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Chapter 1

Introductory Chapter: General Aspects Regarding Homocysteine

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http://dx.doi.org/10.5772/intechopen.81306

1. Historical aspect

The first description of homocysteine (Hcy), a non-proteinogenic amino acid, was introduced within a case study in 1932. The first patient was an 8-year-old child with a mental retardation disorder who died of a myocardial infarction. Meanwhile, research continued; in 1969, Dr. Kilmer McCully was the first to describe the vascular pathology in patients with homocystinuria associated with hemodynamic changes, progressive arterial stenosis, and proliferation of smooth muscle cells. He also noted that homocysteine may have a causal role in any metabolic abnormality. This idea is the basis of his theory that a moderately elevated level of homocysteine is an important risk factor for cardiovascular disease. His theory was sustained only in 1976 through a clinical trial demonstrating an increase in coronary artery disease in people with hyperhomocysteinemia. Since then, a particular interest has been given to studying this relationship.

2. Homocysteine metabolism

Homocysteine metabolism is at the crossroads of several pathways and is itself a product of the de novo pathway of the methionine metabolic reactions catalyzed by S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH).

Homocysteine can be remethylated to methionine via the cobalamin-dependent and cobalamin-independent pathways or can be metabolized to cysteine and other metabolites via transsulfuration pathway [1]. The following enzymes are involved in the homocysteine metabolism: methionine synthase (MS), methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS), methionine synthase reductase (MTRR), and betaine-homocysteine S-methyltransferase (BHMT).

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In remethylation, homocysteine (Hcy) can be converted back to methionine in the remethylation pathway via 5-methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS). In the transsulfuration pathway, Hcy is condensed with serine to form cystathionine via vitamin B6-dependent cystathionine β-synthase (CBS).

For proper function MS requires methylcobalamin (vitamin B12) and methionine synthase reductase (MTRR) [2]. Without MTRR, MS does not convert homocysteine into methionine.

MTHFR regulates the partitioning of folate-activated one-carbon units between the folate-dependent de novo thymidylate and homocysteine remethylation pathways. MTHFR converts 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate (5-MTHF) required for the reaction of remethylation of homocysteine and away from thymidine synthesis. 5-Methyltetrahydrofolate acts as a substrate with vitamin B12 and S-adenosylmethionine serving as cofactors for methionine synthase. The functionality of methionine synthase is maintained by methionine synthase reductase, which catalyzes the reductive reactivation of inactive MS bound to oxidized cobalamin to maintain its active form using S-adenosylmethionine (SAM). Polymorphisms in MS and MTHFR were suggested to act independently to elevate Hcy concentrations by compromising different parts of the pathway that might not interact directly with one another [3].

The genetic variations of MTHFR have been reported to be associated with the gene deficiency and associated with susceptibility to occlusive vascular disease, neural tube defects, Alzheimer's disease, and other forms of dementia [4, 5]. In a study, C677T polymorphism in MTHFR was shown to associate with higher plasma homocysteine and the risk of brain atrophy and brain volume deficit [6]. The mutation of MTHFR results in reduced enzymatic activity and consequently accumulation of homocysteine. Plasma concentrations of folate, B12, and 5-MTHF were reduced in elderly (over 65 years old) patients with dementia [7]. There was no difference found in DNA methylation between demented patients and age-corresponding controls. However, changes in DNA methylation correlated with the folate status. Two single nucleotide polymorphisms (C677T and A1298C) in the methylenetetrahydrofolate (MTHFR) gene are important genetic predictors of Hcy level [8].

It was reported that deficit of B12, B6, and folate can lead to cognitive deficit. High level of homocysteine was observed in B12 deficiency even when the level of folate was sufficient. Only concurrent supplementation of B vitamins and folic acid has been efficient in diminishing the level of Hcy [9].

Methionine is first converted to S-adenosylmethionine, which can lose its methyl group to form S-adenosylhomocysteine (adoHcy). This demethylated product is hydrolyzed to free homocysteine which undergoes a reaction with serine, catalyzed by cystathionine β-synthase, to yield cystathionine. CBS catalyzes the pyridoxal phosphate-dependent conversion of homocysteine to cystathionine. In the animal model, it was shown that during aging the expression of CBS was not changed, whereas activity significantly decreased [10]. Subsequently, the decline in CBS activity due to nitration was attributed to observed elevated level of Hcy. High Hcy levels results from diet with an excess of methionine. In mice models it was shown that high methionine diet brings up the level of homocysteine in Cbs (+/+) and Cbs (+/−) [11].

3. Hyperhomocysteinemia and diseases

The following forms of homocysteine can be found in the plasma:

1. Free Hcy
2. Protein-bound Hcy (S-linked and N-linked)
3. Oxidized forms of Hcy
4. Hcy-thiolactone [1]

Hyperhomocysteinemia (HHcy) may arise from genetic defects of enzymes involved in homocysteine metabolism. There are numerous factors that influence Hcy level like age, gender, cigarette smoking, coffee and alcohol intake, and polymorphisms in genes encoding enzymes acting in one-carbon metabolism.

Hyperhomocysteinemia is defined when plasma level is more than 15 μmol/L [1]. Total concentration of homocysteine in plasma of healthy humans is low, and its level is between 5.0 and 15.0 μmol/L. Several types of HHcy are classified in relation to the total Hcy concentration: moderate (16–30 μM), intermediate (31–100 μM), and severe (higher than 100 μM) [12].

Hcy level associates with all-cause mortality risk in a linear fashion, and the risk of mortality increases for each 5 μmol/L Hcy by 33.6% [13]. In patients with heart failure, the level of Hcy reached 17.8 ± 0.7 μmol/L; Hcy reached the highest level of 20.2 ± 1.5 μmol/L in patients with cognitive impairment. Hcy exerts multiple neurotoxic mechanisms that are relevant in the development of neurodegenerative diseases such as Alzheimer's disease [14]. Hcy at the concentration over 30 μM associates with cognitive dysfunction [15]. The prevalence of hyperhomocysteinemia was significant in patients with hypertension and ischemic heart disease. Chronic hyperhomocysteinemia causes vascular remodeling by instigating vein phenotype in the artery, thus leading to cerebrovascular and vascular dysfunctions. Interestingly, a large proportion of vegetarians develop hyperhomocysteinemia and serum vitamin B12 deficiency [16]. Positive association was reported between Hcy level and physical inactivity.

A high Hcy level associates with an increased reactive oxygen species (ROS) production in the elderly [17–19]. Hcy exerts neurotoxicity by suppressing activities of Na+/K+ ATPase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) and diminishing glutathione content. Redox balance disruptions and excessively generated ROS promote neuronal death in the cerebral cortex. Homocysteine (Hcy) toxicity is mediated by the posttranslational modification of proteins by its metabolite, homocysteine thiolactone (HTL). It was shown that HTL-modified cytochrome c causes conversion of the hexa-coordinate cytochrome c to a penta-coordinate species and conformational alterations affecting the packing of the apolar groups. Such changes lead to the reduction of the heme moiety and activation of peroxidase-like function of cytochrome c [20].

Clinically the measurement of homocysteine is considered important to diagnose homocystinuria to identify individuals with the risk of developing cobalamin or folate deficiency states

and to assess the risk factor for young cardiovascular disease (CVD) patients (<4 years). In known cases of CVD, high homocysteine levels should be used as a prognostic marker for CVD events and mortality. Increased homocysteine levels with low vitamin concentrations should be handled as potential vitamin deficiency state. Supplementation of diets with folic acid, cobalamin, and pyridoxine appears to provide protection by lowering homocysteine levels in the blood.

The homocysteine level increases with an increasing age and is generally higher in males as compared to females. Homocysteine has been suggested to be a risk factor for fracture, but the causal relationship is not yet clear [21]. Homocysteine levels can be taken as an early indicator for the detection of cardiovascular diseases as the Hcy level increases after a myocardial infarction or stroke. No clear cut data is available that rules out homocysteine as a marker for heart disease.

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