Pharmacological Reports 69 (2017) 331–339

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Diabetic nephropathy: A potential savior with 'rotten-egg' smell

George J. Dugbartey

Department of Medicine, Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 20 October 2016
Accepted 9 November 2016
Available online 11 November 2016

Keywords:
Diabetic nephropathy (DN)
Extracellular matrix (ECM)
Hyperglycemia
High glucose
Hydrogen sulfide (H_2S)

ABSTRACT

Diabetic nephropathy (DN) is currently the leading cause of end-stage renal disease. Despite optimal management, DN is still a major contributor to morbidity and mortality of diabetic patients worldwide. The major pathological alterations in DN include excessive accumulation and deposition of extracellular matrix, leading to expansion of mesangial matrix, thickening of glomerular basement membrane and tubulointerstitial fibrosis. At the molecular level, accumulating evidence suggests that hyperglycemia or high glucose mediates renal injury in DN *via* multiple molecular mechanisms such as induction of oxidative stress, upregulation of renal transforming growth factor beta-1 expression, production of proinflammatory cytokines, activation of fibroblasts and renin angiotensin system, and depletion of adenosine triphosphate. Also worrying is the fact that existing therapies only retard the disease progression but do not prevent it. Therefore, there is urgent need to identify novel therapies to target additional disease mechanisms. Hydrogen sulfide (H_2S), the third member of the gasotransmitter family, has recently been identified and demonstrated to possess important therapeutic characteristics that prevent the development and progression of DN in experimental animals by targeting several important molecular pathways, and therefore may represent an alternative or additional therapeutic approach for DN. This review discusses recent experimental findings on the molecular mechanisms underlying the therapeutic effects of H_2S against the development and progression of DN and its clinical application in the future.

Contents

Introduction

Diabetic nephropathy (DN) is one of the most common and serious long-term complications in diabetic patients, affecting about 40% of these patients [1,2]. It is defined as a progressive pathological condition of the kidney caused by angiopathy of

E-mail address: profduu@yahoo.com (G.J. Dugbartey).

http://dx.doi.org/10.1016/j.pharep.2016.11.004
1734-1140/

glomerular capillaries [3]. The angiopathy of these capillaries is characterized by a progressive loss of glomerular filtration surface areas and capillary volume [4,5]. According to United States renal data system, DN is the leading cause of end-stage renal disease, and a major contributing factor to morbidity and mortality of diabetic patients throughout the world [6]. Hence, the guideline of American Diabetes Association suggests an annual test to assess biomarkers of DN in type 1 diabetic patients with diabetic duration of at least 5 years and in all type 2 diabetic patients starting at diagnosis [7]. The pathogenesis of DN manifests as aberrant expansion of the mesangial matrix and thickening of glomerular basement membrane (GBM) due to excessive production, accumulation and deposition of extracellular matrix (ECM) within the glomerular, tubulointerstitial and vascular spaces, and ultimately progresses into glomerulosclerosis, tubulointerstitial fibrosis and vascular remodeling [3,5,8].

The ECM consists of several proteins including collagen and elastin. Collagen is the most abundant protein in the ECM and provides structural support to the cells while elastin provides elasticity to tissues [9,10]. A fine balance exists between collagen and elastin in healthy kidneys, which allows normal renal function. In DN, however, the balance between these ECM proteins is disrupted, causing ECM remodeling and thereby contributes to renal vascular impairment and failure [11,12]. Also, increased activity and levels of matrix metalloproteinase (MMP; a family of calcium-dependent zinc-containing endopeptidases that controls ECM synthesis and degradation, including collagen and elastin), particularly MMP-9, is abundantly expressed in the kidney and serum of type 1 diabetic patients [13,14] and has been reported to contribute to diabetic renal remodeling [15]. In addition, mesangial cell (MC) proliferation and hypertrophy have been reported in the early pathological features of DN in several *in vitro* and *in vivo* studies [16].

Experimental evidence suggests that although advanced glycation end-products and dyslipidemia are associated with organ injury in diabetic patients, hyperglycemia (high blood glucose) or high glucose is likely to be the principal pathological contributor to the development and progression of DN [17]. Hyperglycemia/high glucose contributes to development and progression of DN *via* multiple molecular mechanisms such as induction of oxidative stress and upregulation of renal transforming growth factor beta-1 (TGF-β1) expression, production of proinflammatory cytokines, activation of fibroblasts and renin angiotensin system (RAS), and depletion of adenosine triphosphate (ATP) [18–20]. Apart from hyperglycemia, research has shown that hypertension is another major clinical determinant of DN, and that coexistence of hypertension and hyperglycemia accelerates the development and progression of DN [21,22]. Other metabolic disorders including proteins and gaseous molecules such as hydrogen sulfide and nitric oxide are also associated with diabetes [23–25]. It is important to note that uncontrolled diabetes can result in fluid build-up, hypertension, albuminuria, elevated serum creatinine and blood urea nitrogen and eventually renal failure [26]. Despite the expanded knowledge and understanding of the pathogenesis of DN, the precise mechanism of the pathogenesis and progression of DN is not fully elucidated. Also, effective therapeutic agents are still lacking, as existing ones such as hypoglycemic agents, antihypertensive drugs and RAS inhibitors only slow down the progression of nephropathy but do not prevent it, and thus the number of patients with DN continues to rise. Hence, novel therapeutic interventions are in high demand to target additional disease mechanisms, which could prevent or ameliorate the progression of DN.

Hydrogen sulfide as an additional therapeutic agent against diabetic nephropathy

Over the past decades, researchers have reported biological usefulness and therapeutic potentials of endogenous gaseous signaling molecules collectively known as “gasotransmitters”. Nitric oxide (NO) was the first identified gasotransmitter followed by carbon monoxide (CO) [27,28]. Hydrogen sulfide (H_2S), a gas

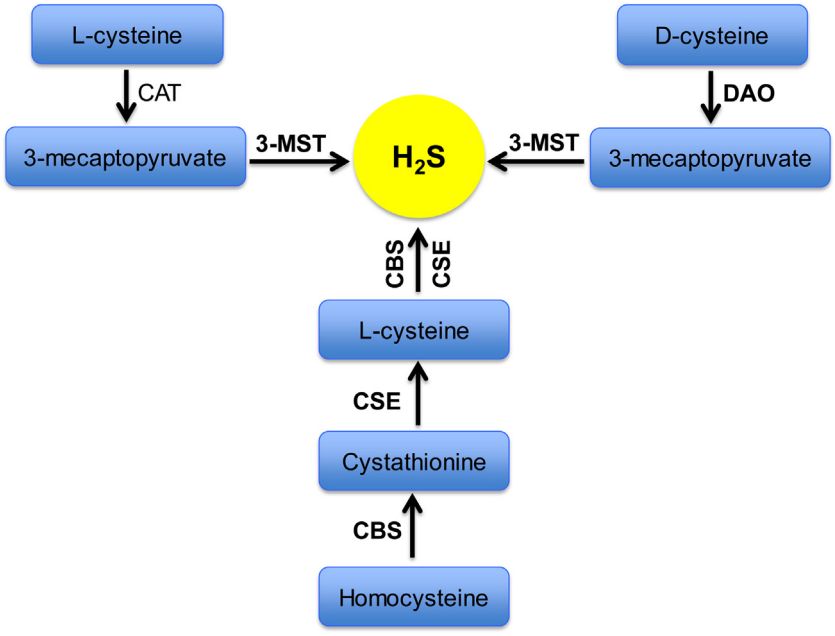

Fig. 1. Overview of endogenous hydrogen sulfide (H_2S) production.
H_2S is endogenously produced by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) using homocysteine and L-cysteine as substrates. L-cysteine can also be converted to 3-mecaptopyruvate as an intermediate product, a reaction catalyzed by cysteine aminotransferase (CAT). The enzyme 3-mecaptopyruvate sulfurtransferase (3-MST) then produces H_2S from 3-mecaptopyruvate, and coupled with D-amino acid oxidase (DAO), 3-MST produces H_2S from exogenously administered D-cysteine.