The Vitamins

Fundamental Aspects in Nutrition and Health

SECOND EDITION

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Folate

Using Streptococcus lactis *R as a test organism, we have obtained in a highly concentrated and probably nearly pure form an acid nutrilite with interesting physiological properties. Four tons of spinach have been extracted and carried through the first stages of concentration . . . . This acid, or one with similar chemical and physiological properties, occurs in a number of animal tissues of which liver and kidney are the best sources . . . . It is especially abundant in green leaves of many kinds, including grass. Because of this fact, we suggest the name "folic acid" [Latin,* folium*—leaf]. Many commercially canned greens are nearly lacking in the substance.* **H. K. Mitchell, E. S. Snell, and R. J. Williams**

Anchoring Concepts

1. *Folate* is the generic descriptor for folic acid (pteroylmonoglutamic acid) and related compounds exhibiting qualitatively the biological activity of folic acid. The term *folates* refers generally to the compounds in this group, including mono- and polyglutamates.
2. Folates are active as coenzymes in single-carbon metabolism.
3. Deficiencies of folate are manifested as anemia and dermatologic lesions.

Learning Objectives

1. To understand the chief natural sources of folates
2. To understand the means of absorption and transport of the folates

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3. To understand the biochemical functions of the folates as coenzymes in single-carbon metabolism, and the relationship of that function to the physiological activities of the vitamin
4. To understand the metabolic interrelationship of folate and vitamin B_{12} and its physiological implications

Vocabulary

Betaine
Cervical paralysis
7,8-Dihydrofolate reductase
FH_2 (dihydrofolic acid)
FH_4 (tetrahydrofolic acid)
Folate
Folate-binding proteins (FBPs)
Folate receptors
Folic acid
Folyl conjugase
Folyl γ-glutamyl hydrolase
Folyl polyglutamates
Folyl polyglutamate synthetase
5-Formimino-FH_4
5-Formyl-FH_4
10-Formyl-FH_4
10-Formyl-FH_4 synthetase
Homocysteine
Leukopenia
Macrocytic anemia
Megaloblasts
5,10-Methenyl-FH_4
Methionine synthetase
Methotrexate
5,10-Methylene-FH_4
5,10-Methylene-FH_4 dehydrogenase
5,10-Methylene-FH_4 reductase
5-Methyl-FH_4
Methyl-folate trap
Pernicious anemia
Pterin ring
Pteroylglutamic acid
Purines
Serine hydroxymethyltransferase
Single-carbon metabolism
Sulfa drugs
Thymidylate (dTMP)
Vitamin B_{12}

I. Significance of Folate

FOLATE IS a vitamin that is often not appreciated, either for its importance in normal metabolism or its relevance to the etiologies of chronic diseases and birth defects. Widely distributed among foods, particularly those of plant foliar origin, this abundant vitamin is underconsumed by people whose food habits do not emphasize plant foods. Intimately related in function with vitamins B_{12} and B_6, its status at the level of subclinical deficiency can be difficult to assess and the full extent of its interrelationships with these vitamins and with amino acids remains incompletely elucidated.

Folate deficiency is an important problem in many parts of the world, particularly where there is poverty and malnutrition. It is an important cause of anemia, second only to nutritional iron deficiency in that regard. Evidence shows that marginal folate status can support apparently normal circulating folate levels while still limiting single-carbon metabolism. Thus, folate is emerging as having an important role in the etiology of homocysteinemia, which has been identified as a risk factor for occlusive vascular disease, cancer, and birth defects. It has been estimated that an increase in mean folate intake of 200 μg/day could reduce coronary artery disease deaths in the United States by 13,500–50,000; and the finding of markedly reduced neural tube defects risk by periconceptional folate treatment has driven folate supplementation efforts in the United States. Still, there must be concern about the use of folate supplements, particularly high-level supplements, as folate is known to mask the **macrocytic anemia** of vitamin B_{12} deficiency, which will lead to neuropathy if not corrected.

For these several reasons, it is important to understand folate nutrition.

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II. Sources of Folate

Distribution in Foods

Folates (**folyl polyglutamates**) occur in a wide variety of foods and feedstuffs of both plant and animal origin (Table 16-1). Liver, mushrooms, and green leafy vegetables are rich sources of folate in human diets; while oilseed meals (for example, soybean meal) and animal by-products are important sources of folate in animal feeds. The folates in foods and feedstuffs are almost exclusively in reduced form as polyglutamyl derivatives of **tetrahydrofolic acid** ($\mathbf{FH_4}$). Very little free folate (folyl monoglutamate) is found in foods or feedstuffs.

Analyses of foods have revealed a wide distribution of general types of folate derivatives, the predominant forms being **5-methyl-FH_4** and **10-formyl-FH_4**. The folates found in organ meats (for example, liver and kidney) are about 40% methyl derivatives, whereas that in milk (and erythrocytes) is exclusively the methyl form. Some plant materials also contain mainly 5-methyl-FH_4 (for example, lettuce, cabbage, orange juice), but others (for example, soybean) contain relatively little of that form (~15%), the rest occurring as the 5- and 10-formyl derivatives. Most of the folates in cabbage are hexa- and heptaglutamates, whereas half of those in soybean are monoglutamates. More than a third of the folates in orange juice are present as monoglutamates and nearly half are present as pentaglutamates. Liver and kidney contain mainly pentaglutamates, and ~60% of the folates in milk are monoglutamates (with only 4–8% each of di- to heptaglutamates).

Table 16-1. Folate Contents of Foods

Food	Folate (μg/100 g)	Food	Folate (μg/100 g)
Dairy products		Other	
Milk	5–12	Eggs	70
Cheese	20	Brewers' yeast	1500
Meats		Vegetables	
Beef	5–18	Asparagus	70–175
Liver		Beans	70
Beef	140–1070	Broccoli	180
Chicken	1810	Brussels sprouts	90–175
Tuna	15	Cabbage	15–45
Cereals		Cauliflower	55–120
Barley	15	Peas	90
Corn	35	Soybeans	360
Rice		Spinach	50–190
Polished	15	Tomatoes	5–30
Unpolished	25	Fruits	
Wheat, whole	30–55	Apples	5
Wheat bran	80	Bananas	30
		Oranges	25

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