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Research Progress on the Effect of 5-Methyltetrahydrofolic Acid on Hyperhomocysteinemia in Pregnancy

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Abstract: As the association of hyperhomocysteinemia in pregnancy with preterm birth, abortion, preeclampsia and other pregnancy complications has attracted increasing attention, 5-methyltetrahydrofolic acid has attracted much attention as a potential treatment. In this paper, the biological mechanism of 5-methyltetrahydrofolic acid, its relationship with hyperhomocysteinemia in pregnancy and clinical studies were reviewed to review the research progress of 5-methyltetrahydrofolic acid in regulating hyperhomocysteine levels in pregnancy. The purpose of this paper is to explore the role and influence of 5-methyltetrahydrofolic acid in the management of hyperhomocysteinemia during pregnancy.

Keywords: 5-Methyltetrahydrofolin; Hyperhomocysteine; Pregnancy Complications; Pregnancy Management

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid, mainly derived from methionine in the diet, and is the product of demethylation of methionine, which is the only source of Hcy [1, 2]. A variety of factors can lead to the accumulation of blood levels of total homocysteine (tHcy), resulting in hyperhomocysteinemia (HHcy), referred to as hyperhomocysteine [2]. Hcy, as a new type of toxin in the human body, has been named “the new generation of cholesterol” internationally. It can accelerate the oxidation of low density lipoprotein by promoting the generation of oxygen free radicals, and can activate the adhesion and aggregation of platelet, damage vascular endothelial cells, and is closely related to pregnancy-related diseases, affecting the pregnancy outcome to a certain extent [3].

In recent years, many studies have suggested that hyperhomocysteinemia may be closely related to adverse pregnancy outcomes and pregnancy complications in pregnant women, and we should actively manage and treat it. We can adopt healthy lifestyle intervention or supplement folic acid, vitamin B12 and other nutritional treatments to prevent or treat hyperhomocysteinemia [2]. Folic acid can effectively reduce the concentration of homocysteine in the blood, and is considered as one of the potential therapeutic drugs for vascular diseases caused by high homocysteine [4]. Folic acid itself is inactive in the human body, and it must be converted into 5-methyltetrahydrofolate by folate metabolizing enzymes in the body before it can participate in the remethylation of homocysteine, thereby reducing the serum homocysteine level and further reducing the occurrence of hyperhomocysteinemia in pregnancy.

1. Pathogenesis of hyperhomocysteinemia

Homocysteine is an intermediate product in the metabolism of methionine. Methionine generates homocysteine under the action of a series of synthases and hydrolases. The specific synthesis pathway is shown in

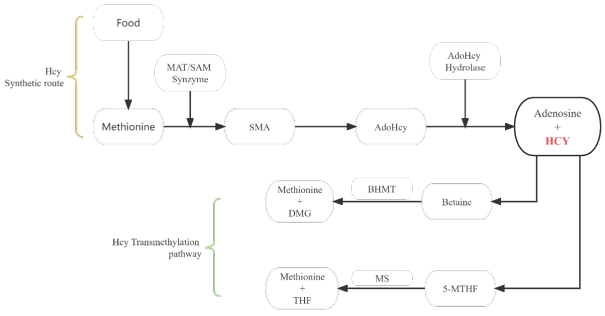

Fig. 1 Hcy synthesis and remethylation pathways

SMA: S-adenosyl methionine, 2.MAT: methionine adenosyltransferase, 3.SMA synthetase: S-Adenosyl methionase, 4.AdoHcy: S-adenosyl homocysteine, 5.Hcy: homocysteine, 6.5-MTHF: 5-methyltetrahydrofolate, 7.MS: methionine synthase, 8.THF: tetrahydrofolate, 9.DMG: dimethylglycine, 10.BHMT: betaine-homocysteine methyltransferase

The metabolic pathways of homocysteine mainly rely on the transmethylation pathway and the transsulfur pathway, and the transmethylation mainly includes two: 1 and 5-methyltetrahydrofolate (5-MTHF) provide methyl for homocysteine metabolism, and tetrahydrofolate (THF) and methionine are catalyzed by methionine synthase (MS). 2, betaine (trimethylglycine, from choline) as a methyl donor, zinc as a cofactor, and then methylated to produce dimethylglycine (DMG) and methionine, as shown in Figure 1 [4, 6-8].

The route of sulfur transfer: cystathione is catalyzed by cystathione bsnthase (CBS) to form cysteine, which is irreverably converted to cysteine by Cystathione c-lyase (CTL). Both enzymes require the assistance of pyridoxal phosphate (vitamin B6). In turn, cystathione, cysteine, and alpha-ketobutyric acid are used in protein synthesis, mediating a range of biological reactions [7, 8].

The causes of hyperhomocysteinemia can be roughly divided into five conditions: cofactor deficiency, enzyme deficiency, excessive methionine intake, certain diseases, and the effects of some drugs. 1, cofactor deficiency: Vitamin B2 is a cofactor of methylenetrahydrofolate reductase (MTHFR), involved in the production of 5-methyltetrahydrofolate reductase; Vitamin B6 is the co-factor of Hcy to thiotransferase; Vitamin B12 is the cofactor of MS, MS is involved in folic acid circulation; Folic acid, also known as vitamin B9, is indispensable in the metabolism of Hcy. B vitamins are water-soluble vitamins that are easily excreted in the urine, resulting in HHcy. Compared with other cofactors, supplementation with 0.5 to 5.0mg of folic acid daily has a good effect on reducing Hcy. 2, enzyme deficiency: enzyme deficiency or genetic errors of enzyme genes are directly related to homocysteine levels. Many studies have indicated that allele mutations of C677T TT and A1298C CC can increase homocysteine levels [9, 10]. CBS deficiency is the most common cause of Hcy increase, and the polymorphism of CBST833C gene can cause mild HHcy in different races. However, not all CBS gene polymorphisms can cause HHcy, and only C699T and T1080C gene polymorphisms can enhance folate and reduce Hcy function. MTHFR C677T and MS A2756G polymorphisms are caused by defects in the MTHFR and MS genes, and individuals with the MTHFR C677T genotype are at higher risk of HHcy in the presence of reduced folate and vitamin B12 levels and high blood lead concentrations. [11, 12]. Zaric et al. showed that decreased MTHFR activity was significantly associated with high homocysteine levels. Mutations in C677T and A1298C can lead to inhibition of MTHFR enzyme activity, resulting in reduced production of 5-MTHF, and thus reduced production of methionine and tetrahydrofolate from 5-MTHF and cysteine, resulting in impaired nucleic acid metabolism and inhibited fetal growth and development. 3, excessive intake of methionine: the only way to obtain methionine is to obtain it from food. Studies have found that the concentration of homocysteine-thiolactone (HTL) in urine of mice with normal diet or balanced diet is not as high as that of mice with high methionine diet, and the high methionine diet also causes changes in plasma HTL, but the changes are not significant. 4, some diseases and drugs caused: (1) Chronic renal failure: Hcy methylase and transferase exist in the kidney, chronic renal failure may inhibit or inactivate the activity of key enzymes of Hcy metabolism, resulting in HHcy; (2) hypothyroidism: Relevant data show that hypothyroidism and thyroid drugs may affect HHcy, but the relevant evidence is lacking; (3) Anemia: the deficiency of folic acid and vitamin B12 will lead to megalloblastic anemia, and the blood cells contain enzymes that transform Hcy, but the deficiency of folic acid and vitamin B12 will lead to abnormal blood cell function, and the enzymes cannot be activated, resulting in the normal transformation of Hcy and the formation of HHcy; (4) Malignant tumors: experiments have confirmed that tumor cells, compared with normal cells, highly release Hcy, and the density of specific areas in tumor cells increases, resulting in the rapid proliferation of tumor cells to deplete folate and inactivate the methylation reaction catalyzed by MS. (5) Drugs: Relevant studies have also shown that cholestyramine and metformin interfere with the absorption of gastrointestinal life-maintaining drugs, and methotrexate, niacin and fibrate derivatives directly interfere with folate and Hcy metabolism [7]. According to the relevant literature in recent years, there are many other disease factors causing the elevation of Hcy, which will not be listed in this paper.

2. The metabolic mechanism of 2, 5-methyltetrahydrofolate in the body

Folic acid can be obtained from foods such as beans and spinach, and can be divided into natural folic acid and synthetic folic acid according to its source, and inactive folic acid and active folic acid according to its activity [13].

Active folate refers to a group of substances, including dihydrofolate, tetrahydrofolate, 5, 10-methylene tetrahydrofolate, 10-formyl-folate and 5-methyltetrahydrofolate, among which 5-methyltetrahydrofolate is the most active form of folate, which is a necessary basic substance for human life activities and a key product of active metabolism of synthetic folate. It is also the main component of natural folic acid. The active folic acid mainly discussed in this paper is 5-methyltetrahydrofolic acid, and its metabolic form in the body is shown in Figure

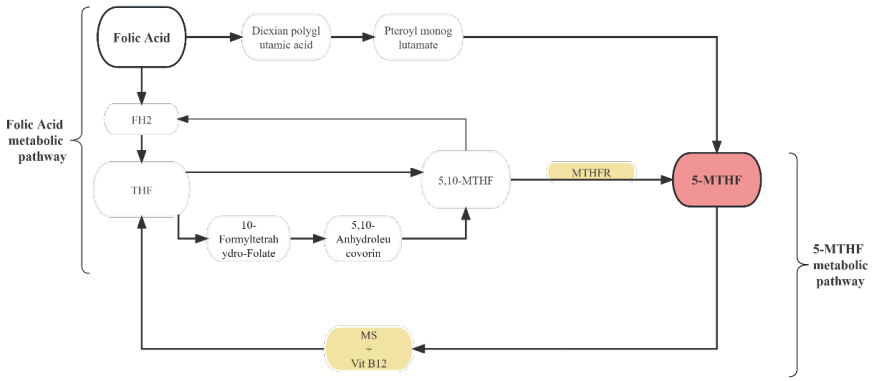

Figure 2 Folic acid metabolism pathway

1.THF: tetrahydrofolate, 2.5,10-MTHF: 5, 10-methyltetrahydrofolate, 3.MTHFR: methyltetrahydrofolate reductase

3. Comparison of 5-methyltetrahydrofolate with ordinary folate

Inactive folic acid generally refers to synthetic folic acid that is not active in itself, and active folic acid generally refers to 5-methyltetrahydrofolic acid that is active without metabolism. 5-MTHF as a component of folate is superior to inactive synthetic folate (pteroylglutamate) of active folate, the two are different biological characteristics of chemical substances, there is a relatively close relationship. The molecular structure is shown in Figure 3.

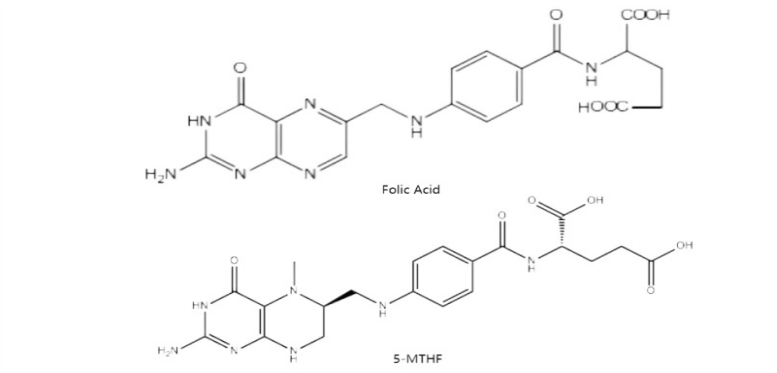

Figure 3 Molecular structure of synthetic folic acid and 5-methyltetrahydrofolic acid [14]

FA contained in supplements and fortified foods is metabolized to 5-MTHF in the body via the folic acid metabolic pathway [15]. In the cytoplasm, 5-MTHF provides methyl for homocysteine remethylation of methionine synthesis, which reduces blood homocysteine levels [16]. 5-MTHF has an advantage over synthetic folic acid in reducing Hcy levels in pregnancy: it is well absorbed even when gastrointestinal pH changes, and its bioavailability is not affected by metabolic defects. Use of 5-MTHF not only prevents the potential negative effects of the presence of unconverted folic acid in the peripheral circulation, but 5-MTHF in place of folic acid reduces the likelihood of hematological symptoms masking vitamin B12 deficiency, reduces interactions with drugs that inhibit dihydrofolate reductase, and overcomes metabolic defects caused by MTHFR polymorphisms [14].

4. 5-methyltetrahydrofolate in relation to hyperhomocysteinemia in pregnancy

Studies have shown that Hcy levels in pregnant women gradually decline to 50% to 60% of pre-conception levels and then remain relatively stable until delivery [17, 18]. Hcy levels increased in the third trimester, but remained low, which was associated with increased amino acid methylation and transmethylation in the third trimester and the needs of fetal growth and development [19]. Hyperhomocysteinemia during pregnancy leads to clinical manifestations of abortion, fetal dysplasia, gestational hypertension, diabetes and other pregnancy complications [20, 21]. Bo Liu et al. [22] designed a randomized controlled study to randomly supplement 164 pregnant women with folic acid (100 μg), L-MTHF (113 μg) or placebo daily supplements at 24 weeks of gestation. tHcy, plasma folic acid and erythrocyte folic acid (RCF) concentrations were analyzed at baseline and in blood collected at 8, 16 and 24 weeks. The study suggests that 5-MTHF is more effective than folic acid in reducing tHcy. 5-methyltetrahydrofolate, as a methyl donor, is involved in the remethylation of Hcy under the catalyst of methionine synthetase and vitamin B12 to reduce Hcy levels during pregnancy. The metabolic pathway is shown in the figure below.

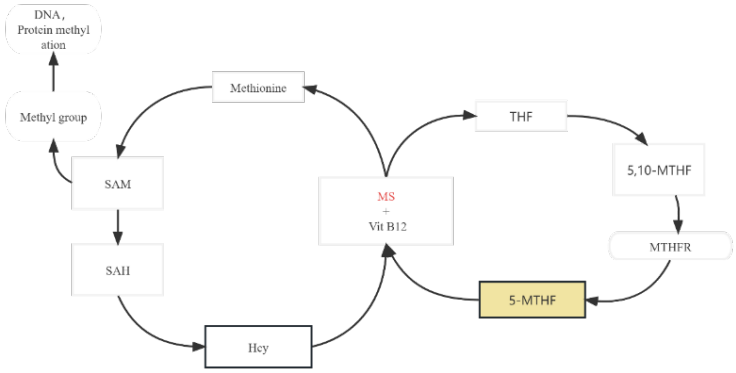

Figure 4. Interrelationship between folic acid and homocysteine metabolism

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism system and the main enzyme that causes folate metabolism disorders. This enzyme catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-MTHF, which provides methyl for Hcy, thereby reducing Hcy levels (Figure 5). According to domestic and foreign literature reports, MTHFR gene polymorphism can not only lead to neural tube malformation in newborns, but also has a close relationship with congenital heart disease, Down syndrome and other neonatal defects [23-26]. Folic acid metabolism enzyme gene polymorphism is the main cause of folic acid metabolism disorders, and there are three main genotypes: MTHFR 667TT, MTHFR 667CT and MTHFR 667CC genotypes, MTHFR 667TT gene carriers are known as severe folic acid metabolism disorders, their folic acid metabolism enzyme activity is only 1/3 of normal people, some even lower, so that the conversion of folic acid in their body is difficult to carry out successfully. Resulting in elevated homocysteine levels [27]. Depending on the metabolic pathway, 5-MTHF is unaffected by possible mutations in the MTHFR gene.

Folate is metabolized to 5-MTHF in the body, and 5-MTHF acts as a methyl donor to re-methylate homocysteine to methionine and reduce tHcy levels in pregnant women, a reaction catalyzed by methionine synthase (MS) and cofactor vitamin B12. A low vitamin B12 state, even when the folate state is sufficient, can trap folic acid as 5-MTHF, leading to impaired purine and pyrimidine synthesis. However, folic acid can be metabolized to tetrahydrofolate (THF) and is directly involved in nucleotide synthesis (Figure 2). Thus, folic acid can mask the hematological (megaloblastic anemia) signs of vitamin B12 deficiency, delay the diagnosis of vitamin B12 deficiency, and allow the neurological complications of vitamin B12 deficiency to progress unchecked [28]. Recent studies have also shown that 5-MTHF supplementation during pregnancy is more effective than folic acid in reducing Hcy levels, reducing the accumulation of unmetabolized folic acid in the body, and avoiding the masking of anemia caused by vitamin B12 deficiency (29).

5. Summary

In recent years, the necessity of folic acid supplementation for the prevention and treatment of hyperhomocysteinemia during pregnancy has been confirmed by many studies. As reported in relevant literatures at home and abroad, there are polymorphisms in the genes of

key enzymes in the process of folic acid metabolism, leading to individual folic acid metabolism disorders. Therefore, the development and research of 5-MTHF becomes the key [13, 21, 30]. However, the mechanism of 5-MTHF in the treatment of hyperhomocysteinemia in pregnancy is not fully understood, and more large randomized controlled studies are needed to verify the isotropic effect of 5-MTHF versus ordinary folic acid in pregnant women. The prophylactic dose and therapeutic dose of 5-MTHF for hyperhomocysteinemia in pregnancy still need to be confirmed and improved by more experiments in the future.

Hcy is an intermediate metabolite, and recurrent higher than normal Hcy levels during pregnancy may be associated with the risk of placenta-mediated complications, such as fetal growth restriction, preterm birth, hypertensive disorders of pregnancy, and recurrent miscarriage. However, the physical, mental and psychological trauma brought by adverse pregnancy outcome to a pregnant woman and a family is indescribable, and even causes irreparable consequences. Therefore, it is particularly important to reduce the Hcy level and reduce the occurrence of pregnancy complications by making pregnant women take 5-MTHF before and during pregnancy. In this paper, we summarized that 5-MTHF May replace folic acid to reduce Hcy level more effectively. Based on this review, we will further use prospective studies and randomized controlled experiments to track the Hcy level and pregnancy outcome of pregnant women who take oral 5-MTHF and ordinary folic acid. To provide favorable experimental evidence for subsequent obstetrical clinicians in pregnancy management of pregnant women.

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