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of children with methylmalonic aciduria (Cooper, 1976).

FOLIC ACID

Chemistry and Metabolic Functions. The structural formula of pteroylglutamic acid (PteGlu₁) is shown in Figure 54-9. Major portions of the molecule include a pteridine ring linked by a methylene bridge to paraaminobenzoic acid, which is joined by an amide linkage to glutamic acid. While pteroylglutamic acid is the common pharmaceutical form of folic acid, it is neither the principal folate congener in food nor the active coenzyme for intracellular metabolism. Following absorption, PteGlu₁ is rapidly reduced at the 5, 6, 7, and 8 positions to tetrahydrofolic acid (H₄PteGlu₁), which then acts as an acceptor of a number of one-carbon units. These are attached at either the 5 or the 10 position of the pteridine ring or bridge these atoms to form a new five-membered ring. The most important forms of the coenzyme that are synthesized by these reactions are listed in Figure 54-9. Each plays a specific role in intracellular metabolism, summarized as follows (*see also* previous section on Relationships between Vitamin B₁₂ and Folic Acid, as well as Figure 54-6):

1. *Conversion of homocysteine to methionine.* This reaction requires CH₃H₄PteGlu as a methyl donor and utilizes vitamin B₁₂ as a cofactor.

2. *Conversion of serine to glycine.* This reaction requires tetrahydrofolate as an acceptor of a methylene group from serine and utilizes pyridoxal phosphate as a cofactor. It results in the formation of 5,10-CH₂H₄PteGlu, an essential coenzyme for the synthesis of thymidylate.

3. *Synthesis of thymidylate.* CH₃H₄PteGlu do-

nates a methyl group to deoxyuridylate for the synthesis of thymidylate—a rate-limiting step in DNA synthesis.

4. *Histidine metabolism.* H₄PteGlu also acts as an acceptor of a formimino group in the conversion of formiminoglutamic acid to glutamic acid.

5. *Synthesis of purines.* Two steps in the synthesis of purine nucleotides require the participation of derivatives of folic acid. Glycinamide ribonucleotide is formylated by 5,10-CHH₄PteGlu; 5-aminoimidazole-4-carboxamide ribonucleotide is formylated by 10-CHOH₄PteGlu. By these reactions carbon atoms at positions 8 and 2, respectively, are incorporated into the growing purine ring.

6. *Utilization or generation of formate.* This reversible reaction utilizes H₄PteGlu and 10-CHOH₄PteGlu.

Daily Requirements. Virtually all food sources are rich in folates, especially fresh green vegetables, liver, yeast, and some fruits. However, protracted cooking can destroy up to 90% of the folate content of such food (Herbert, 1973). Generally, a standard U.S. diet provides 50 to 500 μg of absorbable folate per day, although individuals with high intakes of fresh vegetables and meats will ingest as much as 2 mg per day. In the normal adult, the minimal daily requirement has been estimated at 50 μg, while the pregnant or lactating female and patients with high rates of cell turnover (such as patients with a hemolytic anemia) may require as much as 100 to 200 μg or

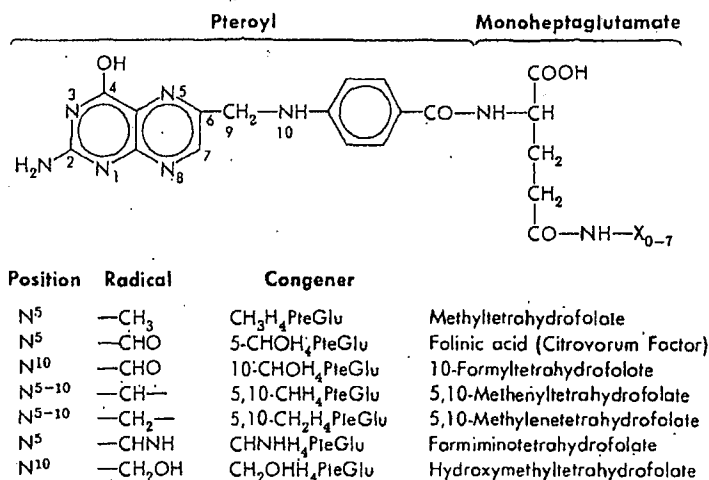


Figure 54-9. The structures and nomenclature of pteroylglutamic acid (folic acid) and congeners.

See text for explanation. X represents additional residues of glutamate; polyglutamates are storage forms of the vitamin. The subscript that designates the number of residues of glutamate is frequently omitted because this number is variable.

more per day. Recommended dietary allowances of folate are presented in Table XVI-1.

Absorption, Distribution, and Elimination. As with vitamin B₁₂, diagnosis and management of deficiencies of folic acid depend on an understanding of the transport pathways and intracellular metabolism of the vitamin (Figure 54-10). Folates present in food are largely in the form of reduced polyglutamates (Tamura and Stokstad, 1973), and absorption requires transport and the action of a pteroyl-γ-glutamyl carboxypeptidase associated with mucosal cell membranes (Rosenberg, 1976). The mucosae of the duodenum and upper part of the jejunum are rich in dihydrofolate reductase and are capable of methylating most, if not all, absorbed, reduced folate. Since most absorption occurs in the proximal portion of the small intestine, it is not unusual for folate deficiency to occur when the jejunum is diseased.

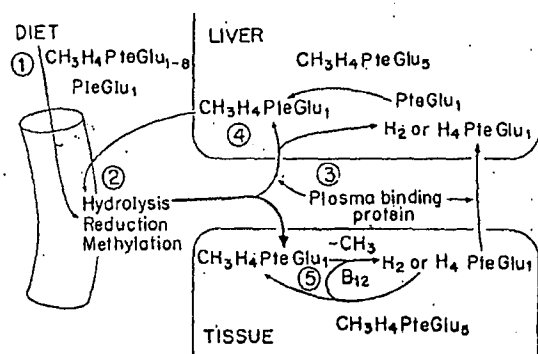


Figure 54-10. Absorption and distribution of folate derivatives.

Dietary sources of folate polyglutamates are hydrolyzed to the monoglutamate, reduced, and methylated to CH₃H₄PteGlu₁ during gastrointestinal transport. Folate deficiency commonly results from (1) inadequate dietary supply and (2) small intestinal disease. In patients with uremia, alcoholism, or hepatic disease there may be defects in (3) the concentration of folate binding proteins in plasma and (4) the flow of CH₃H₄PteGlu₁ into bile for reabsorption and transport to tissue (the folate enterohepatic cycle). Finally, vitamin B₁₂ deficiency will (5) "trap" folate as CH₃H₄PteGlu₁ for its essential roles in purine and pyrimidine synthesis.

Nontropical and tropical sprue are common causes of folate deficiency and megaloblastic anemia (Wellcome Trust Collaborative Study, 1971).

Once absorbed, folate is rapidly transported to tissues as CH₃H₄PteGlu₁. While certain plasma proteins do bind folate derivatives, they have a greater affinity for nonmethylated analogs. The role of such binding proteins in folate homeostasis is not well understood (Rothenberg *et al.*, 1977). An increase in binding capacity is detectable during deficiency of folate and in certain disease states, such as uremia, cancer, and alcoholism, but how binding affects transport and tissue supply requires further investigation.

A constant supply of CH₃H₄PteGlu₁ is maintained by food and by an enterohepatic cycle of the vitamin. The liver actively reduces and methylates PteGlu₁ (and H₂ or H₄PteGlu₁) and then transports the CH₃H₄PteGlu₁ into bile for reabsorption by the gut and subsequent delivery to tissues (Steinberg *et al.*, 1979). This pathway may provide as much as 200 μg or more of folate each day for recirculation to tissues. The importance of the enterohepatic cycle is suggested by studies in animals that show a rapid reduction of the concentration of folate in plasma following either drainage of bile or ingestion of alcohol, which apparently block the release of CH₃H₄PteGlu₁ from hepatic parenchymal cells (Hillman *et al.*, 1977).

Following uptake into cells by a process of receptor-mediated endocytosis (Kamen *et al.*, 1988), CH₃H₄PteGlu acts as a methyl donor for the formation of methylcobalamin and as a source of H₄PteGlu and other folate congeners, as described above. Folate is stored within cells as polyglutamates (Baugh and Krumdieck, 1969; Hoffbrand *et al.*, 1977).

Folate Deficiency. Folate deficiency is a common complication of diseases of the small intestine, which interfere with the absorption of folate from food and the recirculation of folate through the enterohepatic cycle. In acute or chronic alcoholism, daily intake of folate in food may be severely restricted, and the enterohepatic cycle of the vitamin may be impaired by the toxic effect

of alcohol on hepatic parenchymal cells; this is perhaps the most common cause of folate-deficient megaloblastic erythropoiesis. However, it is also the most amenable to therapy, inasmuch as the reinstitution of a normal diet is sufficient to overcome the effect of alcohol. Disease states characterized by a high rate of cell turnover, such as hemolytic anemias, may also be complicated by deficiency of folate (Lindenbaum, 1977). Additionally, drugs that inhibit dihydrofolate reductase (*e.g.*, methotrexate, trimethoprim) or that interfere with the absorption and storage of folate in tissues (*e.g.*, certain anticonvulsants, oral contraceptives) are capable of lowering the concentration of folate in plasma and at times may cause a megaloblastic anemia (Stebbins *et al.*, 1973; Stebbins and Bertino, 1976).

Folate deficiency is recognized by its impact on the hematopoietic system. As with vitamin B₁₂, this fact reflects the increased requirement associated with high rates of cell turnover. The megaloblastic anemia that results from folate deficiency cannot be distinguished from that caused by a deficiency of vitamin B₁₂. This finding is to be expected, because of the final common pathway of the major intracellular metabolic roles of the two vitamins. At the same time, folate deficiency is rarely if ever associated with neurological abnormalities. Thus, the observation of characteristic abnormalities in vibratory and position sense and in motor and sensory pathways rules against the presence of an isolated deficiency of folic acid.

The appearance of megaloblastic anemia following deprivation of folate is much more rapid than that caused by the interruption of the absorption of vitamin B₁₂ (*e.g.*, gastric surgery). This observation reflects the fact that stores of folate are quite limited *in vivo*. In Herbert's classical study of a single normal individual maintained on a diet low in folate for several months, megaloblastic erythropoiesis appeared after approximately 10 to 12 weeks (Herbert, 1962). Subsequent studies have shown that the rate of induction of megaloblastic erythropoiesis varies according to the population studied and the dietary background of the individual (Eichner *et al.*, 1971). A folate

deficiency state may appear in 1 to 4 weeks, depending on the individual's dietary habits and stores of the vitamin.

Folate deficiency is best diagnosed from measurements of folate in plasma and in red cells by use of a microbiological assay or a competitive binding technique. The concentration of folate in plasma is extremely sensitive to changes in dietary intake of the vitamin and the influence of inhibitors of folate metabolism or transport, such as alcohol. Normal folate concentrations in plasma range from 9 to 45 nM (4 to 20 ng/ml). A deficiency state may be considered to be present whenever the value is below 9 nM. In the case of the alcoholic, the plasma folate concentration falls rapidly to values indicative of deficiency within 24 to 48 hours of steady ingestion of alcohol, while megaloblastic erythropoiesis becomes apparent after 1 to 2 weeks (Eichner and Hillman, 1971, 1973). At the same time, the plasma folate concentration will quickly revert to normal once such ingestion is stopped, even while the marrow is still megaloblastic. Such rapid fluctuations tend to detract from the clinical utility of the plasma folate concentration. Measurement of folate in red cells or the adequacy of stores in lymphocytes (by use of the deoxyuridine suppression test) may be employed to diagnose a long-standing deficiency of folic acid (Herbert *et al.*, 1973). (In this test, deoxyuridine fails to suppress the synthesis of DNA if normal amounts of folate are present in the cells.) For either test to be positive, a state of deficiency must have existed for a sufficient time to allow the production of a new population of cells with deficient stores of folate.

Preparations. *Folic acid* (FOLVITE) is marketed as oral preparations, alone or in combination with other vitamins or minerals, and as an aqueous solution for injection. Tablets of folic acid contain either 0.1, 0.4, 0.8, or 1 mg of pteroylglutamic acid. *Folic acid injection* is an aqueous solution of the sodium salt of pteroylglutamic acid.

Leucovorin (folinic acid, 5-CHOH₄PteGlu, *citrovorum factor*) is also available for oral administration or parenteral injection as the Ca²⁺ salt (WELLCOVORIN). Tablets contain either 5, 10, 15, or 25 mg of leucovorin. The principal indication for the use of folinic acid is to circumvent the action of inhibitors of dihydrofolate reductase, such as methotrexate (*see* Chapter 52). It is not indicated for use in the treatment of folic acid deficiency. Certainly, leucovorin should never be used for the treatment of pernicious anemia or other megaloblastic anemias secondary to a deficiency of vitamin B₁₂. Just as with folic acid, its use can result in an apparent response of the hematopoietic system, but neurological damage may occur or progress if already present.

Untoward Effects. There have been rare reports of reactions to parenteral injections of both folic acid and leucovorin. If a patient describes a history of a reaction before

the drug is given, caution should be exercised. Oral folic acid is not toxic for man. Even with doses as high as 15 mg per day, there have been no substantiated reports of side effects. Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin, and primidone and increase the frequency of seizures in susceptible children (Reynolds, 1968). While some studies have not supported these contentions, the U.S. Food and Drug Administration has recommended that oral tablets of folic acid be limited to strengths of 1 mg or less.

General Principles of Therapy. The therapeutic use of folic acid is limited to the prevention and treatment of deficiencies of the vitamin. As with vitamin B₁₂ therapy, effective use of the vitamin depends on accurate diagnosis and an understanding of the mechanisms that are operative in a specific disease state. The following general principles of therapy should be respected:

1. Prophylactic administration of folic acid should be undertaken only when there is a clear indication. Dietary supplementation is necessary when there is an increased requirement that is not satisfied by normal dietary sources. Pregnancy, with the increased demands of the fetus, or lactation, where as much as 50 μ g of folate is lost each day in the breast milk, is an indication for supplementation with folate. The most popular form of supplementation for this situation is a multivitamin preparation that contains 400 to 500 μ g of pteroylglutamic acid. Patients with a disease state characterized by high levels of cell turnover (e.g., a hemolytic anemia) should also receive folic acid prophylactically, usually one or two 1-mg tablets of folic acid each day. Patients receiving total parenteral nutrition should also receive a daily folic acid supplement.

2. As with vitamin B₁₂ deficiency, any patient with folate deficiency and a megaloblastic anemia should be carefully evaluated to determine the underlying cause of the deficiency state. This should include evaluation of the effects of medications, the amount of alcohol intake, the patient's history of travel, and the function of the gastrointestinal tract.

3. Therapy should always be as specific as possible. Multivitamin preparations should be avoided unless there is good reason to suspect deficiency of several vitamins.

4. The potential of mistreating a patient who has vitamin B₁₂ deficiency with folic acid must be kept in mind. The administration of large doses of folic acid can result in an apparent improvement of the megaloblastic anemia, inasmuch as PteGlu is converted by dihydrofolate reductase to H₄PteGlu₁; this circumvents the methylfolate "trap." However, folate therapy does not prevent or alleviate the neurological defects of vitamin B₁₂ deficiency, and these may progress and become irreversible.

Treatment of the Acutely Ill Patient. As described in detail in the section on vitamin B₁₂, treatment of the patient who is acutely ill with megaloblastic anemia should begin with intramuscular injections of both vitamin B₁₂ and folic acid. Inasmuch as the patient requires therapy before the exact cause of the disease has been defined, it is important to avoid the potential problem of a combined deficiency of both vitamin B₁₂ and folic acid. When both are present, therapy with only one vitamin will not provide an optimal response. Long-standing nontropical sprue is one example of a disease in which combined deficiency of B₁₂ and folate is common. When indicated, both vitamin B₁₂ (100 μ g) and folic acid (1 to 5 mg) should be administered intramuscularly, immediately, and the patient should then be maintained on daily oral supplements of 1 to 2 mg of folic acid for the next 1 to 2 weeks. Recommendations for administration of vitamin B₁₂ are described above.

Oral administration of folate is generally satisfactory for all patients who are not acutely ill, regardless of the cause of the deficiency state. Even the patient with tropical or nontropical sprue and a demonstrable defect in absorption of folic acid will respond adequately to such therapy. Abnormalities in the activity of pteroyl- γ -glutamyl carboxypeptidase and the function of mucosal cells will not prevent passive diffusion of sufficient amounts of PteGlu across the mucosal barrier if dosage is adequate, and continued ingestion of alcohol or other drugs will also not prevent an adequate therapeutic response. The effect of most inhibitors of folate transport or dihydrofolate reductase is easily overcome by administration of pharmacological doses of the vitamin. Perhaps the only situation in which this tenet is not true is when vitamin C is severely deficient. The patient with scurvy may suffer from a megaloblastic anemia despite increased intake of folate and normal or high concentrations of the vitamin in plasma and cells.

The therapeutic response may be monitored by study of the hematopoietic system in a fashion

identical to that described for vitamin B₁₂. Within 48 hours of the initiation of appropriate therapy, megaloblastic erythropoiesis disappears and, as efficient erythropoiesis begins, the concentration of iron in plasma falls to normal or below-normal values. The reticulocyte count begins to rise on the second or third day and reaches a peak by the fifth to seventh day; the reticulocyte index reflects the proliferative state of the marrow. Finally, the hematocrit begins to rise during the second week.

It is possible to use this reliable pattern of recovery as the basis for a therapeutic trial. For this purpose, the patient should receive a daily parenteral injection of 50 to 100 µg of folic acid. Administration of doses in excess of 100 µg per day entails the risk of inducing a hematopoietic response in patients who are deficient in vitamin B₁₂, while oral administration of the vitamin may be unreliable because of intestinal malabsorption. A number of other complications may also interfere with the therapeutic trial. The patient with sprue and deficiencies of other vitamins or iron may fail to respond because of these inadequacies. In cases of alcoholism, the presence of hepatic disease, inflammation, or iron deficiency can act to blunt the proliferative response of the marrow and to prevent the correction of the anemia. For these reasons, the therapeutic trial for the evaluation of the patient with a potential deficiency of folic acid has not gained great popularity.

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