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Modern View on the Role of Hyperhomocysteinemia in Cognitive Dysfunction

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Abstract: Homocysteine is an amino acid produced by methionine metabolism, a process dependent on B vitamins, cobalamin, vitamin B6 and folic acid. There is evidence that elevated serum homocysteine levels are associated with cognitive decline and dementia. We review these data in addition to potential mechanisms by which homocysteine acts in the brain to cause cognitive dysfunction, homocysteine metabolism, and factors associated with altering normal metabolism.

Key words: C-reactive protein, hyperhomocysteinemia, cognitive impairment, homocysteine.

Relevance. Homocysteine, a sulfur-containing amino acid, is a metabolite of the essential amino acid methionine and exists at a critical biochemical crossroads of the methionine cycle - between S-adenosylmethionine, an essential ubiquitous methyl donor, and vitamins B12 and folic acid. High levels of homocysteine in the blood signal a disruption of this vital process, which leads to far-reaching biochemical and life-long consequences. The association between homocysteine and cardiovascular disease is well established, and reducing total plasma homocysteine levels by providing dietary cofactors for its metabolism has been shown to reduce the risk of cardiovascular events. Information is emerging on the relationship between homocysteine metabolism and cognitive function, ranging from mild cognitive decline (age-related memory loss) to vascular dementia and Alzheimer's disease. Significant deficiencies of the homocysteine remethylation cofactors cobalamin (B12) and folate, as well as the transsulfuration cofactor vitamin B6, are commonly observed in older adults, resulting in increased homocysteine levels with age. Hyperhomocysteinemia has been shown to be an independent risk factor for cognitive dysfunction. Indirect and direct vascular damage can be caused by homocysteine, which is involved in vascular dementia, with an increased risk of multiple cerebral infarctions and dementia as homocysteine levels increase. A significant correlation was found between the risk of Alzheimer's disease and high plasma homocysteine levels, as well as low levels of folic acid and vitamins B6 and B12. All of these disease associations are thought to be interconnected through increases in homocysteine and S-adenosylhomocysteine levels and subsequent hypomethylation of numerous substances, including DNA and proteins, that make vascular structures and neurons more susceptible to injury and apoptosis. Providing nutritional cofactors for proper functioning of the methionine cycle may improve methylation and protect the brain from damage. Further research is needed to evaluate whether this will reduce the risk of cognitive illness and/or improve cognitive functioning.

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine

and cysteine [1]. Methionine, which is part of natural food proteins, is metabolized in the human body by demethylation with the formation of S - adenosylhomocysteine into homocysteine [8]. The reaction of methionine demethylation is reversible: for example, in the liver, homocysteine is remethylated with the participation of the enzyme homocysteine methyltransferase. In this case, betaine acts as a methyl group donor [33]. Another possible way of homocysteine remethylation under the action of methionine synthetase. This reaction is impossible with a lack of vitamin B12, which is a coenzyme of methionine synthetase. The donor of the methyl group in this case is 5-methylenetetrahydrofolic acid, a coenzyme form of the known antianemic vitamin factor [32]. With a lack of folic acid or vitamin B12, one of the main pathways for homocysteine metabolism can be blocked, leading to hyperhomocysteinemia. Homocysteine can also be catabolized during transsulfuration by conversion to cysteine through cystathionine with the participation of the enzyme cystathionine beta synthetase [14], the coenzyme being vitamin B6 [21]. The products of further transformation of cysteine and methionine are excreted by the kidneys. The basic principles of regulation of homocysteine distribution between the competing remethylation and transsulfuration pathways are described in detail in a series of papers by Finkelstein et al. (2018) [15]. Normally, the level of homocysteine in blood plasma is 5-15 μmol/l [16]. During life, the average level increases by 3-5 μmol/l. This is due to the deterioration of kidney function and other physiological reactions affecting metabolic processes in the body. At the age of 40–42 years, the difference in homocysteine concentrations between men and women is approximately 2 μmol/L, with average values of approximately 11 and 9 μmol/L, respectively [28]. Gender differences are due to greater muscle mass in men, since its formation is accompanied by the synthesis of homocysteine in connection with the formation of creatine and creatinine [21]. This may also be a consequence of the action of sex hormones (Andersson et al., 2022), which was confirmed in a study of male and female transsexuals [22]. According to some researchers, a significant negative correlation has been identified between the concentrations of estradiol and homocysteine in postmenopausal women. In women before menopause, the risk of developing cardiovascular diseases is low, but it is also associated with the level of homocysteine in the blood plasma (Jacques P.F. et al., 2019). When the level of homocysteine increases by more than 15 μmol/l, moderate hyperhomocysteinemia is diagnosed; more than 30 μmol/l – moderate; more than 100 μmol/l – severe hyperhomocysteinemia [14]. Up to 10% of the population has mild, approximately 1% moderate, and 0.02% severe hyperhomocysteinemia, depending on the population (Nygard et al., 2015). In blood plasma, homocysteine exists in four forms: about 1% circulates in the free reduced form, 70-80% in the form bound to albumin, and the remaining 20-30% in the form of disulfides [9]. The term “total plasma homocysteine” usually refers to the combination of all possible forms of homocysteine. Diagnosis of hyperhomocysteinemia is carried out by two main methods: chromatography and enzyme immunoassay. The classic method for determining homocysteine concentration is high-performance liquid chromatography or gas chromatography with mass spectrometry. These are highly sensitive and reliable detection methods, the coefficient of variation is less than 5% (DS30 chromatograph) [15, 16]. At the present stage, due to the need to screen a large number of patients, the enzyme immunoassay method has become the most widely used as a routine clinical and laboratory analysis of homocysteine levels in the blood [19]. Its essence lies in the fact that protein-bound homocysteine is reduced to free and converted into S-adenosylhomocysteine by an enzymatic process, followed by an immunoassay procedure [17]. For differential diagnosis of various forms of hyperhomocysteinemia and detection of hidden metabolic disorders, stress tests with methionine are used. It is most preferable to use this provoking research method in individuals with the presence of other risk factors for cardiovascular

pathology [20]. For this purpose, methionine is administered orally (0.1 g per 1 kg of body weight), and after 4-6 hours the level of homocysteine in the blood is re-determined. In addition, to identify the causes of hyperhomocysteinemia, DNA is used to diagnose hereditary defects in enzymes involved in the metabolism of methionine and folic acid, in particular methylenetetrahydrofolate reductase, and to determine the level of vitamins B6, B12 and folic acid in the blood [5]. To date, many factors have been described that influence the concentration of homocysteine in the blood. The main reasons are changes in the activity of enzymes that ensure metabolic processes, as well as a decrease in the functional capacity of the kidneys, which contributes to impaired excretion of homocysteine from the body in the urine [17]. A decrease in enzyme activity is, for the most part, due to hereditary defects - fermentopathies. Congenital homocysteinuria in combination with hyperhomocysteinemia, occurring in 1 case per 100,000 live births, develops in homozygotes due to deficiency of cystathionine beta synthetase [21]. This disease is inherited in an autosomal recessive manner, clinically manifested by lens dislocation and other eye anomalies, mental retardation (in 50% of cases), and skeletal deformities. Approximately 50% of homozygotes who do not receive treatment develop coronary artery disease and/or cerebrovascular accidents by age 30. In heterozygous forms, which occur in the general population with a frequency of 1 in 150, most often there is no development of hyperhomocysteinemia and any manifestations of cardiovascular pathology [20]. Methionine synthetase deficiency and impairment of its activity associated with hereditary defects are one of the rarest genetically determined causes of hyperhomocysteinemia [30]. On the contrary, the most common fermentopathy leading to increased homocysteine concentrations in the blood is a point mutation in the methylenetetrahydrofolate reductase gene. This mutation leads to the formation of a thermolabile variant of the enzyme, which has half the activity compared to the normal type [22]. The homozygous variant of this mutation (TT genotype) occurs in 10-13% of representatives of the white race and causes an increase in the level of homocysteine in the blood (by an average of 50%) in case of insufficient intake of folate from food [23]. Nutritional factors play a significant role in the development of hyperhomocysteinemia. A diet low in folic acid and vitamins B6 and B12 can lead to a blockade of the corresponding metabolic pathways. Up to 2/3 of all cases of hyperhomocysteinemia are associated with a deficiency of one or more of the above substances [30]. The most important among the vitamins involved in metabolic processes is folic acid. Folate is a direct donor of methyl groups for the conversion of homocysteine to methionine. Vitamins B6 and B12, on the contrary, are not consumed during metabolism, but function only as cofactors. In a meta-analysis of 12 randomized trials, folate intake resulted in a reduction in homocysteine levels (an average of 25%) when folic acid supplementation ranged from 500 to 5000 mcg per day, independent of other dietary and lifestyle factors. This degree of reduction occurred with an average initial homocysteine concentration of 12 μmol/l. At the same time, higher values of initial indicators were accompanied by an even greater decrease [24]. Vitamin B12 supplementation at 500 mcg resulted in an additional 7% reduction in homocysteine levels (Bostom et al, 2015). The concentration of homocysteine in the blood is influenced by coffee consumption [13]. Caffeine can inhibit methionine synthetase [14]. As a result of a survey of 16,000 people, it was found that among men 40-42 years old who drink more than 6 cups of strong coffee per day, the concentration of homocysteine in the blood is 19% higher than among non-drinkers. In women, this difference is even greater – it reaches 28% (Nygard O. et al., 2017). People who drink a lot of coffee tend to smoke more and eat less fresh vegetables and fruits, which may contribute to even higher levels of homocysteine in the blood. However, after controlling for such confounding differences between study groups, the association between high coffee consumption and increased

homocysteine levels was stronger [15]. A high correlation between the amount of coffee consumed and plasma homocysteine levels was established in the Framingham study (Jacques P.F. et al, 2021). Among the factors predisposing to hyperhomocysteinemia, it should be noted drug use, as well as psycho-emotional stress [16]. An increase in homocysteine levels was found in individuals leading a sedentary lifestyle. Daily physical exercise, on the contrary, helps normalize homocysteine levels [20]. A study of the role of hyperhomocysteinemia in the formation of psychological factors associated with the risk of cardiovascular diseases showed that there is a strong positive correlation between hostility, anger and blood homocysteine levels in men. This appears to be one of the first studies of the relationship between hyperhomocysteinemia and psychological risk factors for cardiovascular disease, indicating the possible existence of a mechanism that explains the increase in cardiovascular risk with hostility and anger. Smoking causes a decrease in the blood levels of vitamins B6 and B12 due to the effect of cyanide contained in cigarette smoke on the metabolism of these vitamins [27]. Smoking is one of the strongest lifestyle factors affecting homocysteine levels. The number of cigarettes smoked per day is directly related to the concentration of homocysteine in the blood [20]. A study conducted in Norway found that each cigarette smoked per day increased homocysteine levels by 1% in women and by 0.5% in men [18]. In people suffering from chronic alcoholism, the level of homocysteine in the blood plasma is almost twice as high as in non-drinkers. This is due to the fact that in patients with alcoholism the content of vitamin B6 in the blood plasma and folate in erythrocytes is significantly reduced, which may be the cause of impaired transmethylation and transsulfuration [19]. In addition, ethanol inhibits the activity of methionine synthetase in the liver, thereby increasing the concentration of homocysteine in the blood plasma [10]. The use of certain medications leads to a transient increase in homocysteine levels: nitrous oxide during anesthesia inhibits methionine synthetase [15]; methylprednisolone reduces the concentration of vitamin B6 [20], estrogen-containing contraceptives [11], anticonvulsants disrupt the metabolism of folic acid in the liver [12, 13], theophyllines, competitive inhibitors of phosphodiesterase, cause a decrease in the metabolism of vitamin B6 [16]. Homocysteine metabolism may be significantly affected by impaired renal function [17]. In patients with chronic renal failure, mortality from cardiovascular diseases is increased, which may be due to a decrease in the excretion of creatinine and homocysteine, impaired oxidation of homocysteine to CO2 and sulfates in kidney cells, and an increase in folate excretion, which leads to hyperhomocysteinemia [18]. Proliferative diseases such as psoriasis, systemic lupus erythematosus, lymphoblastic leukemia, breast, ovarian, and pancreatic cancer are accompanied by an increase in the concentration of homocysteine in the blood. Due to the presence of a large number of dividing cells in the body, which consume a huge number of methyl groups, homocysteine metabolism is disrupted [14]. Diseases accompanied by hyperhomocysteinemia include ulcerative colitis, Crohn's disease, celiac disease, enteritis, gastritis, and peptic ulcer. Such pathological conditions are accompanied by a decrease in the absorption of vitamins B6, B12, and folic acid [19].

An effective means of reducing homocysteine levels are supplements of folic acid and vitamins B6 and B12 [37]. Due to the ability of folic acid to lower homocysteine levels, several studies have assessed the effect of folic acid supplementation on various indicators of vascular damage, most notably endothelial dysfunction [12]. Overall, these studies suggest that folic acid supplementation (5-10 mg/day) improves or restores endothelium-dependent vasodilation and may reduce the likelihood of thrombosis by reducing coagulation factor levels in healthy individuals and in patients with high homocysteine concentrations. The observed improvements may be explained by a decrease in homocysteine levels. However, in one study, administration of 5-

methyltetrahydrofolate, a natural form of folic acid, improved endothelial function without affecting hyperhomocysteinemia [13]. The independent positive effect of 5-methylenetetrahydrofolate on endothelial function in diabetic rats was also recently demonstrated in a number of studies [14]. The potential mechanism explaining the beneficial effects of folic acid on endothelial function, independent of homocysteine, remains to be elucidated. It has been suggested that the antioxidant effect may be important [15].

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