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Review Article

Poor re-Methylation of Homocysteine and Trans-Methylation of Methionine: Cause and Effect of Hyper-Homocysteinemia: Which Role for Folic Acid and Vitamins B-6-12 Supplementation?

Federico Cacciapuoti*

Department of Internal Medicine, University of Campania "L. Vanvitelli", Italy

***Corresponding author**
Federico Cacciapuoti, Department of Internal Medicine, University of Campania "L. Vanvitelli", Naples, Italy, Tel: 39-081-566-5022; Email: federicocacciapuoti@gmail.com

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Abstract

Background: Increased homocysteine (Hcy) levels is a consequence of its reduced re-methylation to Methionine (Met) and a cause of insufficient substrates' trans-methylation of that, responsible of several and important functions of the human body.

Aims: In this report, we defined the causes and the mechanisms inducing a reduction of chemical reactions of re-methylation of Hcy to Met and trans-methylation of Met to substrates in the presence of increased Hcy serum concentration (HHcy).

Methods and results: The consequences of HHcy in reducing re-methylation of Hcy and these dependent from insufficient substrates' methylation represent the main causes of several diseases HHcy-related.

Conclusions: The detrimental effects consequent to increased Hcy concentration are obtained both for toxic effects of HHcy (re-methylation) and as consequence of reduced trans-methylation of substrates. Daily supplementation with folic acid and B6-12 vitamins, even through lowers elevated Hcy serum concentration, seems to not prevent secondary cardiovascular acute events, but it is important for primary and secondary prevention of neurologic and psychiatric detrimental events HHcy-related.

ABBREVIATIONS

Hcy: Homocysteine; Met: Methionine; HHcy: Hyper-homocysteine; MS: Methionine Synthase; MTHFR; Methylene-Tetra-Hydrofolate Reductase; TMG: Tri-Methylglycine; DMG: Di-Methylglycine; BHMT: Betaine Homocysteine Methyl Transferase; SAM: S-Adenosyl Methionine; CBS: Cysteine-Beta-Synthase; CGL: Cystathionine-Gamma-Lyase; ATP: Adenosine-Tri-Phosphate; SAH: S-Adenosyl Homocysteine; DNA: Desossi Nucleic Acid; RNA: Ribo Nucleic Acid; MTs: Methyl Transferases; SAHh: SAH Hydrolase; NDMA: N-D-Methyl-Aspartate; ADMA: Asymmetric Dimethylarginine; NO: Nitric Oxide

INTRODUCTION

Homocysteine (Hcy) is a sulfur-containing amino-acid, present in the serum as an intermediate metabolite of the Methionine (Met) cycle [1]. Met is an essential compound prevalently found in meat, sesame seeds, fish, and dairy products. Its deficiency is rare but, when present it may lead to reduced growth rate, along with liver damage and muscle loss. In addition, its deficiency can cause skin lesions and lethargy. Normally, Hcy is rapidly catabolized until its urinary metabolites, to prevent increased Hcy serum concentration [2]. But, an augmented value of plasma Hcy (HHcy) is a risk factor for atherosclerosis and some neuro-degenerative disease, cancer, early health aging, severe psoriasis and other diseases. On the subject, a level less than 13 μmol/L is considered normal; a level between 13 and 30 μml/L is considered mild or moderately elevated (prevalence in population<10%); a value from 31 to 100 μmol/L as intermediate (prevalence<1%) and >100 μmol/L as severe increase (prevalence<0.02%) [3]. HHcy may be induced by genetic and acquired causes. In Table 1 are reported the most frequent factors inducing HHcy.

Once synthetized, the further metabolization of Hcy happens by re-methylation to Met, coming through the enzyme methylenetetrahydrofolate reductase (MTHFR). Another pathway for re-methylation is the Betaine route. On the contrary, the catabolization of Hcy until its urinary products or

glutathione happens via trans-sulfuration pathway. Once re-methylated, a several chemical reactions begin, what conclude with the substrates' trans-methylation (Figure 1). But in HHcy-individuals, both re-methylation and trans-methylation reactions are impaired and can cause some several diseases both for direct toxic effects of Hcy and indirectly.

RE-METHYLATION

Hcy can be swallowed through its re-methylation to Met, by Methionine Synthase (MS). Precisely, this pathway involves the transfer of a methyl-group from 5-methyltetrahydrofolate (5-MTHF) to Hcy, to form Met. On the other hand, 5-MTHF synthesis is catalyzed by methylenetetrahydrofolate-reductase (MTHFR), which uses tetrahydrofolate (THF) as substrate. In turn, the methyl-group transfer from 5-MTHF to Hcy is catalyzed by MS, and requires vitamin $B_{12,}$ as cofactor, that is the precise role of vitamin B_{12} in the re-methylation pathway. Really, this is a leading pathway of Hcy swallow. In fact normally, about 50% of Hcy is remethylated to Met [4].

Among the causes of HHcy, apart from MTHFR deficiency, other numerous factors can be responsible. These include: poor diet, poor lifestyle, some drugs, chronic renal insufficiency, rheumatoid arthritis or poor thyroid function. HHcy is also associated with chronic inflammatory diseases, oestrogen deficiency or advancing age. But among all, the most frequent cause of inherited re-methylation deficiency to Met is the reduced activity of MTHFR enzyme, due to the MTHFR gene polymorphism. That leads to the impaired function or inactivation of this enzyme, which results in mildly elevated level of Hcy, especially in individuals who are also deficient in folate [5,6]. A common variant of the MTHFR gene is a C677T polymorphism, characterized by a cytosine (C) to thymine substitution at position 677. Another MTHFR gene-mutation concerns the gene at position 1298, where adenine (A) was replaced by cytosine (C) (A1298C). A third variant(less frequent) is MTHFR G1793A [7]. But, only two first gene's mutations usually are considered for inherited HHcy. These can be in: Homozygosis-when the same mutation (C677T or A1298C) was transferred by both parents. Heterozygosis-when one parent has transferred one mutation (C677 or A1298C), while the other has transferred a normal gene. Compound heterozygosis-when one parent has transferred one or two mutations and the other has transferred the other mutation, or vice versa. Patients with homozygous mutations tend to have more severe symptoms and health problems respect to heterozygosis patients. Referring to the prevalent damages induced by MTHFR mutations, several experiences showed that: MTHFR C677T mutations prevalently induces cardiovascular problems, elevated Hcy level, stroke, migraine, miscarriages and neural tube defects. On the contrary, MTHFR A1298C mutation is responsible of higher level of fibromyalgia, fatigue, chronic pain, depression of mood, schizophrenia, cancers, and hand tremor and memory loss. MTHFR G1793A was found to be associated with different tumoro-genesis [8]. It must be added that: the1298C mutation in MTHFR gene clearly reduces enzymatic activity of MTHFR (although to a lesser extent than the C677T), but its effect on plasma HHcy is less evident respect to C677T mutation [9]. On the contrary, the role of G1793A gene mutation in MTHFR activity in inducing HHcy appears uncertain too [10].

Betaine pathway

Another way for the conversion of Hcy back to Met (re-methylation) exists, and uses Betaine (coming from Choline) as methyl donor (folate independent re-methylation). Inversely to other metabolic pathways, that only happens in the human liver and in the kidneys [11]. Betaine is found in some microorganisms, plants and animals and is a component of many foods, including wheat, shellfish, spinach, and sugar beets. Betaine, also called

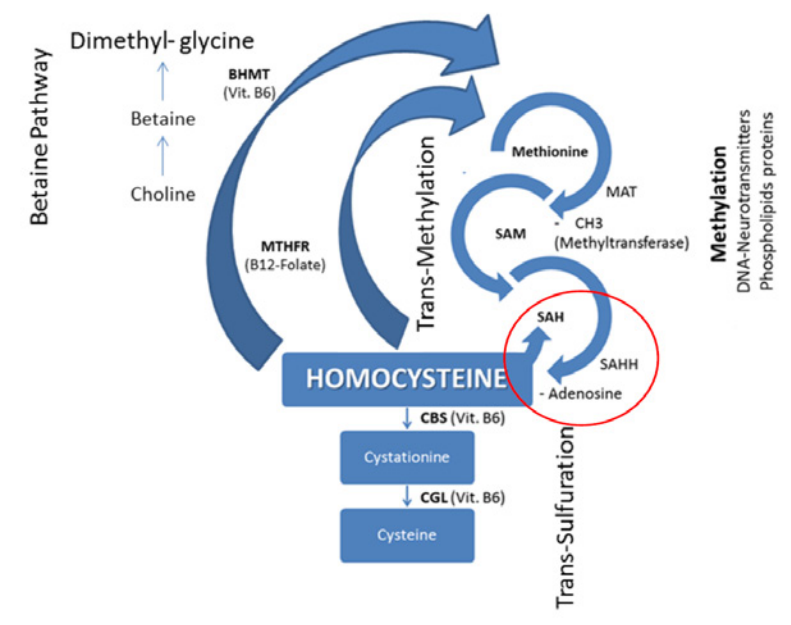

Figure 1 Pathways of homocysteine metabolism are summarized.

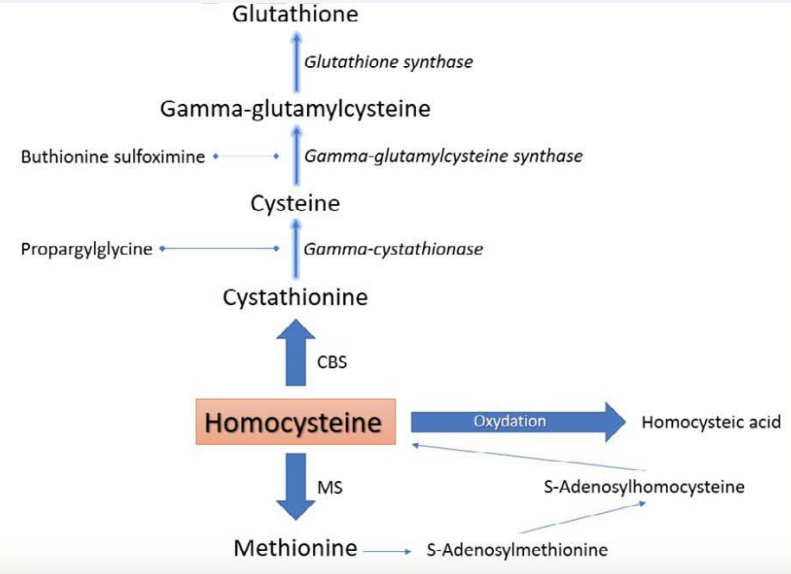

Figure 2 Detailed metabolic ways from cystathionine to glutathione are illustrated in vertical line. The oxidation of homocysteine to homocysteic acid (horizontal line) and the way of Met to Hcy through SAM and SAH are also briefly represented.

Table 1: Inherited and acquired causes of increase homocysteine serum levels
Genetic factors
Cysteine-ß-synthase deficiency
Methionine synthase deficiency
Methylenetetrahydrofolate reductase deficiency
Acquired factors
Deficiences in folate, vitamin B_6, vitamin B_{12}
End stage renal disease
Impaired renal function
Increased age
Hypotiroidism
Malignant diseases
Lifestyle factors
Chronic alcohol consumption
Excessive coffee consumption
Lack of exercise
Smoking
Some drugs
Certain anticonvulsvants
Metformin
Methotrexate
Nitrous oxide
Theophylline

trimethylglycine (TMG), transfers its methyl group (CH3) to Met, changing TMG in dimethylglycine (DMG). Betaine homocysteine methyl transferase (BHMT) is the enzyme that catalyzes the remethylation of Hcy to Met. Referring to the frequency of this route, it must be evidenced that more Betaine is used for Hcy removal in cases of HHcy induced by folate and vitamin B_{12} deprivation. On the contrary, a recent study demonstrated that a high Hcy level induces Betaine depletion [12]. Betaine treatment can reduce the elevated Hcy concentration via the Met cycle, normalizes low plasma Met, increases S-Adenosyl-Methionine (SAM) production, a main methyl donor of the body in transmethylation reaction, and leads to clinical improvement [13].

Trans-sulfuration

Besides the re-methylation reaction to Met, Hcy may be further catabolized until the final products of Met cycle, through the trans-sulfuration pathwyay. This requires vitamin B_6 as cofactor and happens through two steps. The first is catalyzed by the enzyme cysteine-beta-synthase (CBS), the second step is catalyzed by the enzyme cystationine-gamma-lyase (CGL) [14]. Transsulfuration drives to cysteine and taurine, as final urinary products (Figure 1). But, cysteine (in the presence of glutamate, gamma-glutamylcysteine synthase, and ATP) is converted into gamma-glutamylcysteine. In turn, this is changed in glutathione, via the enzyme glutathione synthase, in the presence of glycine and ATP (as source of energy) (Figure 2). The final product (glutathione) plays an important role in cellular anti-oxidant defense and detoxification reactions [15,16]. Contrarily, the oxidation of Hcy leads to homocysteic acid, an excitatory amino acid which binds to N-Methyl-D-Aspartate (NMDA) receptors. The normal function of NMDA receptor stimulates brain-plasticity, a cellular mechanism for learning and memory. On the contrary, when brain ages, the NMDA receptor system becomes progressively hypofunctional, contributing to decreases in memory and learning performance.

On the contrary to re-methylation pathway, less than 50% of Hcy is metabolized through this route. It must be also recorded that the reduced trans-sulfuration process is associated with homocystinuria, autism, cirrhosis, immune-dysfunction or pancreatitis [17]. The real importance of trans-sulfuration may simply be as a catabolic pathway in the destruction of Hcy, rather than an anabolic pathway involved in the production of cysteine [18].

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When re-methylation of Hcy and trans-sulfuration of Met are insufficient to reduce the increased intermediate compound (Hcy), this same accumulate causing a condition of HHcy. The sulfur containing amino acid can favour numerous diseases by direct, toxic effects of Hcy. The mechanisms include oxidative stress (through the production of reactive oxygen species), binding to nitric oxide, endothelial dysfunction, platelets' aggregation, production of homocysteinylated/acylated proteins, and indirectly, via accumulation of its precursor S-acetyl-homocysteine.

TRANS-METHYLATION

It is one of the most important chemical processes, in which a methyl-group (CH_3) is transferred from one compound to another. By transferring CH3 from Met to some substrates, trans-methylation of Met favours the synthesis of amino acids, proteins, neurotransmitters, enzymes, phospholipids, DNA, RNA in every cell and all tissues and organs of the body. It is a common process occurring in further hundred chemical reactions, necessary for normal body's working. The process is a fundamental mechanism for life, and useful for adequately respond to numerous environmental and internal stresses. Specifically, trans-methylation is a primary method of removing toxins from the body, attends to the synthesis of some neurotransmitters and/or phospholipids. In addition, it is involved in cardiovascular healthy, in hormonal regulation, reduces the tendency to cancer or inflammation, protects the body's telomeres, and is useful for other, several human functions]19].

Transmethylation becomes when Met reacts with Adenosine-Tri-Phosphate (ATP) synthetizing S-Adenosyl-Methionine (SAM). The following removal of CH3 from SAM and its transfer to substrates, forms S-Adenosyl-Homocysteine (SAH). The process is catalyzed by some enzymes, called Methyl-Transferases (MTs). In healthy individuals, a proportionate SAM/SAH ratio there is, whereas in the presence of inherited or acquired HHcy, this ratio is impaired for the prevalence of SAH on SAM [20]. But, SAH is a potent inhibitor of MTs, and consequently reduces trans-methylation reactions (favouring hypomethylation) [21,22]. In the presence of normal Hcy concentration, SAH is hydrolyzed in Hcy + Adenosine by SAH-hydrolase (SAHh). But when HHcy there is, the reaction: SAH=Hcy + Adenosine develops in the opposite direction. In fact, the chemical reaction (Figure 1-red circle) is reversible so, Hcy in excess reacts with Adenosine, synthetizing SAH.

CONCLUSIVE REMARKS

Most cells of the body are able to perform Hcy-remethylation and Met-transmethylation. As assessed, two types of reactions are inestricably linked by folate, vitamin B_6, vitamin B_{12}, Betaine and methyl groups. But, the most important compound of these is folate [23]. Concerning that, it was demonstrated that folic acid treatment increases both Hcy-re-methylation and Met-trans-methylation in healthy subjects [24]. With regard to this topic, daily supplementation with folic acid has been shown to lower the plasma Hcy level by approximately 25% and, adding vitamin B_{12}, further lowers the level of approximately 7%, indicating that B vitamins supplement lowers Hcy levels significantly [25].

It is known that elevated plasma Hcy levels are associated with numerous pathologies, as birth defects, atherosclerosis, thrombosis, Alzheimer and Parkinson diseases, diabetes, depression of mood, and other diseases [26,27]. Obviously, folic acid and B vitamins supplementation, lowering total plasma HHcy, should reduce the incidence of these same. But unfortunately, most clinical trials referring to cardiovascular complications, as stroke, non fatal acute myocardial infarction, and peripheral vascular disease [28-32] failed to show a significant benefit of vitamins $B_{6\text{-}12}$ and folic acid supplementation in the secondary prevention of these disorders [33]. The causes of this behaviour are unknown, but could only reported to mildly elevated Hcy levels, whereas other factors contemporary present could be interfere too [33]. It must also added that, although folate and vitamins $B_{6\text{-}12}$ supplementation lowers Hcy levels, they may simultaneously increase atherosclerotic risk and therefore, other events through different mechanisms (Hcy-independent). Specifically, Loscalzo postulated that folic acid and vitamins $B_{6\text{-}12}$ supplementation could promote secondary atherosclerotic events by increasing cell proliferation in atherosclerotic plaques (enhancing DNA-methylation) and/or augmenting levels of asymmetric-dimethylarginine (ADMA) [34,35]. Differently from secondary cardiovascular complications, some neuro-psychiatric derangements in HHcy-individuals could to be prevented by supplementation with folic acid and $B_{6\text{-}12}$ [36-38]. This prevention especially is required in subjects with a low intake or status of the vitamin B_{12} [39]. The reasons of this different behavior are unknown and future experiences are need in this area.

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