Review Article

Cardiovascular pathogenesis in hyperhomocysteinemia

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Increased plasma homocysteine (Hcy) is a significant and independent risk factor for cardiovascular disease. It can cause multi-disease manifestations such as smooth muscle proliferation, premature occlusive vascular disease, progressive arterial stenosis, haemostatic changes, placental vasculopathy, spontaneous early abortion, birth defects, impaired cognitive function and dementia. This review paper summarizes the role of elevated Hcy levels in cardiovascular and other diseases and the molecular mechanisms and pathophysiology involved in the deleterious manifestations of hyperhomocysteinemia. We have collected data from MEDLINE, Current Contents and scientific journals, which included 112 publications from 1932 to 2007. Cardiovascular pathophysiology in hyperhomocysteinemia is a complicated process, possibly due to direct toxicity of Hcy on tissues, low S-adenosylmethionine, high S-adenosylhomocysteine or thrombotic events triggered by stimulation of procoagulant factors and suppression of anticoagulant factors and platelet activation, thereby enhancing oxidative stress, smooth muscle cell proliferation, formation of reactive oxygen species, hypomethylation, induction of unfolded protein responses and extracellular matrix modification. The mechanisms involved in the increased risk of cardiovascular disease still remains a mystery in many respects, and more studies are needed to elucidate this association.

Key Words: Homocysteine, smooth muscle cell, oxidizing stress, teratogenic action, proinflammatory

INTRODUCTION

Homocysteine (Hcy) is a sulfur amino acid derived from methionine during transmethylation. It is a by-product of methionine metabolism, first reported in 1932.[1] For a number of years, some researchers demonstrated that vascular disease of various forms is associated with abnormal methionine metabolism, leading to elevated plasma levels of Hcy.[2,3] Due to its association with various pathological conditions, Hcy gained widespread attention, leading to clarification of the methionine metabolism pathway. Methionine is converted to S-adenosylmethionine (SAM) via the enzyme methionine adenosyltransferase, which is the only methyl-donating pathway in humans.[4] This pathway is essential in the provision of methyl groups to activate biomolecules such as DNA, creatine, phospholipids etc. SAM is demethylated to S-adenosylhomocysteine (SAH), as a product of these methyl-transferase reactions. SAH is hydrolyzed to Hcy in a reversible reaction, in which SAH formation is favored. Once Hcy is formed, it is metabolized through two metabolic pathways: remethylation and transsulfuration. Remethylation is the vitamin-dependent pathway, which converts Hcy back to methionine via the enzyme 5-methyltetrahydrofolate reductase (MTHFR) and the enzyme methionine synthase (MS).[5] Remethylation appears to be the primary modulator of fasting and elevated plasma Hcy concentrations.[6] Transsulfuration requires vitamin B_{12} to convert Hcy to cysteine via a two-step process involving the vitamin B_6-dependent enzyme cystathionine β-synthase (CBS) and cystathionase. Ultimately cysteine is converted to sulfate and excreted

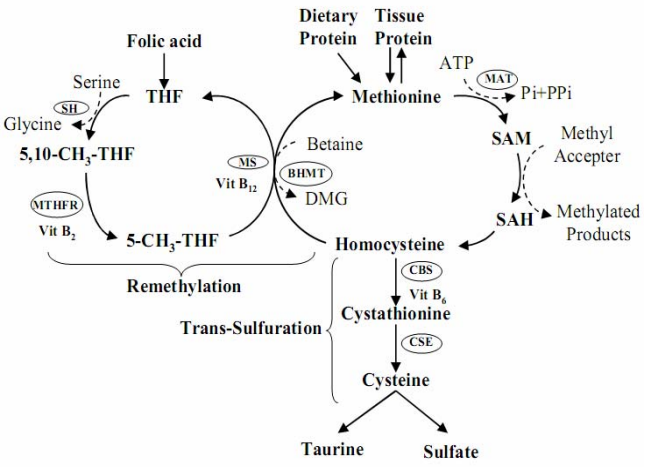

Figure 1. Metabolism of homocysteine. MS: Methionine synthetase; CBS: Cystathionine β-synthase; CSE: Cystathionine γ-lyase; MTHFR: Methylenetetrahydrafolate reductase; BHMT: Betaine-homocysteine methyltransferase; MG: Dimethylglycine; 5, 10-CH_3-THF: 5, 10-Methylene-Tetrahydrofolate; 5-CH_3-THF: 5-Methyl-Tetrahydrofolate; THF: Tetrahydrofolate; SH: Serine hydroxymethyl transferase; Pi: Orthophosphate; PPi: Pyrophosphate

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into the urine (Figure.1).

In the human body, total Hcy (tHcy) reflects the combined pool of free, bound, reduced, and oxidized forms of Hcy in the blood.[7] Normal tHcy levels ranges between 5 and 15 μmol/L (12 μmol/L being the upper reference limit for populations on a folic-acid-fortified diet, as in North America) with elevations of 16 to 30 μmol/L, 31 to 100 μmol/L, and >100 μmol/L classified as mild, moderate, and severe hyperhomocysteinemia (HHcy), respectively.[8,9] Life-threatening HHcy is associated with enzymatic defects at various points of Hcy metabolism.[10-12] Several dietary and lifestyle factors, genetic defects, nutritional deficiencies, and other etiologies can also cause elevations in Hcy.[13,14] A thermolabile variant of MTHFR with reduced enzymatic activity (C677T mutation) is the most common form of genetic HHcy. However, an association of this mutation with increased cardiovascular disease (CVD) risk is manifested only in populations characterized by low baseline folate levels.[15,16] Deficiency of folic acid, vitamin B_6, and vitamin B_{12} accounts for the majority of cases of elevated Hcy in the general population.[17,18]

Despite considerable advances in our understanding of the etiology of CVD, about 30% of CVD cannot be explained by conventional risk factors.[19] It has been suggested that HHcy accounts for the higher prevalence of CVD that is not explained by traditional risk factors.[19] HHcy is known to cause multi-disease manifestations such as premature occlusive vascular disease,[20] smooth muscle proliferation, progressive arterial stenosis,[21] haemostatic changes, nephritic syndrome,[22] placental vasculopathy,[23] birth defects,[24] impaired cognitive function, dementia,[25] and type-2 diabetes.[26] HHcy is also a risk factor for osteoporotic fractures.[27, 24] In 1969, observations in patients with homocystinuria led McCully to suggest that Hcy may be involved in the pathogenesis of arteriosclerosis.[2] In general, clinical and epidemiologic studies show an independent and graded association between Hcy levels and CVD, as well as peripheral artery disease,[28-30]myocardial infarction,[31] and venous thromboembolism.[32-35] Dinleyici et al. recommended the use of plasma tHcy levels as a risk indicator along with other coronary risk factors for detecting and preventing CVD in diabetic children.[5]

Over the past several decades, the mechanism of Hcy-induced vascular disease has been actively investigated using different experimental models, which have provided important insight into our understanding of the role of Hcy in CVD.[19] In experimental studies, the following mechanisms have been suggested to explain the mechanism by which Hcy induces vascular disease:

Endothelial injury

Endothelial dysfunction is an early key event preceding the manifestation of atherosclerosis and vascular disease.[36] Increased cardiovascular risk associated with HHcy has been linked to Hcy-induced endothelial cell (EC) dysfunction. Hcy has a direct toxic action on blood vessel endothelium.[4] EC can inhibit thrombosis through the interconnected regulatory systems: (a) the coagulation cascade; (b) the cellular components of the blood such as leukocytes and platelets and (c) the complement cascade, and also through effects on fibrinolysis and vascular tone, the latter which influences blood flow.[37] Endothelin-1, a vasoactive peptide synthesized mainly by vascular EC, is crucial for normal vasomotor function, limiting inflammatory activation and maintaining a nonthrombogenic endothelial surface.[38] Hcy decreases endothelin-1 biosynthesis, and down-regulates endothelin-1 at the transcriptional level by decreasing preproendothelin-1 promoter activity. Hcy reduces the binding activity of EC nuclear extracts to an AP-1 consensus site. The AP-1 signaling pathway may be of major importance in Hcy-induced endothelial dysfunction. Hcy can also regulate EC growth and apoptosis by inducing PI3K/Akt or p53 signaling and metalloproteinase.[39-41] Hcy, at a physiologically relevant concentration, inhibits EC growth through hypomethylation and cyclin A transcriptional inhibition. Hcy, but not cysteine, markedly increases the level of SAH, a potent inhibitor of cellular methylation in EC and has little effect on vascular smooth muscle cell (VSMC).[42-44] Hcy also induces expression and acceleration of monocyte chemoauractant-protein-1 (MCP-1) and interleukin-8 (IL-8) in human aortic EC and causes a significant alteration in vascular reactivity of pulmonary arteries.[45] This alteration is via oxidative stress in the pulmonary artery endothelium with subsequent DNA damage and the activation of the poly (ADP-ribose) polymerase (PARP) pathway.[46] Hcy significantly inhibits the endothelium-dependent relaxation response to acetylcholine (ACh) in a dose-dependent manner, and decreases cGMP levels increased by ACh in the aorta.[47] Hcy induces impairment of nitric oxide (NO, a potent vasodilator) production through the modulation of Cav-1 expression associated with a loss of the endothelial isoform of NO synthase in caveolae.[48] Hcy can also increase vascular endothelial growth factor (VEGF) expression 4.4-fold due to ATF4-dependent activation of VEGF transcription in the retinal-pigmented epithelial cell line ARPE-19.[49] This leads to impaired synthesis of NO and other vasoactive substances, resulting in endothelial dysfunction.[50] These biological mechanisms might represent an important mechanism for Hcy-induced arteriosclerosis.

Stimulation of vascular smooth muscle cell proliferation

Hcy affects the neural crest–derived SMC and their extracellular matrix proteins in the pharyngeal arch arteries, resulting in an abnormal smooth muscle that interacts with EC, leading to EC detachment. Similarly to what happens in adult life, increased Hcy concentrations leads to vascular damage in the embryo. This prenatal damage might increase the susceptibility to develop vessel pathology later in life.[51] Hcy (0.01–0.25 mmol/L) significantly increases the expression of interleukin-6 (IL-6) mRNA and proteins in rat VSMC. The ability of Hcy to elicit an inflammatory response in rat VSMC occurs through the stimulation of IL-6 production and activation of NF-κB.[52, 53] Activation of vessel wall inflammation by elevated Hcy may contribute to the pathogenesis of atherosclerosis. Hcy acts as a mitogen via a receptor-mediated effect, coupled to diacylglycerol production and protein kinase C activation in VSMC.[54] Hcy can up-regulate the transcription of *c-fos* and *c-jun* which mediates the expression of many cytokines, especially growth factors in the common carotid artery, and activates the essential transcription

factor AP-1 in the cell nucleus. As a consequence, autocrine and paracrine injury of the SMC is initiated with excess proliferation and differentiation of arterial SMC.[55] Hcy significantly inhibits Ca^{2+}- activated K^+ channel (BK_{Ca}, a major factor mediating the degree of depolarization and contraction in vascular smooth muscle) currents in isolated human and rat artery SMC. The reduced and impaired BK_{Ca} by elevated Hcy levels might contribute to the abnormalities seen in vascular diseases.[56] The possible role of Hcy in the formation of atherosclerotic lesions is through a direct proliferative effect on VSMC in a dose-dependent fashion.[57]

Lipid dysregulation and oxidizing stress

Hcy like sulfhydryl compounds can promote the oxidation of LDL, reduce the concentration of HDL cholesterol in plasma by inhibiting the hepatic synthesis of apoA-I, the main HDL apolipoprotein[58] and increase the serum levels of malonyldialdehyde (MDA). Hcy induced lipid dysregulation is an important mechanism linking Hcy to the development of atherosclerosis. The oxidative stress resulting from elevated plasma Hcy can oxidize membrane lipids and proteins and stimulate the activation of NF-κB, and consequently increases the expression of inflammatory factors *in vivo*. Hcy can be converted to highly reactive thiolactone which is able to react with proteins forming -NH-CO- adducts, thus affecting body proteins and enzymes.[59] Such an effect may contribute to atherogenesis by enhancing the inflammatory response of the vascular endothelium,[60] Hcy and copper induces increased extracellular hydrogen peroxide, intracellular ROS and cellular lipid peroxide levels.[61] Prooxidant effect of Hcy on LDL at lower concentrations in the presence of Cu^{2+} was ascribed to the capacity of Hcy to reduce Cu^{2+} to Cu^+ and cause LDL oxidation *in vitro*.[62, 63] Hcy can promote protein oxidation and induce LDL protein modification via the induction of HMG-CoA reductase and nitration or via nitric oxide and copper which promotes LDL uptake by scavenger receptors. The autoxidation of Hcy in the presence of metal ions and oxygen has been shown to result in the generation of ROS, such as hydrogen peroxide.[64] Therefore the rate of the autoxidation process and the rate of generation of ROS available for oxidative reactions depends partly upon the concentration of Hcy and trace metal ions. Hcy-induced ROS can upregulate the expression and translocation of Ref-1 via NADPH oxidase. In turn, Ref-1 increases NF-κB activity and MCP-1 secretion in human monocytes/macrophages, which may accelerate the development of atherosclerosis.[65]

Platelet activation and thrombosis activation

Hcy can enhance the self-oxidation of LDL. Ox-LDL affects the synthesis of nitric oxide and the activity of thrombin equestron which leads to further injury of endodermis function.[66] Destroying the vascular endothelial cell (VEC) and aggregation of icky blood results in thrombopoiesis. Thrombosis activation might be responsible for the increased incidence of both arterial and venous thrombosis in human HHcy.[67] In humans, plasma Hcy affects clot permeability and resistance to lysis, most likely by a mechanism involving fibrinogen modification via HTL. Alteration in the balance between blood clotting and fibrinolysis induced by Hcy leads to an increase in blood viscosity. Hcy decreases the largest von Willebrand factor (a thrombophilic protein) multimers in women with thrombosis,[68] and the activity of thrombomodulin, the thrombin cofactor responsible for protein C activation in the aorta in monkeys.[69] Hcy can initiate coagulation by the TF pathway (through a mechanism involving the free thiol group of the amino acid and by TF gene transcription[70]), enhancement in the activity of blood coagulation factor VII and VI, suppression of the activity of proteinum C and inhibition of the combining of tissue plasminogen activator (t-PA) to EC.[71, 72] Hcy alters the anticoagulant properties of EC to a procoagulant phenotype, which may contribute to cerebral infarction in patients with HHcy.[73] Hcy activates platelets in humans and rats[74, 75] and affects platelet aggregation and the activity of blood coagulation factor-V via increased thromboxane B_2 (TXB_2) and prostaglandin B_2 (PGB_2) induced by hydrosulfuryl-lactone.[76] The alteration of the metabolism of arachidonic acid (AA) induced by Hcy leads to an increase in the synthesis of thromboxane A_2 (TXA_2), which promotes vasoconstriction and platelet aggregation, both in the arteriolar endothelium and platelets. By promoting vascular constriction and platelet aggregation simultaneously, these alterations are likely to contribute to the atherothrombotic vascular diseases described in HHcy.[73] Perturbation of vascular coagulant mechanisms may contribute to the thrombotic tendency seen in patients with homocystinuria. The formation of clots from plasma or fibrinogen could directly contribute to the increased risk of thrombosis in HHcy.[77]

Teratogenic action

Although a number of congenital defects are known to be the result of chromosomal aberrations, a major proportion of congenital malformation appears to be the result of environmental factors including nutritional deficiency or toxicity.[78] Hcy also contributes to the occurrence of congenital defects. Treatment of avian embryos with doses of 0.5-20 μM exogenous Hcy per embryo resulted in physiological increases of Hcy in the embryonic serum and produced heart and neural tube defects that were typical of folate deficiency, in a dose- and time-dependent fashion.[78] Several studies have suggested that neural crest cells might be particularly susceptible to the teratogenic effects of Hcy.[78, 79] Hcy directly disrupts normal neural crest cell formation in vivo and Hcy treatment decreased the number of these cells and increased the number of neural tube cells.[80] Hcy-induced defects are mediated by the inhibition of the *N*-methyl-D-aspartate (NMDA) receptors found on neural crest cells.[81] Hcy treatment disrupts normal development of avian embryos; and this effect is prevented by retinoic acid. Limpach first suggested that Hcy-induced congenital defects are due to the specific ability of Hcy to inhibit the conversion of retinal to retinoic acid. HHcy is frequently associated with congenital defects of the heart and neural tube and is also a suspected pathogenic factor in atherosclerosis and neoplasia.[82]

Monocyte activation and inflammatory reaction

Pathophysiological levels of Hcy alters EC function by upregulating MCP-1 and IL-8 expression and secretion.[83-

[85] MCP-1 is a potent chemokine that stimulates the migration of monocytes into the intima of the arterial wall. MCP-1 enhances the binding of monocytes to the endothelium and their recruitment to the sub-EC space. The infiltration of monocytes into the arterial wall is one of the key events during atherogenesis.[86] Considering that Hcy increases MCP-1 secretion from isolated monocytes in response to low-dose lipopolysaccharide (LPS),[85] Hcy stimulates monocyte series Mac 6 (MM6) and PBMC13 and VSMC, and consequently produces IL-6.[87] Hcy increases vascular cell adhesion molecule (VCAM)-1 mRNA expression in HAEC. Coincubation of HAECs with Hcy and TNF-α synergistically elevated monocyte adhesion as well as VCAM-1 protein expression.[88] Hcy can also increase intercellular adhesion molecule (ICAM)-1 and P-selectin in vena mesenterica and in the aorta.[89, 90] It also plays an important role in the activation of NFκB and formation of nitrotyrosine in the aorta.[60] Hcy may contribute to atherogenesis by enhancing the responsiveness of monocytes to inflammatory stimuli and promoting leukocyte recruitment into atherosclerotic plaque.[91]

Endoplasmatic reticulum stress and unfolded protein response

Endoplasmatic reticulum (ER) stress and unfolded protein response (UPR) is one of the proposed Hcy toxicity mechanisms. The cellular consequence of protein modification with Hcy is ER stress, a condition in which unfolded proteins accumulate in the ER lumen under physiological or pharmacological ER stresses such as a block in protein glycosylation, expression of mutated proteins, or disturbance of calcium homeostasis. The ER is a critical cellular compartment responsible for proper localization and folding of transmembrane and secreted proteins.[92] Disruption of protein folding and maturation activates the UPR, a signaling pathway that results in increased expression of UPR responsive genes, reduced global protein translation and unfolded protein degradation.[4] CBS-deficiency in mice liver significantly increases expression of genes induced by ER stress and genes that regulate the expression of enzymes required for cholesterol and fatty acid biosynthesis and uptake, notably the scavenger receptor class B type I (SR-BI), concomitant with overexpression of SR-BI at the protein level.[93] Hcy induces the expression of GRP78 mRNA and activates PERK in VSMCs, and these responses can be observed during ER stress.[94] Upon exposure to chemical inducers of ER stress, VEGF expression is increased. Hcy also decreases extracellular superoxide dismutase (EC-SOD) mRNA expression and protein secretion, a glycoprotein that protects the vascular wall from oxidative stress.[4]

Prevention and treatment of hyperhomocysteinemia

Because the prevalence of HHcy ranges from 20% to 40% in different populations with CAD, therapeutic control of elevated Hcy concentrations may be important in the prevention of premature vascular disease. Lowering plasma Hcy can improve endothelial function, a marker of atherothrombotic risk.[95, 96] As for therapeutic options, severe and moderate HHcy can be treated with vitamin supplements of folate, B_6 and B_{12}.[97-99] Lower plasma concentrations of folate, vitamins B_{12} and B_6, older age, being male, and living in urban areas were all independently associated with elevated Hcy, with low folate as the strongest determinant.[100-102] Folate supplementation (0.5

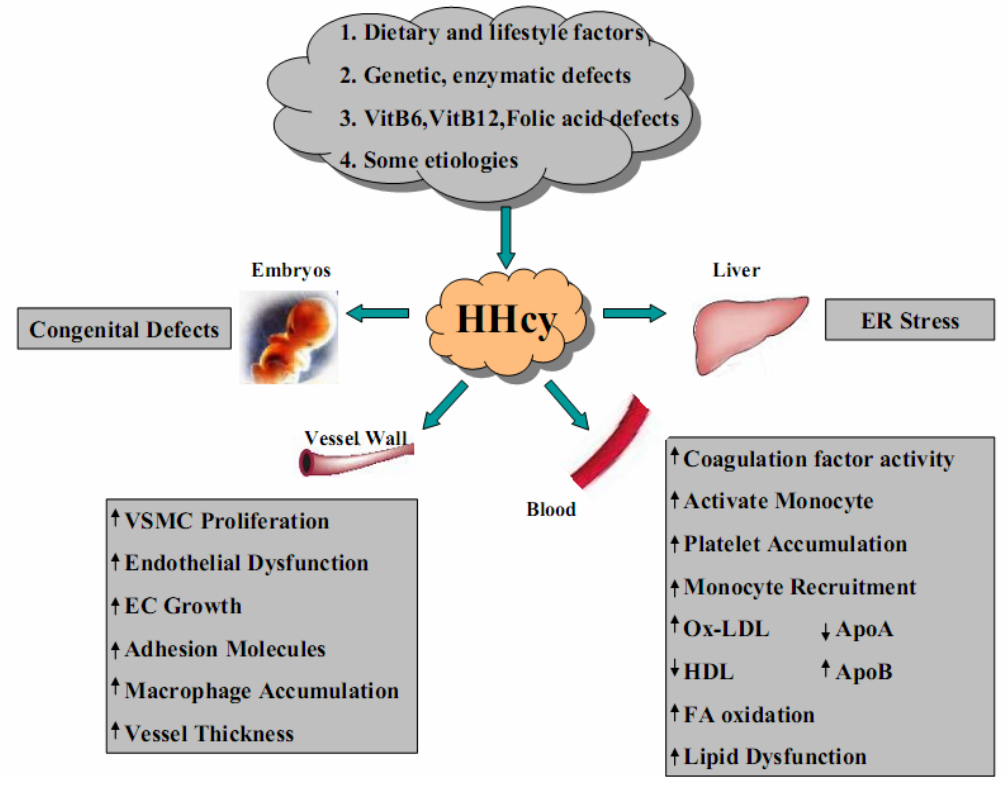

Figure 2. Proposed cardiovascular pathogenesis of hyperhomocysteinemia. HHcy: Hyperhomocysteinemia; EC: Endothelial cell; VSMC: Vascular smooth muscle cell; ER: Endoplasmatic reticulum.

to 5 mg/day) significantly reduces Hcy concentration by 25% in patients with mild to moderate HHcy.[118] Hcy-induced vascular dysfunction is more severe in the presence of low folate.[103] Supplementation with vitamin B_{12} produces a small additional effect (7%), whereas vitamin B_6 treatment alone only reduces post-methionine load concentrations.[104] Daily administration of the combination of folic acid, vitamin B_6, and vitamin B_{12} lowers Hcy levels significantly but does not reduce the incidence of the primary outcome, which is the composite of death from cardiovascular causes, myocardial infarction, and stroke.[105] Individuals with HHcy secondary to renal disease commonly require significantly higher doses of folic acid to achieve maximal therapeutic effect.[106] [6*S*]-5-methyltetrahydrofolate was shown to be an adequate alternative to folic acid in reducing Hcy concentrations.[107]

Betaine (trimethylglycine) reduces fasting Hcy by 12% to 20% without altering folate levels. Betaine is a methyl donor agent that is beneficial in lowering Hcy through the remethylation of methionine. Betaine therapy alone has been shown to prevent vascular events in HHcy and may have clinical benefits in other hyperhomocysteinemic disorders when used as an adjunctive therapy.[108] Choline, a precursor to betaine, decreases fasting and post-methionine load Hcy levels. However, both betaine and choline can have an adverse impact on lipid profiles.[6]

Ginsenoside Rg3, one of the active ingredients in Panax ginseng, has been found to significantly and dose-dependently inhibit Hcy-induced hippocampal cell death, with an EC_{50} value of 28.7 ± 7.5 μM. Ginsenoside Rg3 treatment not only significantly reduced Hcy-induced DNA damage, but also dose-dependently attenuated Hcy-induced caspase-3 activity in vitro.[109] Plasma Hcy demonstrated a significant positive correlation with adrenic acid (22:4n–6) ($r = 0.188$, $p = 0.018$) and a negative correlation with 22:6n–3 ($r = –0.277$, $p = 0.001$) and the ratio of n–3/n–6 ($r = –0.231$, $p = 0.003$). An increased ratio of n–3/n–6 PUFA in platelet phospholipid is associated with decreased thrombotic risks such as plasma Hcy in middle aged and geriatric hyperlipaemia patients.[110] The mechanism that might explain the association between plasma 22:6n–3 and Hcy levels is not clear.[111, 112] There are studies currently being conducted with the aim to demonstrate why and how n–3 PUFA decreases the concentration of Hcy in blood.

CONCLUSIONS

Cardiovascular pathogenesis of hyperhomocysteinemia is a complicated process (Figure 2). Possible explanations include direct toxicity of Hcy on tissues, low SAM or high SAH, thrombotic events triggered by the stimulation of procoagulant factors and suppression of anticoagulant factors and platelet activation, enhanced oxidative stress, SMC proliferation, formation of ROS, hypomethylation, induction of UPR and extracellular matrix modification. The mechanism for which Hcy increases the risk of cardiovascular events still remains a mystery in many aspects. More studies are needed to elucidate this significant relationship.

AUTHOR DISCLOSURES

Tao Huang, Gaofeng Yuan, Zhiguo Zhang, Zuquan Zou and Duo Li, no conflicts of interest.

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Review Article

Cardiovascular pathogenesis in hyperhomocysteinemia

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同型半胱氨酸血症引起心血管疾病的发病机制

血浆同型半胱氨酸升高是心血管疾病的独立危害因子。高同型半胱氨酸血症导致多种疾病发生的主要表现有：平滑肌细胞增殖、闭塞性血管病、动脉狭窄、止血能力的改变、胎盘血管病变、自发性早期流产、出生缺陷、认知能力受损和痴呆。该综述总共搜集了 1932 年到 2007 年间发表于 MEDLINE 以及其他杂志上的 112 篇文章，概述了血浆同型半胱氨酸的升高在心血管病以及其他疾病发生中的作用，同时阐述其在高同型半胱氨酸血症中的病理生理学分子机制。高同型半胱氨酸血症引起心血管疾病的病理生理学是一个复杂的过程，可能的机制是：同型半胱氨酸直接对组织的毒性作用、高 S-腺苷同型半胱氨酸、低 S-腺苷甲硫氨酸、通过刺激凝血因子和抑制抗凝血因子及血小板活性而引起的血栓形成，继而引起氧化应急、平滑肌细胞增殖、活性氧系列的形成、低甲基化、非折叠蛋白反应、细胞外基质改变。同型半胱氨酸增加心血管疾病危险的机制在某些方面仍然不是很清楚，有待更多的研究来解开这个谜底。

關鍵字：同型半胱氨酸、平滑肌细胞、氧化应急、致畸作用、促炎症反应。