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Review Article

Increase of Homocysteinemia/Hydrogen Sulfide (Hcy/H_2S) Ratio Raises Cardiovascular Injuries

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Abstract

Increased Homocysteine Levels (HHcy) is an independent risk factor for atherosclerosis. On the other hand, hydrogen sulfide (H_2S) exerts a protection against cardiovascular injuries. On the contrary, accumulating evidences showed that downregulation of defective catabolism of HHcy, with reduced H_2S synthesis, is involved in the pathogenesis of a variety of cardiovascular diseases. In that occurrence, the detrimental actions on cardiovascular structures performed by HHcy are added to the negative consequences of reduced H_2S (in part unlike each HHcy) on cardiovascular system. Therefore, when the reduced re-methylation pathway of Hcy towards Met (resulting in HHcy) is contemporarily added to the decreased trans-sulfuration pathway (inducing a reduction of H_2S synthesis) cardiovascular impairment significantly increases.

Keywords: Homocysteine; Hydrodgen sulfide; Re-methylation pathway; Trans-sulfuration pathway; Endothelial dysfunction; Cardiovascular injuries

Abbreviations

Hcy: Homocysteine; Met: Methionine; MTHFR: Methylene-Tetra-Hydrofolate Reductase; MS: Methionine; Synthase; GHS": Glutathione; MAT: Methionine-Adenosyl-Transferase; SAM: S-Adenosyl-Methionine; SAH: S-Adenosyl-Homocysteine; DNA: Desossi-Nucleic Acid; RNA: Ribo-Nucleic Acid; DMG: Di-Methyl-Glycine; CßS: Cystationine-ß-Synthase; CSE: Cystationine-Gamma-Lyase; 3-MST: 3-Mercaptopyruvate-Sulfur-Transferase; H_2S: Hydrogen Sulfide; HHcy: HyperHomocysteine; ED: Endothelial Dysfunction; Ecs: Endothelial Cells; NO: Nitric Oxide; DDAH: Dimethylarginine-Dimethyl-Amino Hydrolase; NOS: Nitric Oxide Synthase; ROS: Reactive Oxygen Species; ONOO: Peroxynitrite; TxA2: Tromboxane A2; ADP: Adenosyl-D-Phosphate; OH: Hydroxyl Radical; H_2O_2: Hydrogen Peroxide; cAMP: cyclic Adenosine-Mono-Phosphate; VSMC: Vascular Smooth Muscle Cell; ATP: Adenosin-Tri-Phosphate; VCAM: Adhesion Molecule; MCP-1: Monocyte Chemoattractant Protein-1; NF-kB: Nuclear Factor kB; CAM-1: Adhesion Molecule-1; NaHS: Sodium Hydrosulfide; I/R: Ischemia/Reperfusion

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid derived, as metabolite, by a dietary Methionine (Met). That is present in several aliments, such as meat, fish and dietary products. Further meta bolization of Hcy happens by two means: remethylation to Met and trans-sulfuration to Cysteine and Glutathione (GSH) [1,2]. The former involves the enzymes MethyleneTetra-Hydro-Folate Reductase (MTHFR) and Methionine Synthase (MS). In this pathway, Met is subsequently activated in S-Adenosyl-Methionine (SAM) by Methionine Adenosyl-Transferase (MAT). SAM acts as a methyl donor (-CH3) to some substrates, such as DNA, neurotransmitters, RNA, proteins, amino acids, phospholipids, monoamines, and others by a process of trans-methylation [3,4]. Subsequently, SAM is changed in S-Adenosyl-Homocysteine (SAH). A second route of Hcy re-methylation in not-dependent on folate and requires Betaine as 1C donor (Betaine cycle). The reaction results in the production of Dimethylglycine (DMG) and happens in the liver and kidney alone. Further Hcy-catabolization happens *via* transsulfuration pathway (Figure 1). In this route, Hcy is converted in Cystathionine by the enzyme Cystathionine-ß-Synthase (CBS). That is acted by the enzyme Cystathionine-gamma-Lyase (CSE) to generate Cysteine. In turn Cysteine, through the enzyme 3-Mercaptopyruvate Sulfur-Transferase (3-MST), produces a gaseous and malodorous mediator toxic gas called Hydrogen Sulfide (H_2S). From the gas drives the powerful antioxidant GHS [5]. Among three enzymes involved in transsulfuration pathway, CBS and CSE participate in the interconversion of Hcy in Cysteine. The steps of transsulfuration pathway until the H_2S synthesis are schematized in Figure 2. The majority of studies in this pathway was performed on animals and has focused for CSE [6]. It must be added that, when dietary Met intake is low prevails the remethylation pathway; on the contrary, when Met intake is high prevails the trans-sulfuration pathway.

Normal level of Hcy is less than 15µmo/L. An increased Hcy levels (HHcy) can happen for genetic defects of the enzymes (MTHFR, MS, MAT) and/or folic acid or B12 vitamin (in the re-methylation pathway), or the enzymes (CBS, CSE, 3-MST) and/or B6 (in the transsulfuration pathway).

HHcy may derive from genetic factors, such as polymorphisms of the enzymes involved in Hcy metabolism or a dietary deficiencies of vitamin B6, riboflavin, cobalamin and/or folate. The genetic polymorphisms of the enzymes inducing HHcy include: CBS, MTHFR, MS. Polymorphisms of MTHFR or MS give rise to low or normal level of plasma MET, while deficiency of CBS lead to HHcy. The further Cystationine catabolism towards Cysteine requires the enzyme CSE, whereas the enzyme 3-MST induces H_2S synthesis from L-Cysteine [7].

It is known that HHcy is associated with atherosclerosis and its

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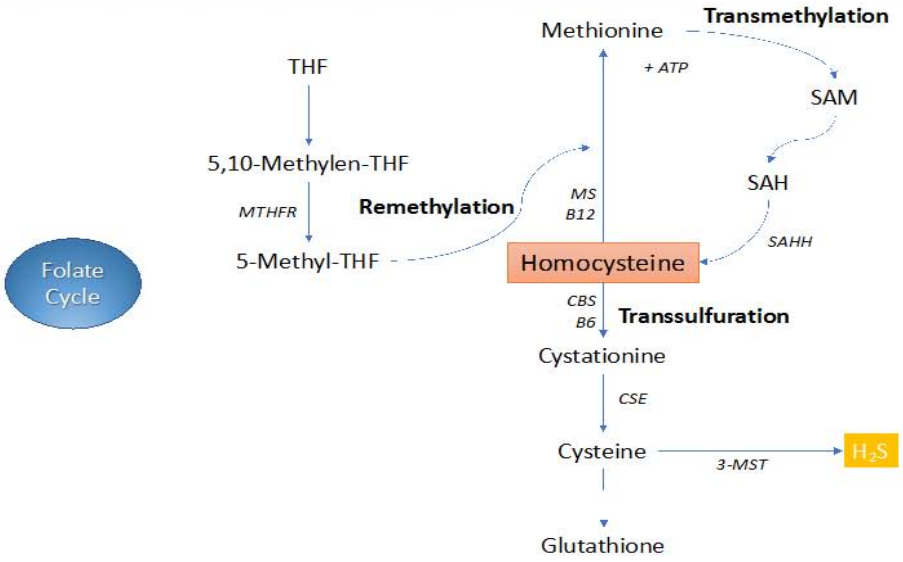

Figure 1: Re-methylation, Trans-methylation and Trans-sulfuration pathways of the homocysteine$_2$ cycle are and hy.

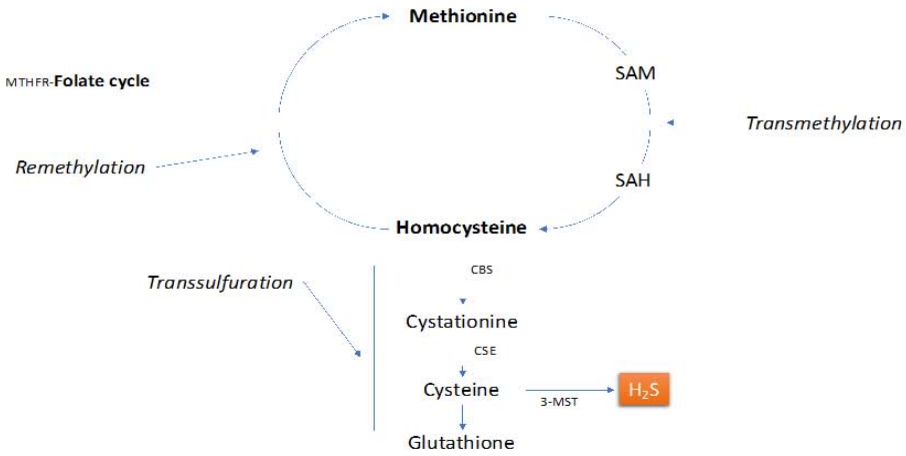

Figure 2: Catabolism of homocysteine through transsulfuration pathway, with hydrogen sulfide (H_2S) synthesis, is reported in detail.

some frequent complications, such as myocardial infarction and stroke or peripheral vascular disease [8]. But, HHcy also favors some neurological disorders, such as dementia, Alzheimer's disease, multiple sclerosis, Parkinson's disease, epilepsy, eclampsia and others [9]. HHcy can cause cardiovascular disease not only "per se" [10] but also, through the deficiency of H_2S [11]. On the subject, the detrimental effects on CV system induced by HHcy are the same caused by H_2S deficiency, and few others only are dependent from H_2S (Figure 3). H_2S is a gaseous and malodorus mediator endogenously produced from Cysteine (transsulfuration pathway). A number of studies demonstrated that H_2S deficiency may be involved in a multitude of pathophysiologic processes, such as impaired vascular tone, oxidative stress, inflammation and atherosclerosis [12,13].

Increase of Hcy/H_2S Ratio

HHcy state causes a decrease in H_2S production because it inhibits CSE activity [12]. Concordandly, deficiency of H_2S was found in hyperhomocysteinemic mice [14]. A reduction of H_2S tissue concentration was also observed in cells exposed to HHcy [15-17]. The decrease of H_2S was attribuited to suppressed H_2S synthesis generating enzymes CBS and CSE. CBS expression predominates in the brain, nervous system, liver and kidneys, while CSE is a major H_2S-sintetizing enzyme present in cardiovascular system [18]. Contrarily to these reports, few studies report elevated H_2S levels in HHcy [19,20]. But, the mechanisms of this anomalous behaviour (increase of H_2S in presence of HHcy) remain unknown.

As previously said, H_2S deficiency is caused by the reduced activity/expression of the enzymes, as CBS, CSE induced by HHcy [21]. H_2S deficiency, derived by reduced activity of these enzymes, acts as the risk factor for cardiovascular disorders [22-25]. Therefore, both HHcy and H_2S deficiency induce cardiovascular disease and the increased HHcy/H_2S ratio, (for raised Hcy concentration and reduced H_2S production) is as a more heavy indicator of cardiovascular injuries. Endothelial Dysfunction (ED) is a prevalent mechanism by which both conditions and its ratio causes cardio-vascular impairment [26] but, other mechanisms happen too.

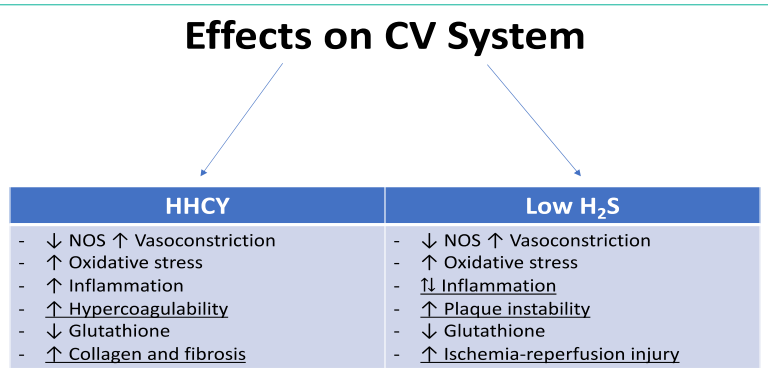

Figure 3: Main effects on CV system of both HHcy and low H_2S. Different effects performed by two conditions are underlined.

Endothelium

The health endothelium is a dynamic organ that regulates vascular tone by balancing vasodilation and vasoconstriction in response to different stimuli. Endothelial Cells (ECs) constitutes a mechanical and biological barrier located between the vessels and tissues, and regulates the exchanges between the interstitial tissue and blood. Endothelium is exposed to shear stress due to the blood flow, that may alter its permeability. So, normal endothelium plays a critical role in cardiovascular homeostasis, by regulating the blood fluidity, coagulation and fibrinolysis, angiogenesis, vascular tone, monocyte/leukocyte adhesion. Specifically, Ecs produce some vasoactive substances to maintain vascular tone. Furgott and Zawadzki firstly described the presence in Ecs of substances inducing vasodilatation, such as Nitric Oxide (NO) and endothelium-derived hyperpolarizing factor and prostacyclin [27]. Other substances favoring vasoconstriction, such as endothelin and thromboxane, were present too. The balance between these two groups of compounds having opposite effects allows to maintain the vascular tone. It must be added that Ecs produce some molecules able to counteract thrombosis, inflammation and smooth muscle cells proliferation [28-30].

Endothelial Dysfunction (ED) consists in the disruption of the integrity of Ecs and refers to the loss of their physiological functions caused by HHcy and H_2S [31-33].

HHcy and Vascular Injury

HHcy reduces the NO synthesis through the inhibition of Dimethylarginine-Dimethyl-Amino-Hydrolase (DDAH). The compound is involved in the metabolism of Asymmetric-D-Methyl-Arginine (ADMA), an enzyme that inhibits Nitric Oxide Synthase (NOS) [34].

HHcy favors the oxidative stress, inducing the formation of Reactive Oxygen Species (ROS) through the inhibition of the expression and function of some anti-oxidant enzymes, such as superoxide dismutase and glutathione peroxidase [35,36]. The superoxide anion (O-2) interacts with NO forming peroxynitrite (ONOO). On the other hand, the production of ONOO is a cause of the thromboxane formation (TxA2), having an arteriolar vasoconstrictive action.

HHcy increase collagen deposition leading vascular fibrosis. In an animal study, Liu et al. demonstrated that the increase of Hcy concentration favors an increase of connective tissue growth factor in vascular smooth muscle cells involved in atherosclerotic plaque progression [37].

HHcy also favours platelets' activation by increasing their sensitivity to ADP [38]. The increased Hcy concentration promotes the activation of Factor V Leiden, impairs the von Willebrand factor secretion, inhibits protein the C activation, so promoting the activation of coagulation cascade, favoring the coagulative process [39].

HHcy, favoring oxidative stress, also causes inflammation process [40].

Finally, HHcy acts on the Glutathione (GSH) synthesis, impairing the ratio oxidized/reduced Glutathione (GSSG/GSH) for reduced GSH synthesis, the main antioxidant compound in the body. This reduction happens for decreased activity of the glutathione peroxidase. The prevalence of GSSG on GSH is the expression of greater oxidative stress. Contrarily, the GSH prevalence protects cells by ROS production [41].

H_2S Deficiency and Vascular Injury

The role of H_2S in the endothelium assumed considerable importance in the last decade. Lower H_2S concentration causes vasocontriction. The vasoconstrictive effect of reduced H_2S concentration derives from the inactivation of NO (through the NOS inactivation) [42].

H_2S deficiency causes oxidative stress. As previous affirmed, this consists in an imbalance between oxidant and antioxidant systems for excessive formation of ROS, as superoxide anion (0_2^-), hydroxyl radical (OH^-), peroxynitrite ($ONOO^-$)) and hydrogen peroxide (H_2O_2). While HHcy directly induces this condition, H_2S deficiency indirectly can cause oxidative stress through the GSH depletion [43]. Particularly, in the presence of H_2S deficiency, ROS decreases cyclic Adenosine-Monophosphate (cAMP) in vascular smooth muscle VSMC, inducing the vasoconstrictive effect [43].

Presumably H_2S performs a twofold, conflicting action on inflammation. At low concentration, it seems to inhibit the inflammation, while at high concentration seems to have a pro-inflammatory effect through the activation of Adenosine-Tri-Phosphate (ATP)-sensitive K+ channels [44]. But, in other studies,

H_2S acts a regulator of leukocyte activation under inflammatory states. In accordance with this, endogenous H_2S deficiency exacerbates leukocyte-mediated inflammation. On the contrary, its normal concentration reduced leukocytes [45]. It was also affirmed that a reduction of H_2S synthesis, for CSE deletion, resulted associate with endothelial inflammation [46]. In addition, H_2S deficiency reduces adhesion molecule-1 (VCAM-1) and Monocyte Chemoattractant Protein-1 (MCP-1). Contrarily, exogenous H_2S administration attenuates Ang II-induced inflammatory response, *via* the inhibition of the NF-kB pathway [47].

In addition, the reduced synthesis of H_2S plays a pathophysiologic role in the development of atherosclerosis and plaque instability [48,49]. Wang at al. demonstrated that H_2S deficiency increased the expression of adhesion molecule-1 (CAM-1) that sustains atherosclerotic process [50].

However, the lack of H_2S favors the atherosclerotic process also by increasing the proliferation of intima and smooth muscle cells [51]. Further, a down regulation of CSE expression seems to have a role in the progression of atherosclerosis and plaque calcification [51]. Concerning that, Wu and al. demonstrated in rats that a vascular calcification-model reduces after NaHS (a generator of H_2S) administration [52].

H_2S deficiency (through CSE reduction) results in decrease of Gluthatione (GSH) biosynthesis [53]. GSH is a tripeptide composed by glutamate, cysteine and glycine. It functions as a powerful cellular antioxidant against oxidative damage caused by ROS. Its deficiency impairs endothelium-dependent vasodilation, increases arterial hypertension, favors pro-inflammatory reaction. Its decreased synthesis induces atherosclerosis, plaques' formation and rupture [54].

Finally, low H_2S favours the heart-injuries depending from ischemia/reperfusion (I/R) through an unspecified mechanisms. I/R may be defined as a condition characterized by a deprivation of blood flow supply followed by the subsequent restoration of reperfusion [55]. It is one of major causes of morbidity and mortality in the world. Injuries of I/R happen in hypertension, atherosclerosis, heart failure and others. The organs involved are: apart from heart, liver, kidney, brain, intestine and others [55]. Several mechanisms are proposed as mediators of the damage induced by I/R, such as activation of complement system, endoplasmic reticulum stress, calcium overload, activation of apoptosis, necrosis, autophagy and others [56].

Conclusions

HHcy is caused by a defective remethylation, for MTHFR or MS genetic polymorphism or folate or vitamin B12 deficiency. An increased Hcy concentration complicates with reduced synthesis of H_2S when a decreased trans-sulfuration pathway is contemporarily present. This comes true in the presence of vitamin B6 deficiency or CBS, CSE or MST genetic polymorphism. On the other hand, HHcy has been reported to inhibit CSE activity altering the transsulfuration pathway, thereby reduce endogenous H_2S production [13]. Consequently, an increased Hcy/H_2S ratio comes, for increase of the numerator and decrease of the denominator. In this condition vascular injuries especially happen, because vascular derangements [10,57] are added to the vascular injuries (due to H_2S deficiency) [21,58]. Thus, the Hcy/H_2S ratio can be considered as a biomarker able to induce vascular injuries more than HHcy and H_2S deficiency esteemed separately. But, further investigations must be performed to definitively verify this acquisition.

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