A Study of Pathophysiology of Homocysteine in Causing Acute Myocardial Infarction: A Study in a Rural Medical College of Himachal Pradesh

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Abstract: Homocysteine, sulfhydryl group containing amino acid, is intermediate product during metabolism of the amino acids methionine and cysteine. Homocysteine is nonprotein amino acid which behaves as both a substrate and product of methionine. Homocysteine has key role in methylation cycle, within which a methyl group is transferred to a different substrate Formed homocysteine can be utilized in two ways: 1) homocysteine can be remethylated to methionine by catalytic activity of the enzyme N5, N10-methylenetetrahydrofolate reductase; 2) homocysteine can be converted to cysteine in a reaction that is catalyzed by cystathionine β-synthase (CBS). In this article, we tend to describe the pathophysiology of homocysteine in causing acute myocardial infarction.

Keywords: Metabolism, Homocysteine, Pathophysiology, Acute Myocardial Infarction.

INTRODUCTION

Metabolic Fate of Homocysteine and Related Compounds

Methionine is an essential amino acid, whose quantity in the body depends exclusively on the diet. Metabolic importance of methionine is reflected in the large number of transmethylation reactions, which result in transfer of one carbon methyl group to various substrates (DNA, RNA, proteins, phospholipids, polysaccharides, catecholamine, choline) during the methionine cycle. Methionine is also source in synthesis of other sulfur-containing compounds (cysteine and taurine). Taking into account the limitation of dietary supply of methionine, it should be paid attention on importance of methionine synthesis by remethylation of homocysteine.

During the methionine cycle, the first step is conversion of methionine to S-adenosylmethionine (SAM), in reaction regulated by ATP and enzyme methionine adenosyltransferase (MAT). Methyl groups can be transferred from SAM to various substrate molecules in reaction catalyzed by various methyltransferases. During these reactions SAM is transformed into S-adenosylhomocysteine (SAH). SAH is then hydrolyzed to adenosine and homocysteine in reversible reaction regulated enzyme SAH hydrolase. This point has a key role in the further direction of homocysteine metabolism - remethylation or transsulfuration.

Homocysteine undergo the remethylation process in case of methionine deficiency. This metabolic pathway requires folic acid as donor of methyl groups for methionine restoration (Pizzolo et al., 2011). Remethylation is catalyzed by methionine synthase (MS), enzyme that uses vitamin B12 (cobalamin) as cofactor and 5-methyltetrahydrofolate (5-MTHF) as methyl group donor. In this reaction methyl group is transferred from 5-MTHF to homocysteine, resulting in forming new methionine, which can be used for protein synthesis or converted to SAH, again.

Transsulfuration pathway occurs if methionine is present in sufficient amount. The crucial enzyme in this metabolic pathway of homocysteine is cystathionine β-synthase (CBS), enzyme that requires vitamin B6 as cofactor, and catalyzes reaction of serine and homocysteine to form cystathionine. In next step cystathionine is hydrolyzed by γ-cystathionase.
(CTH) (also requires vitamin B6) to cysteine and a-ketobutyrate. Some studies showed that exercise can affect the homocysteine metabolism by transsulfuration pathway and decrease homocysteine accumulation and oxidative stress.

If there is impairment of remethylation and/or transsulfuration pathway, homocysteine will accumulate in cells, and in these cases of increasing concentrations of homocysteine, it can be converted to more toxic metabolite homocysteine-thiolactone. Enzyme that catalyzes this reaction in all types of cells is methionyl-tRNA synthetase (MetRS), and this conversion takes place in two phases. The first phase involves the activation of carboxyl group of homocysteine by ATP and formation of MetRS-bound homocysteinyl adenylyl. During the second phase the side chain thiolate displaces the AMP group from the activated carboxyl group of homocysteine, forming homocysteine thiolactone.

Homocysteine thiolactone, as a highly reactive compound can acylate amino groups of large number of proteins, forming homocysteinyl groups linked by peptide bonds to proteins, and thus causing the changes in their activity. On the other hand, homocysteine thiolactone can be hydrolyzed by action of calcium dependent enzyme, serum homocysteine thiolactonase, to homocysteine.

In human plasma homocysteine is present in various forms, most of it is bound by disulfide bonds to plasma proteins, mainly albumins (around 70%). Approximately 20–30% of plasma homocysteine forms homocysteine dimers or forms dimers with other thios, and less then 2% is present as free thiol. Thus in most of the investigations it was determined total plasma homocysteine, which includes all the above mentioned forms of homocysteine.

**Basic Mechanisms in Development of Hyperhomocysteinemia**

Numerous factors can affect the total plasma homocysteine (tHcy) levels in human plasma, such as gender (woman have lower tHcy than men), nutrition habits (diet deficient in folate, vitamin B6 and B12 leads to increment of tHcy), lifestyle habits (smoking, alcohol consumption, sedentary way of living).

Hyperhomocysteinemia is a condition characterized by increased values of total plasma homocysteine (tHcy) levels in human plasma, above 15 μmol/L. Depending on the value of tHcy, hyperhomocysteinemia is classified as mild (tHcy is between 16-30 μmol/L), intermediate (tHcy is between 31-100 μmol/L) and severe (tHcy above 100 μmol/L). There are also extremely grave forms of hyperhomocysteinemia accompanied by the appearance of homocysteine in the urine (homocysteinuria), when tHcy are even greater than 500 μmol/L.

Hyperhomocysteinemia is caused by imbalance in processes and factors involved in the metabolism of homocysteine. Hyperhomocysteinemia can result from four main disorders: 1) genetic abnormalities of enzymes involved in homocysteine metabolism, 2) nutritional deficiencies in folate, vitamin B6 and vitamin B12, 3) methionine rich diet, and 4) decreased renal function. Two enzymes and three vitamins play a key role in the regulation of circulating homocysteine levels.

The deficiency in enzymes involved homocysteine metabolism (5,10-methylene tetrahydrofolate reductase (MTHFR), methionine synthase (MS), and cystathionine-β-synthase (CBS)) are rare cause of hyperhomocysteinemia, but can cause the most severe forms of this condition. The most common disorder of enzymes involved in homocysteine metabolism probably is polymorphism of gene coding for the MTHFR (C-to-T substitution at nucleotide 677, and subsequent substitution of Val with Ala), causing the production of thermo labile variant of enzyme. MTHFR catalyzes the reduction of 5,10- methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF), in a NADPH-dependent reaction. Although this disorder usually causes mild to moderate hyperhomocysteinemia, the results of recent studies indicate the relationship of MTHFR polymorphism with other diseases. Other mutations of MTHFR gene can cause much more severe forms of hyperhomocysteinemia and consequent disorders. MS plays central role in methionine cycle and folate metabolism. This enzyme catalyze transfer of methyl group from 5-MTHF to homocysteine resulting in regeneration of methionine. Decrement in MS activity will also cause the decrease in SAM content, which acts as methyl group donor for large number of compounds, including DNA, RNA, and proteins. On the other hand decrease of SAM level will increase production of 5-MTHF, whereby MS is only enzyme in mammalian cells that can utilize 5-MTHF, which results in accumulation of 5-MTHF and trapping of folate in this form in cells. The most common genetic cause of severe hyperhomocysteinemia is CBS deficiency, which can result in 40-fold increase of tHcy and homocysteinuria in homozygous. CBS catalyses the formation of cystathionine from homocysteine and serine during transsulfuration pathway of homocysteine metabolism. Inhibition of CBS activity cause increase of methionine production, and subsequent increase level of SAM. Increased SAM content will decrease activity of MTHFR by feedback mechanism, thereby inhibiting remethylation pathway also.

Hyperhomocysteinemia can also occur due to dietary insufficient intake of folate (vitamin B9), vitamin B12 and vitamin B6. These vitamins act as cofactors of enzymes included in homocysteine metabolism, and their blood levels are inversely correlated to tHcy. Because of that many disorders accompanied with hyperhomocysteinemia are treated with B
vitamins complex.\textsuperscript{xviii} Beside the role in maintaining of the methylation reactions, folate have crucial role in growth and cell division, which is of particular importance during fetal development.\textsuperscript{xix} Even in acute application, folic acid exhibit favorable impact on heart and coronary circulation by increasing the outflow of NO, and reducing the production of free radicals.\textsuperscript{xvi} Deficiency of folate in pregnancy leads to neural tube defects and other developmental defects\textsuperscript{xvii}. Additionally occurs mild to moderate hyperhomocysteinemia, which is also associated with a range of disorders. Vitamin B\textsubscript{12} acts as cofactor for MS, and its deficiency causes impairment of remethylation of homocysteine, hyperhomocysteinemia and stockpiling of 5-MTHF.\textsuperscript{xviii} Vitamin B\textsubscript{6} deficiency is related to impairment of CBS function, considering that act as cofactor of this enzyme.\textsuperscript{xviii}

The high methionine intake by diet will cause the increase of tHcy level in plasma considering that half of methionine taken by food is converted to homocysteine\textsuperscript{xvii}. Thus the excessive dietary intake of groceries rich in methionine (meat, fish) can cause hyperhomocysteinemia. On the other hand, vegetarians can also develop hyperhomocysteinemia due to reduced intake of vitamin B\textsubscript{12}.\textsuperscript{xvi}

**CONCLUSION**

Kidney is organ that has central role in metabolism of homocysteine, because it contains all metabolizing enzymes: MS, CBS and CTH. Rise in values of tHcy is observed in early stages of renal failure, and during progression of the disease the values of tHcy increase.\textsuperscript{xx} The hyperhomocysteinemia in patients with terminal phases of renal failure (dialysed patients) could be the consequence of several causes: the decreased renal excretion of homocysteine due to impaired renal function, disturbance in homocysteine metabolism, alimentary deficiency in vitamins included in homocysteine metabolism, and undiagnosed genetic abnormalities of metabolizing enzymes.\textsuperscript{xxv} Increased tHcy levels can also be increased due to drugs that interfere to metabolic pathways of folate, vitamin B\textsubscript{6} and vitamin B\textsubscript{12}.

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