

Renoprotection by hydrogen sulfide in hyperhomocysteinemia

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Homocysteine (Hcy) is a sulfur-containing amino acid, which forms as an intermediate during methionine metabolism. High levels of plasma Hcy, also known as hyperhomocysteinemia (HHcy), are always associated with kidney insufficiency [4,5,26,31]. Results from recent studies have indicated that HHcy downregulates hydrogen sulfide (H₂S) level [22] and reduces endothelial nitric oxide synthase (eNOS) [18]. In addition, through imbalance of matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMP), Hcy accumulates extracellular matrix (ECM) protein in the peri-glomerular space [21,23,24]. These contribute to renovascular remodeling including renal fibrosis and dysfunction. Although Hcy is known for independent vascular risk factor, the mechanism of renal fibrosis in HHcy is largely unknown. In the tissue, Hcy however metabolizes by three endogenous enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST) to produce H₂S, a gaseous molecule of tremendous biological importance. This editorial highlights some of the recent updates and future directions of renoprotection by H₂S in HHcy.

Significance

Several mechanisms are proposed of which, a) sustained and abnormal elevation of glomerular arterial wall stress, b) initiation of complex and progressive glomerular remodeling, and c) renal microvascular impairment and vasoconstriction [20] are well documented, and may contribute to pathophysiological renal disorders during kidney insufficiency. The mechanism of glomerulosclerosis and increased wall stress in HHcy is due to alter extracellular matrix (ECM) components [33,34] in the glomerulus. Among ECM components, collagen, elastin, proteinases and their tissue inhibitors play major roles in the formation and degradation of ECM under physiological and pathological conditions [29,30]. Matrix metalloproteinases (MMPs) maintain collagen/elastin homeostasis in the matrix and therefore, contribute to ECM modulation. Endogenously MMPs activities are regulated by inhibitors of metalloproteinases (TIMPs) [25,28,33]. Although, reduction of Hcy level is directly associated with amelioration of MMP activity [24] and matrix accumulation in the kidney mesangial cells [33], the mechanism of MMP activation and collagen accumulation in Hcy-induced glomerulo-vascular nephropathy is still incompletely defined. On the other hand, decreased bioavailability of nitric oxide (NO) is the primary reason for endothelial injury and vascular dysfunction in HHcy [17]. While endothelial NO synthase (eNOS) is the main enzyme producing endothelial-dependent NO production [6], the generation of NO from eNOS is dependent on many factors. One of them is caveolar protein, caveolin-1. Through scaffolding domain caveolin-1 binds to and inhibits eNOS [2]. In addition, by increasing intracellular calcium caveolin-1 indirectly affects eNOS function [32]. Nevertheless, there is a lack of information to these above mechanisms, which may contribute to HHcy related renovascular diseases and deserves thorough investigation.

While scientists are striving to find out possible mechanism(s) and effective therapy, it is important to mention that in the recent past, several interventional trials have failed to demonstrate any clinical benefit of Hcy-lowering therapy [1,3,7,15,16,27]. There were several limitations of these trials, including limitations of Hcy measurement; where tissue levels of Hcy were never been measured. Interestingly,

previous studies from our laboratory have demonstrated elevated tissue levels of Hcy in kidney [24] and heart [19]. In HHcy kidney the levels of CSE, an enzyme responsible for conversion of Hcy to H₂S, (which is a potent antioxidant, vasorelaxing and anti-hypertensive agent) was decreased [23], suggesting the mechanism of increased tissue levels of Hcy in HHcy. Also, this result indirectly emphasized insufficient production of H₂S in HHcy. In addition, we have recently reported that gene therapy of CBS and CSE reduced mesangial inflammation, a contributing mechanism of vascular remodeling and dysfunction, through H₂S generation [22].

Challenges

a) One of the mechanisms by which plasma Hcy increases is CBS mutation. However, mutation or alteration of methylenetetrahydrofolate reductase (MTHFR) gene has been identified in people with homocystinuria. While CBS, CSE and 3-MST metabolizes Hcy to produce H₂S, MTHFR remethylate Hcy in the presence of co-factor (such as B12 vitamin) back to methionine, the homocysteine precursor. Therefore, in addition to CBS, CSE and 3-MST triple gene therapy, exploration of MTHR gene therapy may also delineate whether similar results can be achieved by reverting Hcy back to methionine.

b) The prevalence of modest Hcy elevations in chronic renal disease is far greater than the prevalence of genetic mutations leading to marked HHcy. Although gene therapy can provide a “proof of principle”, studies to define relative enzyme activity in the setting of chronic renal disease would provide more immediately clinically-relevant information.

Future directions

At elevated levels Hcy converts to Hcy-thiolactone [10-12]. Hcy-thiolactone is a reactive metabolite that causes protein N-homocysteinylation through the formation of amide bonds with protein lysine residues [11], which alters or impairs the protein's function [12], and has been reported to be elevated in HHcy [8,9,13,14]. In addition to caveolin-1 upregulation, it is possible that HHcy may homocysteinylylate eNOS, which will further decrease NO production resulting in renovascular impairment. The H₂S has a sulfur molecule and may uncouple protein-S-S-Hcy bridge [12], thereby dehomocysteinylylate protein, including eNOS. Also, Hcy has been reported to homocysteinylylate Cytochrome c [12] of mitochondrial electron transport chain causing depolarization of mitochondria that may lead to mitochondrial damage or even death (mitophagy). H₂S

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by cross linking with disulfide bridges may repolarize mitochondria and protects from mitophagy. These possible mechanisms need to be explored in future.

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