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Homocysteine to Hydrogen Sulfide or Hypertension

Utpal Sen, **Paras K. Mishra**, **Neetu Tyagi**, and **Suresh C. Tyagi**
Department of Physiology & Biophysics, University of Louisville School of Medicine, 500 South Preston Street, Louisville, KY 40202, USA

Utpal Sen: u0sen001@louisville.edu

Abstract

Hyperhomocysteinemia, an increased level of plasma homocysteine, is an independent risk factor for the development of premature arterial fibrosis with peripheral and cerebro-vascular, neurogenic and hypertensive heart disease, coronary occlusion and myocardial infarction, as well as venous thromboembolism. It is reported that hyperhomocysteinemia causes vascular dysfunction by two major routes: (1) increasing blood pressure and, (2) impairing the vasorelaxation activity of endothelial-derived nitric oxide. The homocysteine activates metalloproteinases and induces collagen synthesis and causes imbalances of elastin/collagen ratio which compromise vascular elastance. The metabolites from hyperhomocysteinemic endothelium could modify components of the underlying muscle cells, leading to vascular dysfunction and hypertension. Homocysteine metabolizes in the body to produce H_2S, which is a strong antioxidant and vasorelaxation factor. At an elevated level, homocysteine inactivates proteins by homocysteinylation including its endogenous metabolizing enzyme, cystathionine γ-lyase. Thus, reduced production of H_2S during hyperhomocysteinemia exemplifies hypertension and vascular diseases. In light of the present information, this review focuses on the mechanism of hyperhomocysteinemia-associated hypertension and highlights the novel modulatory role of H_2S to ameliorate hypertension.

Keywords

Homocysteine; Hypertension; Hydrogen sulfide; Vascular remodeling

Introduction

To accommodate pressure load, vessels undergo structural and functional adaptation. Elastic compliance consists of a vessel's capacity to stretch on load and return to normal at normal load. Chronic changes in blood pressure, however, lead to a persistence of mechanical load on the vessel wall and induces resistance to stretch. The resistance to stretch to accommodate for load may lead to the development of hypertension. The development of hypertension in 95% of hypertensive patients is idiopathic and multifactorial [1]. Components such as circulating plasma factors, vascular endothelium, smooth muscle contractile apparatus, and homeostasis of extracellular matrix (ECM) surrounding the smooth muscle, in milieu, play a coordinated role to perform proper vascular function. Alteration in anyone of these components may result in impairment of vessel's response to stress and may lead to hypertension.

Correspondence to: Utpal Sen, u0sen001@louisville.edu.

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One of such circulating factors is plasma homocysteine and elevated level of homocysteine is known as hyperhomocysteinemia. There are four ways by which hyperhomocysteinemia is developed (Fig. 1): (1) methionine-rich protein diet; (2) vitamin B_{12}/folate deficiency; (3) heterozygous/homozygous cystathionine-β synthase (CBS) activity; (4) obstruction of renal clearance. Studies have demonstrated that a methionine-rich protein diet leads to increased levels of plasma homocysteine [2]. A diet of fruits and vegetables, which is low in methionine, leads to decreased hypertension [3] and improves vascular function [4]. Half of the dietary methionine is metabolically converted to homocysteine. Homocysteine is accumulated because the metabolic conversion to cysteine and their excretion are impaired [5]. This could lead to a decrease in the body's ability to clear homocysteine and reduction in the levels of cysteine. Also, it is known that increased levels of homocysteine leads to reduced bioavailability of glutathione peroxidase activity [6]. This could lead to decreased redox of glutathione. In addition, the oxidative metal ion (Cu^{2+}) concentration is elevated in hyperhomocysteinemic patients [7,8]. Collectively, these studies suggest that increased plasma homocysteine is an important factor in causing the elevation of plasma redox stress. Therefore, body's inability to clear metabolic by-product homocysteine could lead to hyperhomocysteinemia and redox stress.

Arteriosclerosis is one of the primary causes of arterial hypertension. Acute/chronic inflammatory and redox processes facilitate atherosclerotic and arteriosclerotic lesion formation [9] and induce vasoconstriction and hypertension [10]. Although in hyperhomocysteinemia-associated hypertension, such as renovascular hypertension, endothelial dysfunction and vascular hypertrophy have been observed, the precise mechanism by which homocysteine causes vascular dysfunction and contributes to hypertension are largely unknown. Several mechanisms have been proposed, these include: (1) homocysteine causes endothelial injury and vascular hypertrophy by redox pathway; (2) this leads to increased blood pressure; (3) the molecular mechanism of endothelial dysfunction includes reduced bioavailability of nitric oxide (NO) due to elevated levels of homocysteine which causes nitration of tyrosine in proteins, such as actin and myosin; (4) homocysteine also activates certain metalloproteinases which can cause degradation of collagen and elastin leading to vascular hypertrophy.

Homocysteine is a Precursor for Endogenous Hydrogen Sulfide Generation

Homocysteine is a thiol-containing non-protein amino acid that is formed during the metabolism of the essential amino acid methionine and is recognized as an independent cardiovascular risk factor, such as arterial vascular disease [11]. An elevated plasma level of homocysteine known as hyperhomocysteinemia has been associated with hypertension [12–14]. Although several lines of evidences suggested the integrated physiological role of homocysteine to cause multi-organ damage, probably related to impair endothelial and smooth muscle function, the precise molecular mechanisms by which it mediates these adverse effects are still unknown. Under normal physiological conditions, homocysteine metabolizes to produce cysteine which is a substrate of two pyridoxol-5′-phosphate (PLP)-dependent enzymes—CBS and cystathionine-γ lyase (CSE) for endogenous production of hydrogen sulfide (H_2S) (Fig. 2).

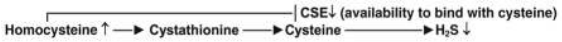
Hydrogen sulfide (H_2S) is known for decades as a toxic gas which has intoxication effect on central nervous system; however, very recently H_2S has been recognized as a key vasorelaxant gaseous molecule [15]. Physiologically, as stated earlier, H_2S generates from L-cysteine, catalyzed by either CBS and/or CSE [16]. Recently, a PLP-independent enzyme, 3-mercaptopyruvate sulfurtransferase (3-MST), has been reported as a possible candidate for H_2S production [17,18] (Fig. 2). Unlike CBS and CSE, 3-MST uses 3-mercaptopyruvate as a substrate, which is a metabolite of cysteine and α-ketoglutarate (α-KG) by cysteine

aminotransferase (CAT), to produce H_2S [18]. The expression of CBS, CSE, and 3-MST are tissue specific. In some tissues CBS is the main H_2S-generating enzyme, while CSE and 3-MST on the others. For example, CBS is highly expressed in the hippocampus and cerebellum and is a predominant H_2S-generating enzyme in the brain and nervous tissues [19]. On the other hand, CSE expression in the vascular smooth muscle was initially demonstrated by Hosoki et al. [20]. Later, it was reported to be expressed mainly in the liver, kidney, and vascular smooth muscle [21,22] with a major H_2S producing enzyme in the cardiovascular system [22]. Recent evidence suggested that CSE is also expressed in the vascular endothelial cells and capable of producing H_2S [15]. Unlike CBS and CSE, to date, 3-MST has only been reported as a H_2S producing enzyme in the vascular endothelium [17,18]. H_2S, however, can also be generated by a condensation reaction between cysteine and homocysteine [23] (Fig. 2).

Homocysteine at higher level has been reported to inhibit CSE activity in the rat liver [24] and at pathological condition, hyperhomocysteinemia alter the transulfuration pathway by inhibiting CSE enzyme activity [25]; thereby reduce endogenous production of H_2S in the body. Accumulating evidences indicated that H_2S is a physiological vasorelaxant and reduced production of H_2S in the vascular tissue leads to hypertension [15,26]. Thus, the role of hyperhomocysteinemia in essential hypertension is not surprising.

Cysteine Versus Homocysteine and Hypertension

Compared with the levels of cysteine (~100 μM) in normal individuals, the levels of homocysteine (~20 μM), even in homocysteinemia patients, are much lower. Therefore, the question arises regarding the contribution of homocysteine to the production of H_2S. It is interesting to point out that homocysteine and cysteine both are substrates for H_2S generation; and CSE enzyme mainly uses cysteine to produce H_2S endogenously. Biochemically during hyperhomocysteinemia, homocysteine competes for binding to CSE with cysteine; therefore, increases in homocysteine will decrease H_2S production from cysteine through substrate inhibition [25,27]. The reaction occurs as follows:



Furthermore, protein homocysteinylation is a major reaction in the presence of thiolactone and homocysteinylation led to protein damage; this was manifested as multimerization and precipitation of extremely modified proteins [28]. Although there is no direct evidence, the activity of CSE may be severely impaired during hyperhomocysteinemia due to damage and precipitation of modified-CSE that results in attenuated H_2S generation from both cysteine and homocysteine leading to hypertension. However, at present this mechanism, if exists at all, is not elucidated and warrants investigation.

Hyperhomocysteinemia, Vascular Dysfunction, and Hypertension: Role of H_2S

Elevated levels of plasma homocysteine, known as hyperhomocysteinemia, is recognized as an independent risk factor for the development of premature arterial fibrosis with peripheral and cerebrovascular, neurogenic, hypertensive heart disease, coronary occlusion and myocardial infarction, as well as venous thromboembolism [12,29–32]. Compared to low homocysteine, high plasma levels of homocysteine show increase in the chance of death due to heart disease [33]. Furthermore, levels of homocysteine greater than 20 μM in plasma of patients with coronary heart disease were associated with a 35% increase in mortality [34].

Several studies have implicated hyperhomocysteinemia as a risk factor for hypertension. In the "Hordaland Homocysteine Study" of about 16,000 people of 40–67 years old with no history of hypertension, diabetes or coronary vascular disease, the plasma homocysteine levels were positively related to blood pressure [35]. Similarly, Malinow et al. [36] found that hypertensive men with no history of atherosclerotic disease had higher homocysteine levels than non-hypertensive men. Sutton-Tyrrell et al. [12] also found a significant association of homocysteine levels with systolic hypertension.

Vascular dysfunction, such as endothelial dysfunction and vascular hypertrophy, is a hallmark of hypertension and several lines of evidences support the role of homocysteine causing vascular dysfunction [37,38]. Studies have also indicated that a number of forms causing hypertension are associated with elevated plasma levels of homocysteine. Although homocysteine has been documented to affect endothelial and vascular smooth muscle function, the importance of homocysteine in mediating the vascular dysfunction and hypertension is still incompletely defined. Furthermore, the molecular mechanisms whereby hyperhomocysteinemia results in vascular dysfunction are still unclear. In addition to vascular dysfunction by nitration of contractile (actin and myosin) and ECM proteins, homocysteine causes vascular dysfunction by reducing the bioavailability of endothelial NO. Also, homocysteine activates matrix metalloproteinases (MMPs) and collagenolysis, leading to vascular hypertrophy.

To understand the mechanism by which homocysteine causes hypertension, we studied the effects of hyperhomocysteinemia on endothelial endocardium and human coronary arteries. The results demonstrated that endothelium is impaired in hyperhomocysteinemic endocardium and vessels [39,40]. The homocysteine activates metalloproteinases and induces collagenolysis [39]. The metabolites from hyperhomocysteinemic endothelium could modify components of the underlying muscle cells, leading to vascular dysfunction and hypertension [13]. In the rat model of hyperhomocysteinemia, a recent study suggests that H_2S levels and the H_2S-generating enzyme CSE activity in the myocardium were decreased [25]. Also, the activities of myocardial mitochondrial respiratory enzymes related to reactive oxygen species (ROS) metabolism were significantly dysfunctional in hyperhomocysteinemic rats [25]. Interestingly, this study demonstrated that intraperitoneal administration of H_2S restored the enzymatic activities and reduced oxidative stress by scavenging H_2O_2 and superoxide ($O_2^{\bullet -}$) generated by Hcy in isolated myocardial mitochondria. The expression of CSE enzyme in the portal vein was initially reported by Hosoki et al. [20] and inhibition of this enzyme blocked H_2S production. Also, in vitro relaxation of norepinephrine precontracted portal vein by NaHS (a H_2S donor) was documented by the same group [20]. Later, in a rat model of hyperhomocysteinemia, Distrutti et al. [41] reported that homocysteine caused reduced NO release from sinusoidal endothelial cells resulting in hepatic stellate cell contraction, whereas perfusion of the liver with sodium sulfide (a H_2S donor) resulted in vasodilation, suggesting the portal hypertension caused by hyperhomocysteinemia was being counteracted by H_2S. Thus, these findings clearly indicate that hyperhomocysteinemia not only impairs the endothelium through oxidative stress but also impairs CSE/H_2S pathway causing hypertension and H_2S plays a significant role to normalize the blood pressure caused by hyperhomocysteinemia.

Hyperhomocysteinemia, Formation of Nitrotyrosine, and Hypertension

Homocysteine causes endothelial dysfunction [42] and is associated with hypertension in humans [12]; but, the mechanisms remain poorly understood. It is known that homocysteine inhibits growth, reduces cell density, and causes a dose dependent decrease in DNA synthesis in vascular endothelial cells [43]. Additionally, it reduces bioavailability of endothelial-derived NO [44] and induces iNOS [45]. The mechanism underlying reduced

bioavailability of NO includes: (1) homocysteine reduces thioredoxin and increases NAD(P)H oxidase resulting in generation of superoxide ($O_2^{\bullet -}$); (2) elevated level of homocysteine also reduces endogenous generation of H_2S, therefore increases oxidative stress; (3) the superoxide reacts with NO to form peroxynitrite ($ONOO^-$); (4) peroxynitrite reacts with protein tyrosine residues resulting in protein modification (please see Fig. 3). We demonstrated that homocysteine activated protease-activated receptor-4, which induces production of ROS by increasing NAD(P)H oxidase and decreasing thioredoxin expression and reduces NO bioavailability in cultured cardiac microvascular endothelial cell [46]. Lentz et al. [47] have reported that diet-induced moderate hyperhomocysteinemia in monkeys exhibited increased platelet-mediated vasoconstriction, impaired endothelial-dependent vasodilation, and decreased thrombomodulin-dependent activation of protein C. We have demonstrated that normal human coronary artery is responsive to homocysteine, whereas the atherosclerotic artery is not [39]. The tissue levels of homocysteine in atherosclerotic artery were 10-fold higher than normal artery [39] and homocysteine treatment induces hypertension in pigs and rats [2,48]. The ex vivo treatment of aortas with homocysteine for 14 days in tissue culture conditions produces endothelium disruption and arteriosclerotic lesions, similar to in vivo [49]. These studies suggested a role of homocysteine in vascular structure and function which may be due to protein modification by peroxynitrite that generated from homocysteine-induced $O_2^{\bullet -}$ production.

Homocysteine, Vascular Smooth Muscle Cell (VSMC) Proliferation, and Hypertension: Modulatory Role of H_2S

Homocysteine is known to diminish bioavailability of NO and increases oxidative stress. This inhibits vasodilation and causes hypertension. Vascular relaxation is very much dependent on proper coordination between endothelial and smooth muscle cell (SMC) and arterial resistance increases with the proliferation of these cells. In an attempt to examine the effect of homocystine on human VSMC, we isolated VSMC from idiopathic dilated cardiomyopathic hearts [50]. Coronaries in these hearts were apparently normal and homocysteine found to induce SMC proliferation in vitro [50]. Similar results were previously reported by Tsai et al. [51]. One of the pathophysiological mechanisms of hyperhomocysteinemia-associated hypertension underlies on the SMC proliferation which alters the elastic properties of the vascular wall [52]. As homocysteine competes with cysteine to bind CSE [25,27] and hyperhomocysteinemia decreases the CSE activity [25], it could be speculated that during hyperhomocysteinemia H_2S production will be diminished. Therefore, it not surprising that genetic manipulation to increase endogenous production of H_2S will inhibit SMC proliferation and will maintain vascular elastic compliance to retain normal blood pressure during hyperhomocysteinemia. In fact, in vitro experimental evidence suggested that overexpression of H_2S forming enzyme, CSE inhibited cell proliferation primarily through increased H_2S production [53]. Homocystine induces collagen synthesis and expression and increases intimal–medial thickness [48,54]. This consequently reduces elastin/collagen ratio which impairs vascular compliance resulting in increased systemic vascular resistance and sustained arterial hypertension.

Calcium (Ca^{2+}) Handling, Collagen Expression, and Hypertension

Regulation of intracellular calcium plays a key role in hypertension. Acute intracellular calcium overload in VSMCs increases peripheral vascular resistance, produces hypercontractility, and elevates blood pressure [55]. It is reported that progressive elevation of calcium destroys the structural integrity of the artery and arteriolar walls [56]. Calcium has also been shown to promote for the synthesis and deposition of collagen in the vascular wall, because calcium channel blockers reduce ECM collagen synthesis [57,58]. The

collagen during hyperhomocysteinemia can oxidatively modify and deposit in the ECM. Collagen and elastin are two major components of connective tissue and homeostasis of these two proteins in the vascular bed regulate proper elasticity of blood flow through vessels. While elastin allows tissues to resume their shape after stretching or contracting, the collagen of the ECM supports most tissues and gives cells structure from the outside. The imbalance between elastin and collagen destroys proper elasticity of the vessel and excessive collagen deposition causes vascular stiffness and fibrosis. This creates vascular resistance for proper blood flow that results in hypertension. We have reported that homocysteine induces ECM production via intracellular calcium release [59]. Depleting extracellular calcium did not alter homocysteine-effect on intracellular calcium; however, thapsigargin pretreatment, which depletes intracellular Ca^{2+} stores, abolished the homocysteine effect demonstrating its dependence on intracellular Ca^{2+} stores [59]. Therefore, regulation of intracellular calcium seems to play a role in ECM remodeling during hyperhomocysteinemia, although regulation of intracellular calcium by H_2S has been shown with conflicting results. For example, Nagai et al. [60] have shown that H_2S increases intracellular Ca^{2+} and induces calcium waves in astrocytes and this increase was largely by inducing Ca^{2+}influx rather than through release from intracellular Ca^{2+}stores; whereas Pan et al. [61] reported that H_2S-preconditioning regulated intracellular calcium handling which facilitated intracellular Ca^{2+} removal via both accelerating uptake of Ca^{2+}into sarcoplasmic reticulum and enhancing Ca^{2+} extrusion through Na^+/Ca^{2+} exchanger in a PKC-dependent manner in cardiomyocytes. While H_2S activated Ca^{2+} channels to induce Ca^{2+}influx to mediate signals between neurons and glia, the intracellular Ca^{2+}removal in H_2S preconditioning cardiomyocyte was against myocyte hypercontracture that protected heart against ischemia–reperfusion insult. Thus, H_2S played a differential role of intracellular Ca^{2+}regulation in neuronal cells where Ca^{2+} influx mediates signals between neighboring cells and in cardiomyocytes where H_2S protected heart against Ca^{2+} overload and hypercontracture. We demonstrated that pretreatment of VSMC with homocysteine increases the ability to react with potent agonist, such as angiotensin II, which normally has no effect on intra-cellular Ca^{2+}. After homocysteine pretreatment, VSMCs were extremely responsive to angiotensin II at concentrations well below the physiologic range. This result suggested that an initial effect of homocysteine is to induce release of intracellular Ca^{2+} in VSMC and may induce vascular reactivity. The transient in Ca^{2+}correlates with the effect on ECM associated with homocysteine [59]. The effects of homocysteine on collagen production correlated with its effect in intracellular Ca^{2+} and were mediated by multiple intracellular signaling pathways in VSMC [59]. These include protein kinase C, nitric oxide synthase (NOS), phospholipase A_2, HMG co-A reductase, tyrosine kinase, and calcium channel [59]. A possible mechanism of homocysteine-induced ECM production and hypertension in VSMC has been depicted in Fig. 4.

Contractile Proteins and Hypertension: H_2S is a Key Player

Alterations in the composition and distribution of isoforms of contractile proteins in hypertension have been demonstrated [62,63]. However, little has been reported on either the modification or the changes in the composition of these proteins in hyperhomocysteinemia. Several consequences are observed leading to vascular damage by homocysteine. These include endothelial cell desquamation [64], oxidative modification of low density lipoproteins [65], increased adhesion of monocytes to the vessel wall [66], and impaired vascular response to the endothelium-dependent relaxing factor (NO) [47]. Impaired flow-mediated vasodilation has been demonstrated in healthy humans after an acute increase in plasma homocysteine [42]. Although flow-mediated vasodilation is largely dependent on the release of NO, it focuses only on the vasomotor response of the endothelium. However, due to its connection in controlling underlying VSMC function, it is plausible that it also modifies the underlying contractile apparatus. In an aortic banding and

two kidney one clip Goldblatt hypertension, formation of nitrotyrosine in the aorta and kidney was enhanced [67,68]. However, in these studies the role of protein labeled with nitrotyrosine in vasoconstriction was not addressed. Homocysteine induces proliferation in VSMCs [43,50] and H_2S has been shown to inhibit rat aortic VSMC proliferation [69]. However, the link between endothelial dysfunction and proliferation of VSMCs is unclear. We also demonstrated that factors released from endothelium inhibit homocysteine-induced contraction of endocardium [40], while others have demonstrated that H_2S potentiates NO production via enhancement of extracellular signal-regulated kinase activation in rat VSMC [70]. Thus, the homocysteine-mediated vascular contraction may be mediated through decreased production of H_2S in the VSMCs in hyperhomocysteinemia. We also demonstrated that de-endothelialized endocardium enhanced contraction to homocysteine [40]. These results suggest plausible modification (nitrotyrosine) of contractile apparatus in underlying muscle cells in myocardium [40]. Based on the current literature, we conclude that homocysteine neutralizes endothelial NO and modifies underlying smooth muscle actin and myosin by redox mediated peroxynitrite generation and nitrotyrosine formation. This initiates the cascades of vascular ECM remodeling, fibrosis, and vasoconstriction. H_2S, being an $O_2^{\bullet -}$ scavenger neutralizes oxidative stress, thus either endogenous activation of H_2S producing enzymes and/or supplementation of H_2S may protects smooth muscle protein from being oxidative modification and reduce hypertension in hyperhomocysteinemia. Future studies are required to confirm or cancel this concept.

ECM, Protein Homocysteinylation, and Hypertension: Importance of H_2S for Vascular Elastance

The vascular fibrosis, stiffness, atherosclerosis, and arteriosclerosis are associated with hypertension [31]. Studies in animal models of hyperhomocysteinemia suggested that hyperhomocysteinemia develops more like arteriosclerotic/prothrombotic than like atherosclerotic lesions [71–73]. Homocysteine induces ECM fibrillar collagen [50,74] and elastinolytic proteinase in VSMCs [75]. A high-protein diet causes abdominal aortic dysfunction by reducing elastic compliance [76]. Considerable endothelial damage and loss of endothelium-derived NO [77], collagen synthesis and deposition [74], and increase expression of connective tissue growth factor (CTGF) in VSMC both in vivo and in vitro [78] were observed in hyperhomocysteinemic condition. These findings suggest that homocysteine contribute to progression of atherosclerosis that may lead to hypertension. A possible mechanism is shown in Fig. 5.

Hypertension results from persistent vasoconstriction, smooth muscle growth, and ECM remodeling of arteries. The dynamics of elastin and collagen are physiological processes in the normal arteries and imbalances of elastin/collagen ratio cause vascular dysfunction. For example, excessive collagen deposition or oxidative modification of collagen (glycated collagen) in the basement membrane can cause vascular stiffness and hypertension. MMPs degrade extracellular protein collagen and elastin, but the turnover of collagen is faster than elastin, therefore, during oxidative stress glycated collagen deposits in the ECM causing vascular stiffness and hypertension. Homocysteine has been reported to cause arterial stiffness by modulating elastin/collagen ratio [79] resulting in hypertension. On the other hand hyperhomocysteinemia has been shown to decrease H_2S [25] and decrease in plasma H_2S has been reported to cause hypertension [15], whereas NaHS (a H_2S donor) significantly increased plasma H_2S, decreased mean pulmonary arterial pressure in rats [80]. NaHS also inhibited the proliferation of smooth muscle cells in the pulmonary artery wall. The expression of collagen I and III were decreased by NaHS in the pulmonary arteries of rats under hypoxia suggesting that H_2S played an important role in the development of hypoxic pulmonary vascular structural remodeling resulting in reduced arterial pressure

[80]. MMPs are matrix-degrading enzymes involved in ECM turnover and promotes smooth muscle cell (SMC) and endothelial cell proliferation and migration. Tissue inhibitors of metalloproteinases (TIMPs) are natural inhibitors of MMPs and imbalance of MMPs/TIMPs axis could lead to abnormal ECM deposition and form tissue fibrosis. We have reported that homocysteine activates latent resident tissue MMPs [39,81] and inhibition of MMPs triggers fibrosis [82]; therefore reduces hypertension [83]. In a one kidney hypertensive mouse model we also demonstrated that hyperhomocysteinemia induced MMP-2 and -9 activation was normalized with H_2S supplementation that prevented renal damage [84]. Renal insufficiency due to reno-vascular damage is linked to hypertension; therefore, in hyperhomocysteinemia, treatment with H_2S could be a therapeutic approach to prevent deleterious vascular remodeling and hypertension.

Hyperhomocysteinemia, Angiotensin, and Hypertension

Angiotensin II is the main peptide of rennin–angiotensin system and activation of angiotensin type 1 (AT1) receptor leads to the production of ROS. Although studies have demonstrated AT1 receptor-mediated production of ECM components, very little is known about AT1 receptor regulation and its consequences in hyperhomocysteinemia. We have demonstrated that homocysteine induced the AT1-receptor induced MMP-9 and collagen synthesis in vascular endothelial cells [85]. Laggner et al. [86] showed that H_2S inhibited angiotensin-converting enzyme (ACE) activity of endothelial cells. Therefore, it is possible that during hyperhomocysteinemia reduced-H_2S will promote ACE activity that may lead to upregulation of angiotensin II and subsequently hypertension. However, this mechanism needs to be investigated thoroughly before a conclusion can be drawn. A possible pathway of angiotensin II modulation by H_2S during hyperhomocysteinemia resulting in vascular fibrosis and hypertension has been shown in Fig. 6.

Concluding Remarks and Perspective

To understand the cause and effect of relationship between homocysteine-mediated nitrotyrosine formation and vascular dysfunction, it is essential to determine whether NOS is induced in hyperhomocysteinemic subjects and H_2S therapy can modulate this effect. We have demonstrated that homocysteine induces iNOS and reduces eNOS in endothelial cells [45,46] and reduces bioavailability of NO through the formation of nitrotyrosine. However, whether this mechanism is related to reduce plasma H_2S content that may further exacerbates protein modification through nitration of tyrosine residue and complement hyperhomocysteinemia-associated hypertension needs to be determined. Actin and myosin are the primary components of vascular smooth muscle proteins associated with contractile function and have abundant exposed tyrosine in them. Together, the formation of nitrotyrosine in actin and myosin and induction of NOS may demonstrate that these components are affected by homocysteine. Although many ECM components such as elastin, collagen, and proteoglycans also contain exposed tyrosine, their modification may affect primarily the structure. However, tyrosine modification in TIMP-4, which regulates the vascular ECM remodeling, may reduce its ability to regulate MMP and causes adverse ECM remodeling, impairs vascular function and may develop hypertension.

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Abbreviations

AT1	Angiotensin type 1
CBS	Cystathionine-β synthase
CSE	Cystathionine-γ lyase
CTGF	Connective tissue growth factor
ECM	Extracellular matrix
H_2S	Hydrogen sulfide
MMP	Matrix metalloproteinase
NO	Nitric oxide
NOS	Nitric oxide synthase
$O_2^{\bullet-}$	Superoxide
ROS	Reactive oxygen species
TIMP	Tissue inhibitor of metalloproteinase
VSMC	Vascular smooth muscle cell

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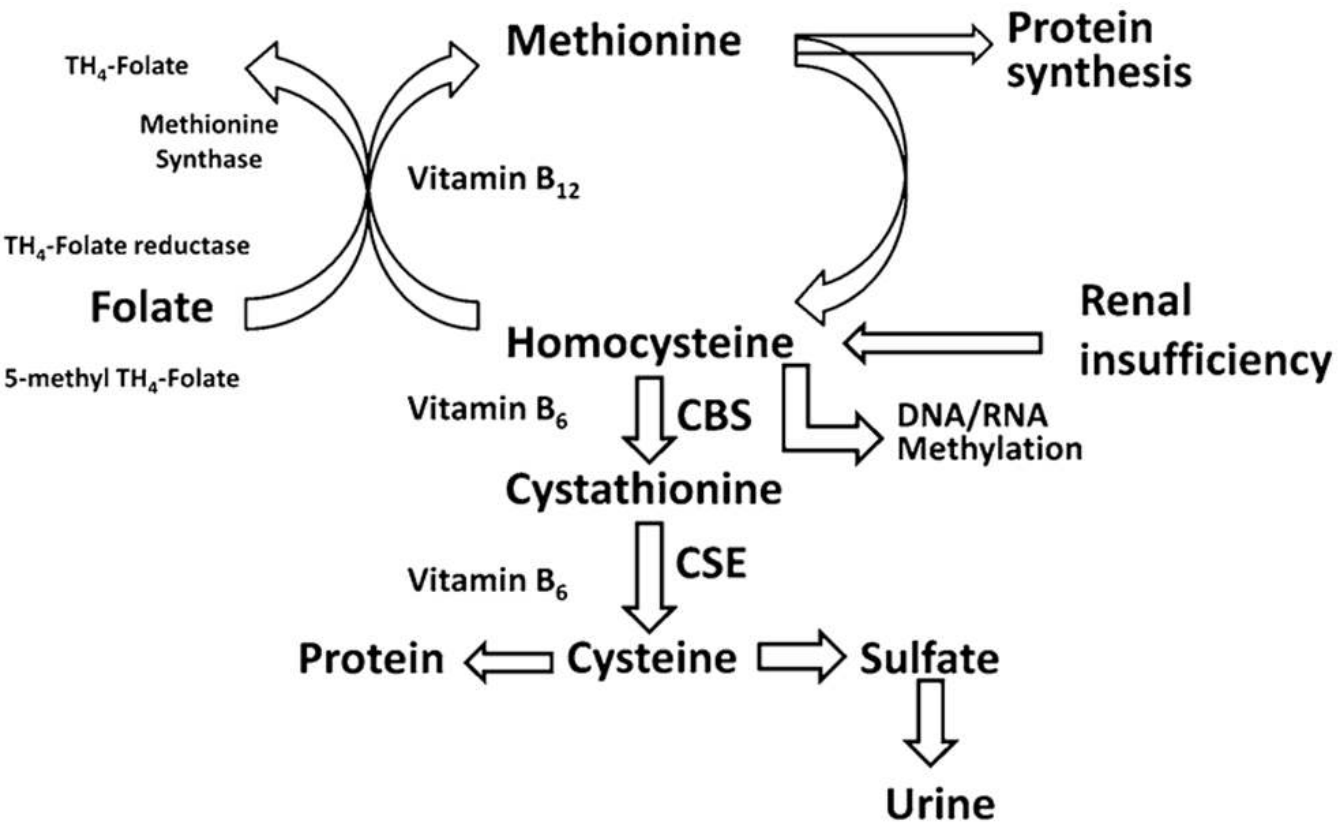

Fig. 1.
Schematic of methionine metabolism and development of hyperhomocysteinemia. Homocysteine in the body further metabolizes to produce sulfate and excretes through kidney

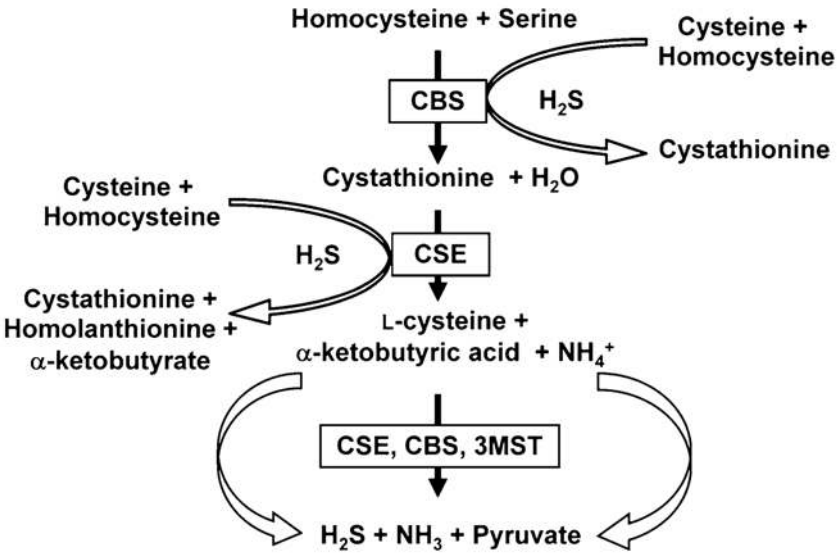

Fig. 2.

Schematic of homocysteine metabolism and formation of endogenous hydrogen sulfide (H_2S). *CBS* cystathionine *β*-synthase, *CSE* cystathionine *γ*-lyase, *3MST* 3-mercaptopyruvate sulfurtransferase

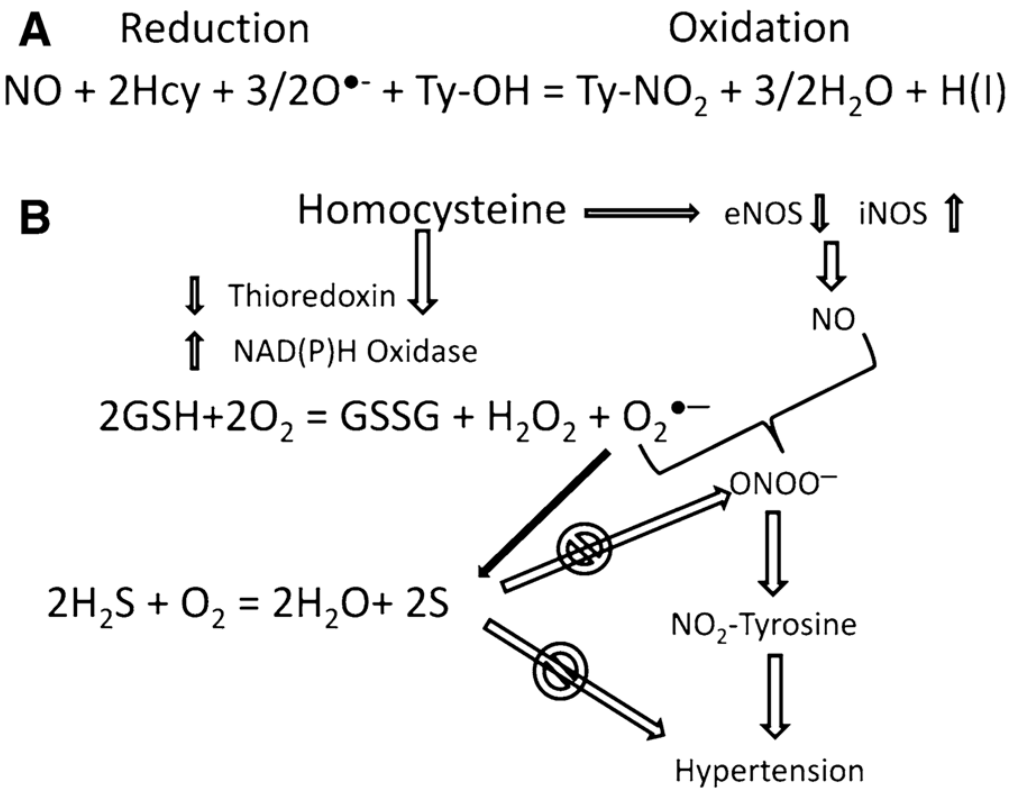

Fig. 3.

a Oxidation reduction and formation of nitrotyrosine by homocysteine. **b** Homocysteine causes reduction of thioredoxin and increases superoxide production by inducing NAD(P)H oxidase. Homocysteine also induces eNOS and iNOS to produce NO. Reaction of NO and tyrosine forms peroxynitrite and causes nitrosylation of protein tyrosine residues, such as actin and myosin. This leads to impairment of contractility and resulting in hypertension. H2S scavenges superoxide; therefore, reduces hypertension

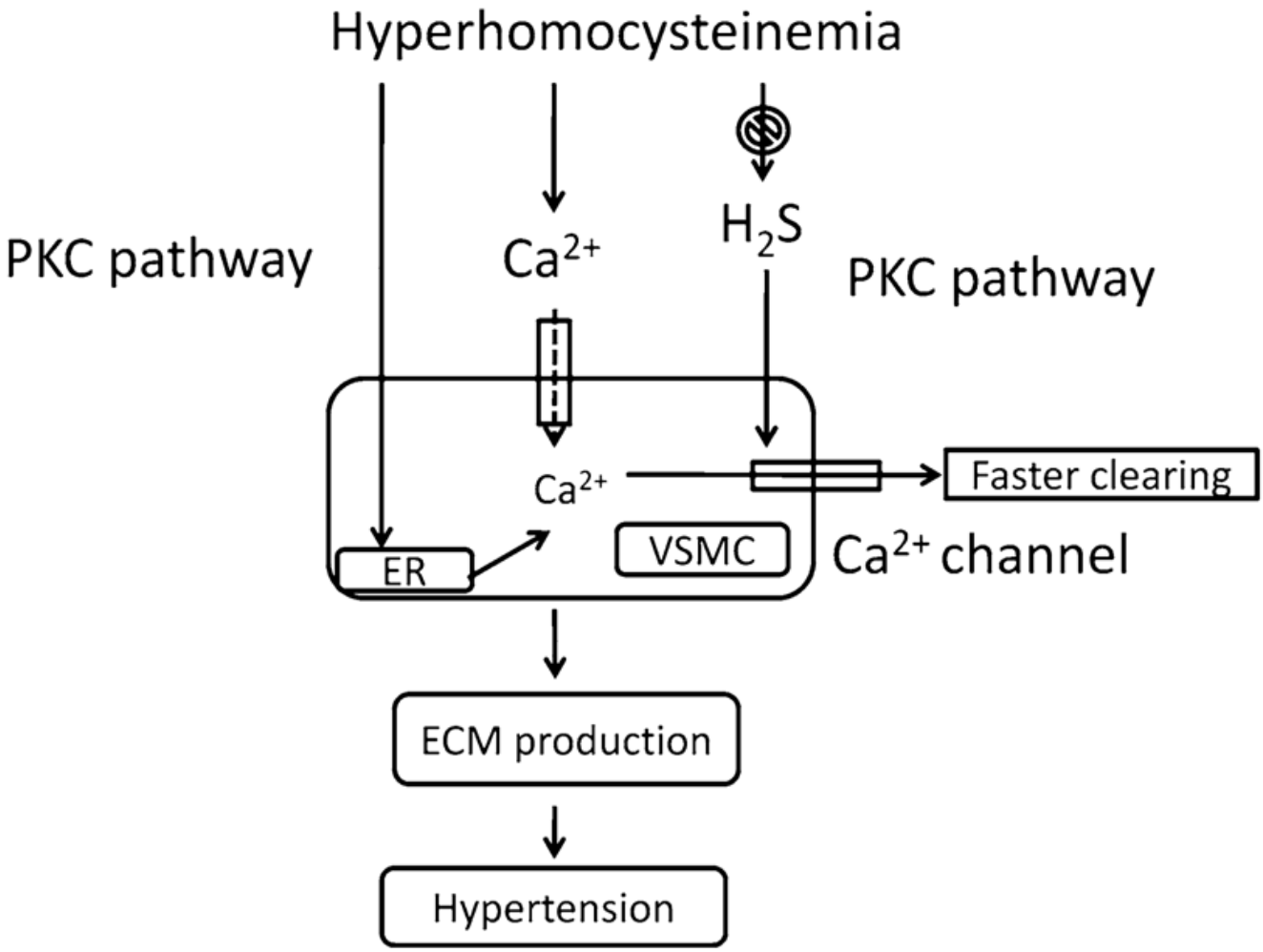

Fig. 4.

Homocysteine induces intracellular Ca^{2+} release and ECM production which results in vascular contraction and stiffness. H_2S helps faster release of intracellular calcium thereby prevents contractility and ECM formation

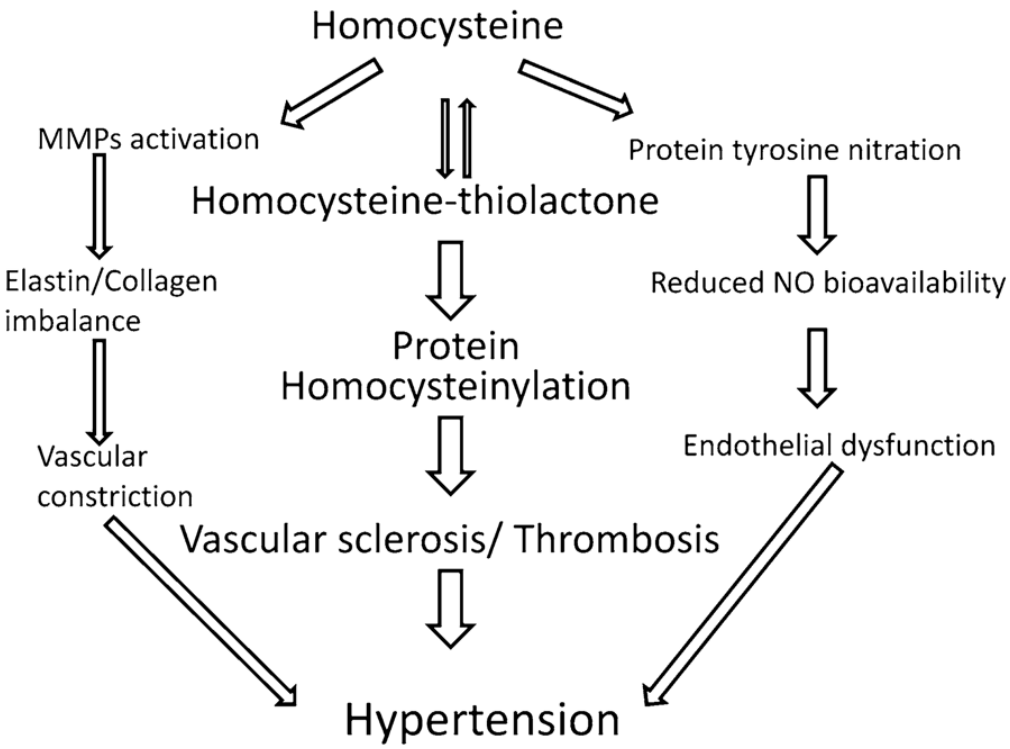

Fig. 5.
Schematic of homocysteine-induced MMP activation, protein homocysteinylation and endothelial dysfunction that causes hypertension

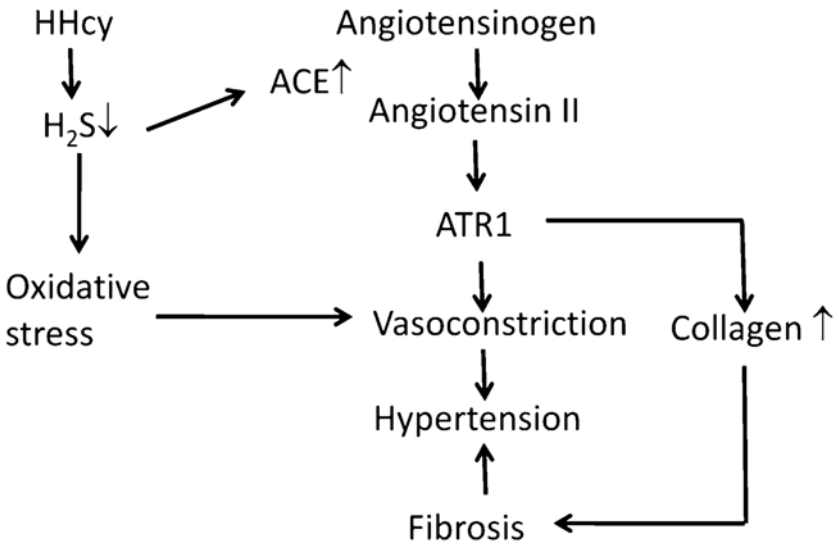

Fig. 6.
Schematic relationship of hyperhomocysteinemia, reduced H_2S and upregulation of angiotensin that may develop hypertension