2 Folic Acid

The terms *folic acid* and *folate* are often used interchangeably for this water-soluble B-complex vitamin. Folic acid, the more stable form, occurs rarely in foods or the human body but is the form most often used in vitamin supplements and fortified foods. Naturally occurring folates exist in many chemical forms. They are found in foods as well as in metabolically active forms in the human body.[1] In the following discussion, forms found in food or the body are referred to as *folates*, whereas the form found in supplements or fortified foods is referred to as *folic acid*.

Function

One-carbon Metabolism

The only function of folate coenzymes in the body appears to be in mediating the transfer of one-carbon units.[2] Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids.[3]

Nucleic acid metabolism. Folate coenzymes play a vital role in DNA metabolism through two different pathways (**Fig. 2.1**):

1. The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes.
2. A folate coenzyme is required for the synthesis of methionine, and methionine is required for the synthesis of *S*-adenosylmethionine (SAM).

SAM is a methyl group (one-carbon unit) donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA. Methylation of DNA may be important in cancer prevention.

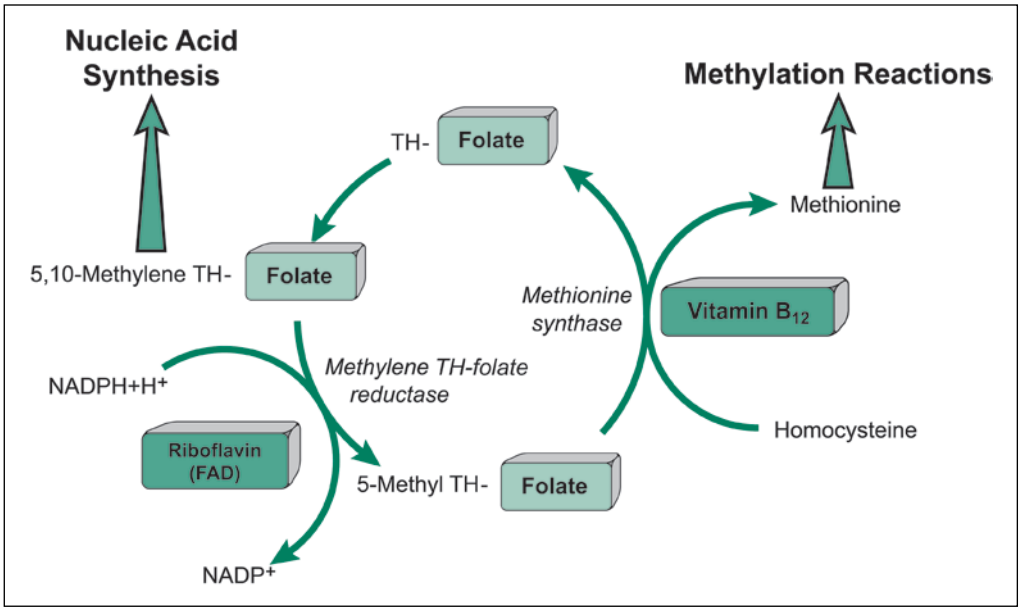

Fig. 2.1 Folate and nucleic acid metabolism: 5,10-methylene tetrahydrofolate (THF) is required for the synthesis of nucleic acids, and 5-methyl THF is required for the formation of methionine from homocysteine. Methionine, in the form of *S*-adenosylmethionine, is required for many biological methylation reactions, including DNA methylation. Methylene TH-folate reductase is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methylene THF to 5-methyl THF.

Amino acid metabolism. Folate coenzymes are required for the metabolism of several important amino acids. The synthesis of methionine from homocysteine requires a folate coenzyme as well as a vitamin B_{12}-dependent enzyme. Thus, folate deficiency can result in decreased synthesis of methionine and a build-up of homocysteine. Increased levels of homocysteine may be a risk factor for heart disease as well as several other chronic diseases.

Nutrient Interactions

The metabolism of homocysteine, an intermediate in the metabolism of sulfur-containing amino acids, provides an example of the interrelationships of nutrients necessary for optimal physiological function and health. Healthy individuals use two different pathways to metabolize homocysteine (**Fig. 2.2**). One pathway (methionine synthase) synthesizes methionine from homocysteine and depends on a folate coenzyme and a vitamin B_{12}-dependent enzyme. The other pathway converts homocysteine to another amino acid, cysteine, and requires two vitamin B_6-dependent enzymes. Thus, the amount of homocysteine in the blood is regulated by three vitamins: folate, vitamin B_{12}, and vitamin B_6.[4]

Deficiency

Causes

Folate deficiency is most often caused by a dietary insufficiency; however, it can occur in a number of other situations, for example, alcoholism is associated with low dietary intake and diminished absorption of folate, which can lead to

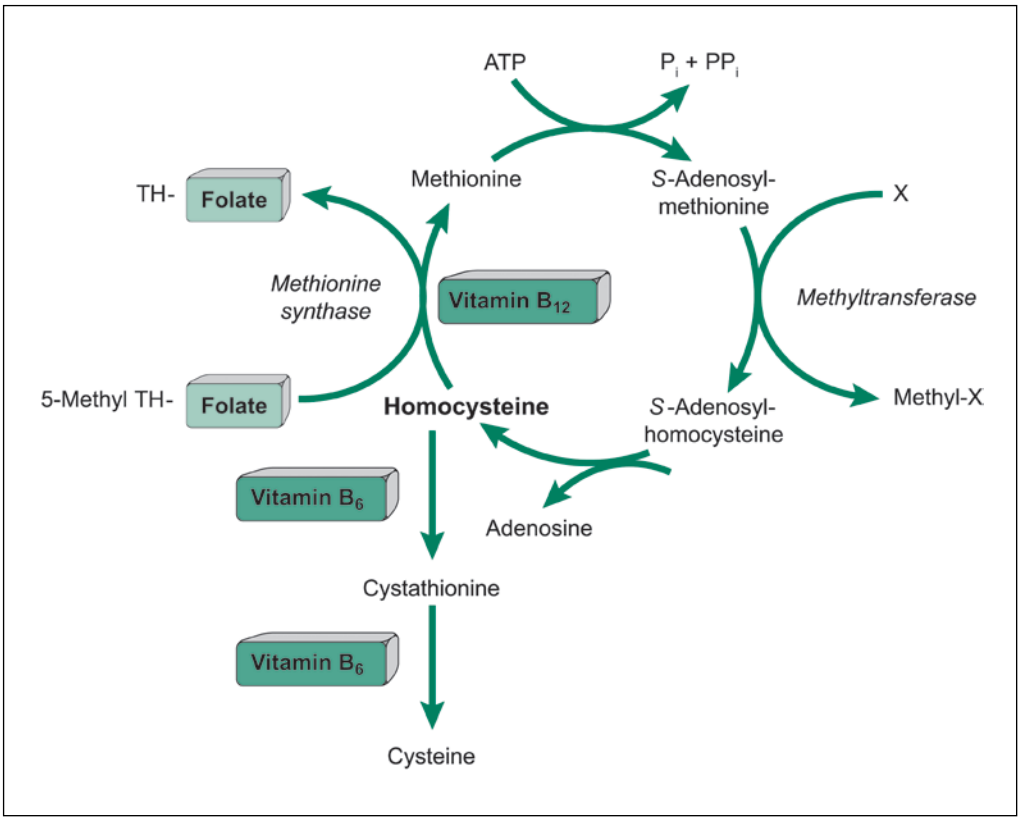

Fig. 2.2 Homocysteine metabolism: *S*-adenosylhomocysteine is formed during *S*-adenosylmethionine-dependent methylation reactions, and the hydrolysis of *S*-adenosylhomocysteine results in homocysteine. Homocysteine may be remethylated to form methionine by a folate-dependent reaction that is catalyzed by methionine synthase, a vitamin B_{12}-dependent enzyme. Alternately, homocysteine may be metabolized to cysteine in reactions catalyzed by two vitamin B_6-dependent enzymes.

folate deficiency. In addition, certain conditions such as pregnancy or cancer result in increased rates of cell division and metabolism, causing an increase in the body's demand for folate.[5] Several medications may also contribute to deficiency (see "Drug Interactions," p. 14).

Symptoms

Individuals in the early stages of folate deficiency may not show obvious symptoms, but their blood levels of homocysteine may increase. Rapidly dividing cells are most vulnerable to the effects of folate deficiency, so when the folate supply to the rapidly dividing cells of the bone marrow is inadequate, blood cell division becomes abnormal, resulting in fewer but larger red blood cells. This type of anemia is called *megaloblastic* or *macrocytic* anemia, referring to the enlarged, immature red blood cells. Neutrophils, a type of white blood cell, become hypersegmented, a change that can be found by examining a blood sample microscopically. As normal red blood cells have a lifetime in the circulation of approximately 4 months, it can take months for folate-deficient individuals to develop the characteristic megaloblastic anemia. Progression of such an anemia leads to decreased oxygen-carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath.[1] It is important to point out that megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B_{12} deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia.

Recommended Dietary Allowance

Traditionally, the dietary folate requirement was defined as the amount needed to prevent a deficiency severe enough to cause symptoms such as anemia. The most recent recommended dietary allowance (RDA) (**Table 2.1**) was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, as judged by the absence of abnormal hematological indicators. Red cell folate has been shown to correlate with liver folate stores. Maintenance of normal blood homocysteine levels, an indicator of one-carbon metabolism, was considered only as an ancillary indicator of adequate folate intake. As pregnancy is associated with a significant increase in cell division and other metabolic processes that require folate coenzymes, the RDA for pregnant women is considerably higher than for women who are not pregnant.[3] However, the prevention of neural tube defects (NTDs) was not considered when setting the RDA for pregnant women. Rather, reducing the risk of NTDs was considered in a separate recommendation for women capable of becoming pregnant, because the crucial events in neural tube development occur before many women are aware that they are pregnant.[6]

Dietary Folate Equivalents

When the Food and Nutrition Board (FNB) of the Institute of Medicine set the new dietary recommendation for folate, they introduced a new unit, the dietary folate equivalent (DFE):

Table 2.1 Recommended dietary allowance for folate in DFEs

Life stage	Age	Males (µg/day)	Females (µg/day)
Infants	0–6 months	65 (AI)	65 (AI)
Infants	7–12 months	80 (AI)	80 (AI)
Children	1–3 years	150	150
Children	4–8 years	200	200
Children	9–13 years	300	300
Adolescents	14–18 years	400	400
Adults	≥ 19 years	400	400
Pregnancy	All ages	–	600
Breast-feeding	All ages	–	500

AI, adequate intake; DFE, dietary folate equivalent.