late stage DN is characterized by proteinuria, a decline in renal function, decreasing glomerular filtration rate (GFR), severe glomerulosclerosis, and interstitial fibrosis [3]. The pathophysiology of DN is associated with the interactions between metabolic and hemodynamic alteration, oxidative stress, inflammation, and activation of the renin-angiotensin system (RAS) [4] (Fig. 1). These activate inflammatory, ischemic, and fibrotic pathways leading to mesangial matrix accumulation, podocyte loss, glomerular basement membrane (GBM) thickening, endothelial dysfunction, tubular atrophy, tubulointerstitial inflammation and fibrosis [5]. The consequences of these molecular alterations result in functional and structural changes that clinically manifest as increasing albuminuria or proteinuria and impaired renal function [6,7].

2. Pathogenesis of diabetic nephropathy

Both metabolic and hemodynamic stimuli lead to the activation of intracellular signaling pathways and transcription factors, thus triggering the production and release of cytokines and growth factors, which mediate and/or amplify renal damage [8]. Although the mechanisms leading to the pathological changes in DN are still not fully understood, the important events in the pathogenesis of hyperglycemia-induced renal injury and diabetic nephropathy are oxidative stress, inflammation, fibrosis and apoptosis [9]. Moreover, the imbalance of vasoactive factors also contributes to the development and progression of diabetic-induced kidney complications including enhanced renal vasoconstrictors such as angiotensin II (Ang II) and reduced vasodilators such as nitric oxide (NO) [10]. Increasing evidence of experimental studies has shown non-hemodynamic effects of renal Ang II during progressive kidney injury [11]. Ang II is a kidney growth factor that modulates cell growth and extracellular matrix (ECM) synthesis and degradation [12,13]. Ang II regulates mesangial cell growth via inducing proliferation or hypertrophy depending on the intracellular balance between growth factors, and increases the expression and synthesis of ECM proteins, such as fibronectin, laminin, and collagens [12]. In DN, an increased Ang II activity not only causes hypertrophy of various renal cells but also has a direct effect on arteriolar smooth muscle, resulting in increased renal vascular pressure [14]. Excessive renal Ang II activity increases glomerular permeability by a variety of mechanisms such as a high intraglomerular transmembrane pressure, suppressed synthesis of negatively charged proteoglycans and nephrin, and enhanced synthesis of extracellular matrix components [15]. In addition, high glucose also induces synthesis of Ang II and Ang II type I receptor (AT_1R) expression in renal mesangial cells and podocytes via increasing overall renin level and activity and elevation of mechanical stretch by increased intraglomerular capillary pressure [8]. Activation of RAS leads to the stimulation of the kidney cell proliferation and the expression of growth factors or cytokines such as transforming growth factor β (TGFβ), vascular endothelial growth factor (VEGF), and monocyte chemotactic protein 1 (MCP-1)which may directly or indirectly contribute to renal fibrosis, increased reactive oxygen species (ROS) and apoptosis [3,14,16].

Moreover, hyperglycemia provokes the non-enzymatic reaction of glucose and other glycating protein derived both from glucose and from increased fatty acid oxidation, which results in the generation of advanced glycation end products (AGEs) in kidney cells [9]. In cultured glomerular endothelial and mesangial cells, the glycated albumin and AGE-rich proteins increase protein kinase C (PKC) activity, TGFβ levels and ECM expansion [17]. In non-obese diabetic and *db/db* mice, the intake of food-derived AGEs contributed to diabetic nephropathy while a diet with low AGEs provided renoprotection [18]. Furthermore, a study in diabetic transgenic mice with overexpressed receptors for AGEs (RAGE) showed developed renal and mesangial expansion, glomerular hypertrophy, advanced glomerulosclerosis, and increased serum creatinine along with albuminuria compared with diabetic mice without the RAGE transgenic gene [19].

The diacylglycerol (DAG)-PKC pathway which can be activated by the metabolic and hemodynamic factors is also involved in the

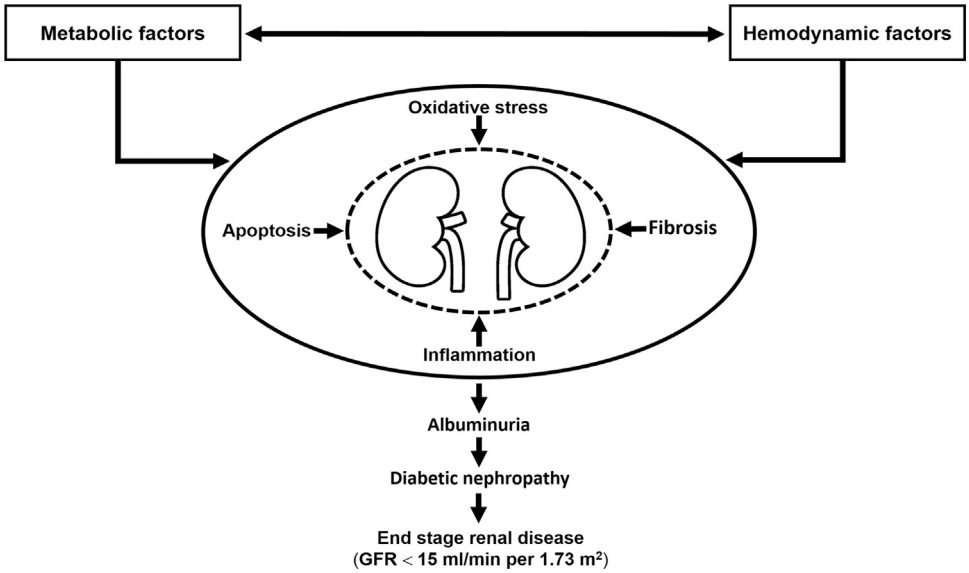

Fig. 1. Pathways involved in the development of diabetic kidney disease.