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Perspective

Global Methylation and Regulatory Mirnas are affected by Folate and Vitamin B12 Deficiency in the Maternal/Parental Diet

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PERSPECTIVE

Nutritional factors impact DNA methylation, which is a key component of the epigenetic network. Folate serves as a one-carbon carrier in the one-carbon cycle, and vitamin B12 serves as a co-factor for the enzyme methionine synthase. Both folate and vitamin B12 are essential DNA methylation regulators that play a crucial role in early life development. Previous research has focused on the individual effects of these vitamins during pregnancy, but more recently, the attention has shifted to the combined effects of both vitamins throughout pregnancy. As a result, the goal of this work was to see how different dietary folate and B12 ratios affected the expression of transporters, associated miRNAs, and DNA methylation in C57BL/6 mice. For four weeks, female mice were fed diets containing nine different folate and B12 combinations. They were mated, and the offspring (F1) were fed the same food for six weeks after weaning. At day 20 of pregnancy, maternal and fetal (F2) samples were obtained. In both the F1 and F2 generations, a lack of folate resulted in an increase in the expression of folate transporters; however, a lack of B12 (BDFN) resulted in an increase in the expression in both generations. Except for TC-II in the kidney, which was shown to be decreased in the F1 generation, B12 transporters/proteins were found to be increased with B12 deficiency in both F1 and F2 generations. In both F1 and F2 generations, miR-483 expression was found to be raised in all conditions of folate and B12, whereas insufficient B12 situations led to an increase in miR-221 expression in both F1 and F2 generations. In F1 generation, the level of miR-133 was shown to be higher in the BDFN group; however, in F2 generation, the change in expression was tissue and sex specific. In maternal tissues (F1), global DNA methylation was reduced by folate and B12 deficit, but elevated by folate deficiency in the placenta (F1) and in all conditions in fetal tissues (F2). Folate, often known as vitamin B9, is a methyl carrier that is required for the synthesis of nucleotides and methionine1. It is derived from dietary sources.

Vitamin B12, a member of the B vitamin family, is also important in one-carbon metabolism. Vitamin B12 works as a co-factor for the enzyme methionine synthase when a methyl group from 5-methyl tetrahydrofolate is transferred to homocysteine to produce methionine. In B12 deficiency, folate is trapped as 5-methyltetrahydrofolate, resulting in a buildup of homocysteine and a reduction in methionine3 synthesis. Only bacteria have the machinery to generate folate and B12, and humans must meet their B12 requirements through diet. Transporters and binding proteins, such as the Proton-coupled Folate Transporter (PCFT), Reduced Folate Carrier (RFC), and Folate Receptor (FR and FR) for folate, and LMBR1 Domain containing (LMBRD1) and trans-cobalamin II (TC-II) for vitamin B12, are present to mediate transfer into cells.

RFC is the only folate transporter with widespread expression, whereas PCFT and FRs have tissue-specific expression. Dietary deficiencies of folate and vitamin B12 are among the most frequent deficiencies in India, and have been linked to pregnancy-related problems including NTD. Since the USFDA mandated folic acid fortification of food in 1996, cases of folate deficiency have become uncommon. Due to vegetarian eating habits and lower social and economic position, B12 deficiency is common in India's reproductive age group. People take more folic acid than is indicated due to the habit of prescribing folic acid from the periconceptual phase through pregnancy, and research reveals that B12 deficiency is concealed by high serum folate levels, resulting in neurological damage.

In this line, a study conducted in Pune, India, found that high folate levels in pregnant women with low B12 levels were linked to the development of insulin resistance in their children, implying that the ratio of both vitamins, rather than individual amounts, is critical for good fetal growth. In a study conducted in Mysore, insufficient B12 was linked to an increased risk of gestational diabetes mellitus (GDM). Both B12 and folate are crucial for DNA methylation because they are critical determinants of one carbon metabolism, in which S-adenosyl methionine (SAM) is generated, and it is a known that differences in gene expression are caused by differential DNA methylation patterns that are set in utero. The level of 5 methyl cytosine, a conserved epigenetic mark linked to gene silence, was shown to be high in embryos, declining with maturity. When folate levels are low, global DNA methylation declines, and when folate levels are high, it increases.

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In this respect, a sheep study found that maternal folate and B12 dietary restriction causes hypomethylation in adult male offspring, which leads to increased obesity and insulin resistance. DNMT1, a DNA methyltransferase, preserves methylation patterns during DNA replication, while DNMT3A and DNMT3B catalyse *de novo* DNA methylation. Hypermethylation and hypomethylation are related with downregulating and reactivating gene expression, respectively, when DNMT levels are altered. Previous research has found that a folate- and methyl-deficient diet increases DNMT1, DNMT3A, and DNMT3B expression in the livers of rats, and that folate fortification enhances DNMT1 expression in the human cervix. The expression of DNMT1 and DNMT3A was shown to be up-regulated in the uteruses of pseudo-pregnant mice in another investigation connected to folate deficit. B12 supplementation has previously been demonstrated to have a considerable impact on DNA methylation of genes linked to type-2 diabetes, both alone and in combination with folic acid.