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METABOLIC DISORDERS OF FOLATE CASCADE PROCESS

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Abstract
The folate cycle is a cascade process of converting folic acid into a derivative available for absorption by the body, 5-methyltetrahydrofolate. The process is controlled by the enzyme methylenetetrahydrofolate reductase (MTHFR). Folate metabolism is a source of one-carbon fragments (methyl group -CH3) for vital cellular processes: purine nucleotide biosynthesis and conversion of uridine monophosphate into thymidylate; DNA and RNA methylation.

Keywords: folate cycle, vitamin B12, methionine synthases, DNA and RNA.

Introduction

Associated with the folate cycle is the cycle of methionine formation from homocysteine, which occurs with the participation of vitamin B12 and two enzymes: methionine synthase (MTR) and methionine synthase reductase (MTRR). The methyl group in the reduction of 5-methyltetrahydrofolate to tetrahydrofolate is transferred to vitamin B12, which then gives it to homocysteine, forming methionine with the help of the enzyme methionine synthase reductase (MTR). However, in some cases, B12 can be oxidised, leading to inhibition of methionine synthase [1,3,5,7,9]. The enzyme requires reductive methylation by the enzyme methionine synthase reductase (MTRR) to maintain its activity. Methionine in turn enters the methylation cycle: under the action of methionine adenosyltransferase, S-adenosylmethionine (SAM) is formed from it, which is used by methyltransferases as a universal methyl donor. Disorders of folate metabolism affect DNA stability in two major ways. The first relates to de novo synthesis of nucleotides. Low levels of 5,10-methylenetetrahydrofolate lead to suppression of thymidylate synthesis, resulting in an unbalanced nucleotide pool. This disrupts repair processes, leading to DNA damage. The second way refers to SAM production. Insufficient SAM level in the cell leads to insufficient DNA methylation, which causes disruption of gene expression regulation [2,4,6,,10]. Since folate metabolism is an important link in basic biological processes, its disorders, including genetically determined ones, are considered as a

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high-risk factor for the development of pathological conditions: cardiovascular diseases, oncological diseases, reproductive disorders and fetal development pathologies. Two processes related to the folate cycle are considered to contribute to the development of CVD: homocysteine accumulation and disruption of DNA methylation processes. The main damaging effect of increased homocysteine levels is the activation of atherothrombosis through the following mechanisms: increase in the level of blood coagulation factor III (tissue thromboplastin); decrease in the activity of protein C; decrease in the level of heparin sulfate; decrease in the level of thrombomodulin; activation of coagulation factors V and XII; activation of platelet adhesion and aggregation; inhibition of tissue plasminogen activator binding to endotheliocytes; development of endothelial dysfunction (reduction of NO synthesis); apoptosis of endotheliocytes; pro-inflammatory, pro-oxidant effects; modification of low-density lipoproteins. Homocysteine in high concentrations competes with SAM for binding sites on DNA methyltransferases and may cause passive loss of methylation in replicating DNA [2,4,5,6,11,12,13]. It was found that patients with homocysteine levels >15.3 µmol/l had a 1.7-fold higher risk of death from all cardiovascular causes, a 3.4-fold higher risk of myocardial infarction, and a 4.3-fold higher risk of stroke than patients with homocysteine levels not exceeding 10.5 µmol/l [2,14,15].

In addition, homocysteine, being an agonist of glutamate receptors, is a partial agonist of glycine receptors. In conditions such as stroke and brain injury, when glycine concentrations increase, even small concentrations of homocysteine begin to exert pronounced neurotoxic effects. Toxic to the nervous tissue is also the effect of free radicals formed when the concentration of homocysteine increases [2,11,13,15,16]. The peculiarity of homocysteine metabolism in endothelial cells is its elimination only by remethylation, which directly depends on the sufficiency of folate in the body and full functioning of the MTHFR enzyme. Genetics of folate metabolism and circulatory diseases The role of genetically determined disorders of folate metabolism has been proven for patients with MI and ischaemic stroke: in a group of patients under 55 years of age, the presence of the MTHFR C667T polymorphism was associated with thrombotic events (MI + ischaemic stroke) (OR 1.41). In a meta-analysis, a dose-dependent association between MTHFR C667T genotype and risk of stroke/transient ischaemic attack was shown (heterozygotes (MTHFR 667 ST genotype): OR 1.17; homozygotes (MTHFR 667 TT genotype): OR 1.37). A stronger association was found in the tomographically confirmed ischaemic stroke group (heterozygotes: OR 1.18; homozygotes: OR 1.48) [3,12,13].

To date, a genetically determined decrease in the activity of folate cycle enzymes and homocysteine metabolism cycle in the absence of correction of folate levels in the body is associated with the risk of CVD development specifically in terms of DNA hypomethylation. Changes in methylation levels affect genes associated with a wide range of pathologies that make up the cardiovascular continuum. Hypo- or hypermethylation of these genes has been found in diseased areas of the vascular wall and atherosclerotic plaques compared to unaltered vessel sections [9, 10, 13, 16]. Nevertheless, it should be noted that carriage of conditionally "unfavourable" allelic variants of folate cycle enzyme genes increases the risk of CVD in the absence of correction of folate levels in the body. For example, in a large meta-analysis it was shown that carriage of MTHFR C667T polymorphic alleles did not affect the prognosis of

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patients with normal folic acid levels, whereas in low folate status the risk of major coronary events was increased by 32% in heterozygous carriers and by 44% in homozygous carriers of the 667TT allele. Similar data were obtained for patients aged over 35 years with a stable course of CHD, among whom a tendency to increased CCO was noted even in carriers of the potentially favourable "wild" genotype who had concomitant folic acid deficiency [7]. Regular intake of folic acid (at a dose of about 200 µg/day) significantly reduces blood homocysteine levels and reduces annual mortality from cardiovascular disease. The probability of coronary catastrophe at minimal blood folate concentration (less than 6.8 nmol/l) was 69% higher compared to the group of CHD patients whose blood folate content exceeded 13.6 nmol/l (OR 1.69) [2,8].

The most frequent genetically determined folate cycle disorders are associated with the development of venous and arterial thrombosis, with numerous studies indicating that isolated polymorphisms of the MTHFR gene are not an independent cause of these pathological conditions. The effect is observed in the case of a combined genotype: the presence of genetically determined disorders of the haemostasis system (primarily Leiden mutation and prothrombin gene mutation) and folate cycle gene polymorphisms. The latter significantly increase the negative phenotypic manifestations of haemostasis system factors [6, 7,8,9].

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